Clinical trial results:
PHASE 3, RANDOMIZED, OPEN LABEL STUDY OF THE EFFICACY AND SAFETY OF PF-02341066 VERSUS STANDARD OF CARE CHEMOTHERAPY (PEMETREXED OR DOCETAXEL) IN PATIENTS WITH ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) HARBORING A TRANSLOCATION OR INVERSION EVENT INVOLVING THE ANAPLASTIC LYMPHOMA KINASE (ALK) GENE LOCUS

Summary

EudraCT number	2009-012595-27
Trial protocol	GB NL DE PL ES HU FR GR IT IE BG SE
Global end of trial date	05 January 2016

Results information

Result version number	v1 (current)
This version publication date	19 November 2016
First version publication date	19 November 2016

Trial information

Trial identification

Sponsor protocol code	A8081007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00932893
WHO universal trial number (UTN)	-

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, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, 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	14 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2012
Global end of trial reached?	Yes
Global end of trial date	05 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that crizotinib was superior to standard of care chemotherapy, pemetrexed or docetaxel, in prolonging Progression Free Survival (PFS) in patients with advanced Non-small cell lung cancer (NSCLC) whose tumors harbor a translocation or inversion event involving the anaplastic lymphoma kinase (ALK) gene locus and who had received only 1 prior chemotherapy regimen for advanced NSCLC and this regimen must have been platinum-based.

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 Council on Harmonization (ICH) 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	18 September 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	66 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	China: 23
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Japan: 68
Country: Number of subjects enrolled	Korea, Republic of: 50
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Sweden: 3

Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	347
EEA total number of subjects	131

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)	297
From 65 to 84 years	49
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

histologically or cytologically proven diagnosis of locally advanced or metastatic nonsmall cell lung cancer; positive for translocation or inversion in ALK gene locus; progressive disease after only 1 prior platinum based chemotherapy regimen.

Pre-assignment

Screening details:

Screening procedures were completed up to 28 days before randomization to study treatment. Post-screening, 4 participants discontinued the study and did not go on to receive the first dose of study treatment. A total of 343 participants were randomized and received at least one dose of study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Crizotinib

Arm description:

Crizotinib (PF-02341066) 250 mg (administered as two 100-mg tablets and one 50-mg tablet) orally twice daily continuously in 21-day cycles. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent occurred.

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

Dosage and administration details:

250 mg tablets twice a day

Arm title	Chemotherapy

Arm description:

Pemetrexed 500 mg per square meter (mg/m^2) intravenous infusion over 10 minutes or docetaxel 75 mg/m^2 intravenous infusion over 1 hour on Day 1 of 21-day cycle, as per investigator discretion. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent occurred.

Arm type	Active comparator
Investigational medicinal product name	Pemetrexed or Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

500mg/m2 of pemetrexed or 75mg/m2 of docetaxel

Number of subjects in period 1	Crizotinib	Chemotherapy
Started	173	174
Randomized and not treated	1 [1]	3 [2]
Randomized and treated	172	171
Completed	40	4
Not completed	133	170
Adverse event, serious fatal	115	24
Consent withdrawn by subject	5	2
Unspecified	5	144
Lost to follow-up	8	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 173 subjects were enrolled however 1 subject withdrew prior to treatment and was never treated.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 174 subjects were enrolled however 3 subjects withdrew prior to treatment and were never treated.

Baseline characteristics

Reporting groups	
Reporting group title	Crizotinib
Reporting group description:	
Crizotinib (PF-02341066) 250 mg (administered as two 100-mg tablets and one 50-mg tablet) orally twice daily continuously in 21-day cycles. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent occurred.	
Reporting group title	Chemotherapy
Reporting group description:	
Pemetrexed 500 mg per square meter (mg/m^2) intravenous infusion over 10 minutes or docetaxel 75 mg/m^2 intravenous infusion over 1 hour on Day 1 of 21-day cycle, as per investigator discretion. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent occurred.	

Reporting group values	Crizotinib	Chemotherapy	Total
Number of subjects	173	174	347
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	146	151	297
From 65-84 years	27	22	49
85 years and over	0	1	1
Age Continuous Units: years			
arithmetic mean	50.3	49.8	
standard deviation	± 13.1	± 13	-
Gender, Male/Female Units: participants			
Female	98	95	193
Male	75	79	154

End points

End points reporting groups

Reporting group title	Crizotinib
Reporting group description:	
Crizotinib (PF-02341066) 250 mg (administered as two 100-mg tablets and one 50-mg tablet) orally twice daily continuously in 21-day cycles. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent occurred.	
Reporting group title	Chemotherapy
Reporting group description:	
Pemetrexed 500 mg per square meter (mg/m^2) intravenous infusion over 10 minutes or docetaxel 75 mg/m^2 intravenous infusion over 1 hour on Day 1 of 21-day cycle, as per investigator discretion. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent occurred.	

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description:	
PFS: Time in months from randomization to first documentation of objective disease progression as determined by independent radiology review or to death due to any cause, whichever occurred first. PFS was calculated as (first event date minus the date of randomization plus 1) divided by 30.4. Progression is defined using Response Evaluation Criteria in Solid Tumors Criteria version 1.1 (RECIST v1.1), as at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions.	
End point type	Primary
End point timeframe:	
Randomization until progressive disease (PD) or initiation of antitumor therapy in the absence of PD or death, assessed every 6 weeks (up to 112 weeks)	

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	174		
Units: months				
median (confidence interval 95%)	7.7 (6 to 8.8)	3 (2.6 to 4.3)		

Statistical analyses

Statistical analysis title	Progression Free Survival
Statistical analysis description:	
P-value was obtained from 1-sided log-rank test stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) score, brain metastases, and prior epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) treatment. The hazard ratio and corresponding 95% confidence interval (CI) from the stratified Cox Proportional Hazards model were also presented.	
Comparison groups	Crizotinib v Chemotherapy

Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.487
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.371
upper limit	0.638

Notes:

[1] - To control family-wise Type 1 error, a step-down procedure was applied in following order: PFS, objective response rate (ORR), overall survival (OS), and disease control rate (DCR). Statistical significance: 1-sided at alpha=0.025.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS: Time in months from randomization to date of death due to any cause. OS was calculated as (the death date minus the date of randomization plus 1) divided by 30.4.

End point type	Secondary

End point timeframe:

Randomization until death (up to 4.5 years)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	174		
Units: months				
median (confidence interval 95%)	21.7 (18.9 to 30.5)	21.9 (16.8 to 26)		

Statistical analyses

Statistical analysis title	Overall Survival

Statistical analysis description:

P-value was obtained from 1-sided log-rank test stratified by ECOG PS score, brain metastases, and prior EGFR TKI treatment. The hazard ratio and corresponding 95% CI from the stratified Cox proportional hazards model were also presented.

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1145 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.854

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.661
upper limit	1.104

Notes:

[2] - Statistical significance: 1-sided at alpha=0.025

Secondary: Overall Survival Probability at Months 6 and 12

End point title	Overall Survival Probability at Months 6 and 12

End point description:

Overall survival probability at Month 6 and 12 was defined as the probability of survival at 6 and 12 months respectively, after the randomization of study treatment. The survival probability was estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Month 6, 12

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	174		
Units: percentage				
number (confidence interval 95%)				
Month 6	86.6 (80.5 to 90.9)	83.8 (77.4 to 88.5)		
Month 12	70.4 (62.9 to 76.7)	66.7 (59.1 to 73.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response rate (ORR)

End point title	Objective Response rate (ORR)

End point description:

Percentage of participants with objective response based on assessment of complete response (CR) or partial response (PR) according to RECIST v1.1. CR: disappearance of all target and non-target lesions and normalization of tumor marker level, all lymph nodes must be non-pathological in size (<10 millimeter [mm] short axis). PR: at least 30 percent (%) decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. Objective response is based on independent radiology review.

End point type	Secondary

End point timeframe:

Randomization until PD or initiation of antitumor therapy in the absence of PD or death, assessed every 6 weeks (up to 112 weeks)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	174		
Units: percentage of participants				
number (confidence interval 95%)	65.3 (57.7 to 72.4)	19.5 (13.9 to 26.2)		

Statistical analyses

Statistical analysis title	Participants % with OR

Statistical analysis description:

P-value was obtained from Cochran-Mantel-Haenszel (CMH) test stratified by ECOG PS, brain metastases, and prior EGFR TKI treatment. The risk ratio and corresponding 95% CI from the stratified CMH test were also reported.

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	3.394
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.463
upper limit	4.676

Notes:

[3] - Statistical significance: 2-sided at alpha=0.025.

Secondary: Percentage of Participants With Disease Control at Week 6

End point title	Percentage of Participants With Disease Control at Week 6

End point description:

Disease control: participants with CR, PR, or stable disease (SD) according to RECIST v1.1. CR: disappearance of all target and non-target lesions and normalization of tumor marker level, all lymph nodes must be non-pathological in size (<10 mm short axis). PR: at least 30 % decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum diameters while on study. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions. Disease control is based on independent radiology review.

End point type	Secondary

End point timeframe:

Week 6

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	174		
Units: percentage of participants				
number (confidence interval 95%)	81.5 (74.9 to 87)	55.2 (47.5 to 62.7)		

Statistical analyses

Statistical analysis title	Participants % With Disease Control at Week 6
Statistical analysis description:	
P-value was obtained from CMH test stratified by ECOG PS, brain metastases, and prior EGFR TKI treatment. The risk ratio and corresponding 95% CI from the stratified CMH test were also reported.	
Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.502
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.297
upper limit	1.741

Notes:

[4] - Statistical significance: 2-sided at alpha=0.0004.

Secondary: Percentage of Participants With Disease Control at Week 12

End point title	Percentage of Participants With Disease Control at Week 12
End point description:	
Disease control: participants with CR, PR, or SD according to RECIST v1.1. CR: disappearance of all target and non-target lesions and normalization of tumor marker level, all lymph nodes must be non-pathological in size (<10 mm short axis). PR: at least 30 % decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. PD: at least a 20% increase (including an absolute increase of at least 5 mm) in the sum of diameters of target lesions, taking as reference the smallest sum on study and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions.	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	174		
Units: percentage of participants				
number (confidence interval 95%)	64.2 (56.5 to 71.3)	38.5 (31.2 to 46.2)		

Statistical analyses

Statistical analysis title	Participants % With Disease Control at Week 12

Statistical analysis description:

P-value was obtained from CMH test stratified by ECOG PS, brain metastases, and prior EGFR TKI treatment. The risk ratio and corresponding 95% CI from the stratified CMH test were also reported.

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.697
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.368
upper limit	2.103

Notes:

[5] - Statistical significance: 2-sided at alpha=0.0004.

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

Time in weeks from the first documentation of objective tumor response to objective tumor progression or death due to any cause. Duration of tumor response was calculated as (the date of the first documentation of objective tumor progression or death due to any cause minus the date of the first CR or PR that was subsequently confirmed plus 1) divided by 7.02. DR was calculated for the subgroup of participants with a confirmed objective tumor response.

End point type	Secondary

End point timeframe:

Randomization until PD or initiation of antitumor therapy in the absence of PD or death, assessed every 6 weeks (up to 112 weeks)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	34		
Units: weeks				
median (confidence interval 95%)	32.1 (26.4 to 42.3)	24.4 (15 to 36)		

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:

Time from date of randomization to first documentation of objective tumor response. TTR was calculated for the subgroup of participants with objective tumor response. Objective tumor response was defined as CR or PR according to RECIST v1.1. CR: disappearance of all target and non-target lesions and normalization of tumor marker level, all lymph nodes must be non-pathological in size (<10 mm short axis). PR: at least 30 % decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

End point type	Secondary

End point timeframe:

Randomization until PD or initiation of antitumor therapy in the absence of PD or death, assessed every 6 weeks (up to 112 weeks)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	34		
Units: weeks				
median (full range (min-max))	6.3 (4.4 to 48.4)	12.6 (5 to 37.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Crizotinib

End point title	Plasma Concentration of Crizotinib[6]

End point description:

Only participants receiving crizotinib were to be analyzed for this outcome measure as per planned analysis.

End point type	Secondary

End point timeframe:

Pre-dose on Cycle 1 Day 1 and Cycle Day 15, and Day 1 of Cycle 1, 2, 3, 5

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants receiving crizotinib were to be analyzed for this outcome measure as per planned analysis.

End point values	Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	152			
Units: nanogram per milliliter (ng/mL)				
geometric mean (standard deviation)				
Cycle 1 Day 1 (n=15)	0 (± 0)			
Cycle 1 Day 15 (n=92)	298 (± 148)			
Cycle 2 Day 1 (n=62)	293 (± 154)			
Cycle 3 Day 1 (n=61)	306 (± 135)			
Cycle 5 Day 1 (n=47)	291 (± 156)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Categorical Maximum QTcF for Crizotinib

End point title	Number of Participants With Categorical Maximum QTcF for Crizotinib[7]

End point description:

QT interval corrected using Fridericia's formula (QTcF): QT interval (time corresponding to the beginning of depolarization to re-polarization of the ventricles) divided by cube root of RR interval. Maximum QTcF was categorized as less than (<) 450 milliseconds (msec), 450 msec to <480 msec, 480 msec to <500 msec, and more than or equal to (>=) 500 msec. A participant is reported only once under the maximum QTcF interval observed at any of the time-points. Only participants receiving crizotinib were to be analyzed for this outcome measure as per planned analysis.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1 of Cycle 1, 2 to 6 hours post-dose on Day 1 of Cycle 1, 2

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants receiving crizotinib were to be analyzed for this outcome measure as per planned analysis.

End point values	Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	155			
Units: participants				
<450 msec	137			
450 msec to <480 msec	9			
480 msec to <500 msec	1			
>=500 msec	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Soluble c-Met Ectodomain and Hepatocyte Growth Factor Scatter Proteins

End point title	Plasma Concentration of Soluble c-Met Ectodomain and Hepatocyte Growth Factor Scatter Proteins

End point description:

Descriptive statistics (absolute value and change from baseline as measured by ratio to baseline) for each best overall response category (CR, PR, SD, PD or combined) have been used to summarize the data from optional soluble c-Met ectodomain assays for crizotinib treated patients.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1 of Cycle 1, 2 to 6 hours post-dose on Day 1 of Cycle 2, end of treatment (up to 112 weeks)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	0[8]		
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (N = 81)	1428.3 (± 363.9)	()		
Cycle 2 Day 1 6-hour post dose (N = 69)	1683 (± 325.6)	()		
End of treatment (N = 40)	1751.8 (± 327.9)	()		

Notes:

[8] - Participants from the SA population that received crizotinib were used for this analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in Participant Reported Pain, Dyspnea, and Cough

End point title	Time to Deterioration (TTD) in Participant Reported Pain, Dyspnea, and Cough

End point description:

TTD in pain (pain in chest from European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Supplement Module for Lung Cancer [EORTC QLQ-LC13]), dyspnea (from EORTC QLQ-LC13), or cough (from EORTC QLQ-LC13) symptoms was defined as the time from randomization to the earliest time the participant's score showed a 10 point or higher increase from baseline in any of the three symptoms from the instrument. The transformed score of pain, dyspnea, and cough symptom scales of EORTC QLQ-LC13 range from 0 to 100, greater scores = higher symptom severity.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment (up to 112 weeks)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	151		
Units: months				
median (confidence interval 95%)	4.5 (3 to 6.9)	1.4 (1 to 1.6)		

Statistical analyses

Statistical analysis title	TTD in Participant Reported Pain, Dyspnea & Cough

Statistical analysis description:

The p-value was obtained from 2-sided unstratified log-rank test. The hazard ratio and corresponding 95% CI from the Cox Proportional Hazards model were also presented.

Comparison groups	Crizotinib v Chemotherapy
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.497
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.373
upper limit	0.661

Secondary: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

End point title	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

End point description:

EORTC QLQ-C30: included global health status/quality of life (QoL), functional scales (physical, role, cognitive, emotional, and social), symptom scales (fatigue, pain, nausea/vomiting), and single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, and financial difficulties). Most questions used 4- point scale (1 'Not at All' to 4 'Very Much'); 2 questions used 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores averaged, transformed to 0-100 scale; higher score for Global Qol/functional scales=better level of QoL/functioning or higher score for symptom scale=greater degree of symptoms.

End point type	Secondary

End point timeframe:

Baseline, Day (D) 1 of each cycle (C) until disease progression, end of treatment (EOT, up to 112 weeks)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	163		
Units: units on a scale				
arithmetic mean (standard deviation)				
Global QoL: Baseline (n=165, 162)	57.2 (± 21.5)	58.1 (± 22.2)		
Global QoL: C2D1 (n=154, 133)	64.5 (± 21.8)	58.1 (± 23.1)		
Global QoL: C3D1 (n=154, 106)	65.2 (± 22.1)	59.4 (± 23.1)		
Global QoL: C4D1 (n=135, 90)	68.4 (± 19.6)	61.1 (± 20.8)		
Global QoL: C5D1 (n=123, 74)	68.5 (± 20.2)	64.1 (± 22.7)		
Global QoL: C6D1 (n=120, 70)	68.3 (± 19.8)	67.5 (± 23.5)		
Global QoL: C7D1 (n=114, 52)	69.5 (± 19.3)	66.5 (± 23.1)		
Global QoL: C8D1 (n=110, 43)	68.7 (± 20.1)	66.9 (± 25.3)		
Global QoL: C9D1 (n=101, 37)	68.7 (± 21)	66.4 (± 27.8)		
Global QoL: C10D1 (n=94, 33)	67 (± 21.6)	67.4 (± 26.8)		
Global QoL: C11D1 (n=83, 25)	69.5 (± 20.2)	71 (± 21.8)		
Global QoL: C12D1 (n=76, 23)	67.9 (± 22)	65.6 (± 24.1)		
Global QoL: C13D1 (n=74, 21)	66.8 (± 23.6)	66.7 (± 23.6)		
Global QoL: C14D1 (n=66, 19)	71.5 (± 20)	65.8 (± 23.4)		
Global QoL: C15D1 (n=62, 16)	69 (± 22.2)	66.1 (± 24.1)		
Global QoL: C16D1 (n=53, 12)	69.7 (± 18.1)	63.2 (± 25.5)		
Global QoL: C17D1 (n=47, 11)	67.6 (± 20.5)	69.7 (± 23.4)		
Global QoL: C18D1 (n=44, 11)	65.7 (± 19.9)	70.5 (± 22.5)		
Global QoL: C19D1 (n=40, 9)	69.2 (± 19.2)	72.2 (± 20)		
Global QoL: C20D1 (n=35, 8)	64.3 (± 20.6)	60.4 (± 21.2)		
Global QoL: C21D1 (n=30, 8)	65 (± 18.4)	63.5 (± 23.5)		
Global QoL: C22D1 (n=24, 7)	70.8 (± 19.3)	64.3 (± 24.9)		
Global QoL: C23D1 (n=23, 4)	67 (± 22.5)	50 (± 19.2)		
Global QoL: C24D1 (n=20, 3)	67.1 (± 18.8)	55.6 (± 19.2)		
Global QoL: C25D1 (n=18, 3)	67.1 (± 17.7)	61.1 (± 19.2)		
Global QoL: C26D1 (n=14, 3)	60.7 (± 22)	55.6 (± 12.7)		
Global QoL: C27D1 (n=14, 2)	58.9 (± 20.3)	41.7 (± 0)		
Global QoL: C28D1 (n=11, 2)	66.7 (± 18.3)	54.2 (± 17.7)		
Global QoL: C29D1 (n=8, 2)	59.4 (± 18.6)	41.7 (± 11.8)		
Global QoL: C30D1 (n=8, 1)	64.6 (± 19.3)	33.3 (± 0)		
Global QoL: C31D1 (n=7, 0)	64.3 (± 17.2)	0 (± 0)		
Global QoL: C32D1 (n=6, 0)	59.7 (± 17)	0 (± 0)		
Global QoL: C33D1 (n=6, 0)	66.7 (± 18.3)	0 (± 0)		
Global QoL: C34D1 (n=5, 0)	68.3 (± 14.9)	0 (± 0)		
Global QoL: C35D1 (n=4, 0)	60.4 (± 22.9)	0 (± 0)		
Global QoL: C36D1 (n=1, 0)	66.7 (± 0)	0 (± 0)		
Global QoL: C37D1 (n=1, 0)	66.7 (± 0)	0 (± 0)		
Physical Functioning: Baseline (n=165, 163)	76.3 (± 20.7)	75.8 (± 21.9)		
Physical Functioning: C2D1 (n=155, 133)	79.2 (± 20.9)	73.5 (± 22.3)		
Physical Functioning: C3D1 (n=154, 106)	82.3 (± 18.1)	75.5 (± 20.2)		
Physical Functioning: C4D1 (n=135, 91)	83.8 (± 16.2)	76.6 (± 20.2)		
Physical Functioning: C5D1 (n=123, 74)	84.5 (± 16.2)	78.6 (± 23)		
Physical Functioning: C6D1 (n=120, 70)	86.2 (± 16.7)	80.7 (± 19.7)		
Physical Functioning: C7D1 (n=115, 52)	86.7 (± 15)	80.3 (± 19.7)		

Physical Functioning: C8D1 (n=111, 43)	86.5 (± 16.3)	81.6 (± 18.5)		
Physical Functioning: C9D1 (n=101, 37)	87.7 (± 14.2)	82.3 (± 19.1)		
Physical Functioning: C10D1 (n=94, 33)	87.9 (± 14.8)	81.8 (± 20.7)		
Physical Functioning: C11D1 (n=84, 25)	87.2 (± 16.7)	83.2 (± 19)		
Physical Functioning: C12D1 (n=76, 23)	88.1 (± 15.3)	79.7 (± 22.8)		
Physical Functioning: C13D1 (n=74, 21)	89.3 (± 13.9)	78.4 (± 23.6)		
Physical Functioning: C14D1 (n=66, 19)	89 (± 14.3)	80 (± 21.4)		
Physical Functioning: C15D1 (n=62, 16)	87.8 (± 15.3)	82.9 (± 15.4)		
Physical Functioning: C16D1 (n=53, 12)	89.3 (± 11.5)	81.1 (± 19.5)		
Physical Functioning: C17D1 (n=47, 11)	86.6 (± 16.8)	81.8 (± 15.8)		
Physical Functioning: C18D1 (n=45, 11)	88.4 (± 13.3)	82.4 (± 16.1)		
Physical Functioning: C19D1 (n=40, 9)	88.3 (± 12.4)	81.5 (± 12.8)		
Physical Functioning: C20D1 (n=35, 8)	87.6 (± 12.7)	79.2 (± 17.3)		
Physical Functioning: C21D1 (n=30, 8)	88.4 (± 10.9)	77.5 (± 22.5)		
Physical Functioning: C22D1 (n=24, 7)	90.6 (± 8.3)	78.1 (± 24.3)		
Physical Functioning: C23D1 (n=23, 4)	88 (± 13.1)	60 (± 27.2)		
Physical Functioning: C24D1 (n=20, 3)	85 (± 14)	64.4 (± 32.9)		
Physical Functioning: C25D1 (n=18, 3)	87.4 (± 11.6)	60 (± 29.1)		
Physical Functioning: C26D1 (n=14, 3)	80.5 (± 25.3)	62.2 (± 30.8)		
Physical Functioning: C27D1 (n=14, 2)	78.6 (± 27.8)	50 (± 23.6)		
Physical Functioning: C28D1 (n=11, 2)	81.8 (± 24.1)	60 (± 18.9)		
Physical Functioning: C29D1 (n=8, 2)	85 (± 15)	46.7 (± 28.3)		
Physical Functioning: C30D1 (n=8, 1)	82.5 (± 21.4)	26.7 (± 0)		
Physical Functioning: C31D1 (n=7, 0)	83.8 (± 17.2)	0 (± 0)		
Physical Functioning: C32D1 (n=6, 0)	88.9 (± 9.1)	0 (± 0)		
Physical Functioning: C33D1 (n=6, 0)	90 (± 7)	0 (± 0)		
Physical Functioning: C34D1 (n=5, 0)	85.3 (± 7.3)	0 (± 0)		
Physical Functioning: C35D1 (n=4, 0)	91.7 (± 3.3)	0 (± 0)		
Physical Functioning: C36D1 (n=1, 0)	86.7 (± 0)	0 (± 0)		
Physical Functioning: C37D1 (n=1, 0)	86.7 (± 0)	0 (± 0)		
Role Functioning: Baseline (n=165, 163)	69.3 (± 28.7)	66.6 (± 30.2)		
Role Functioning: C2D1 (n=155, 133)	73.8 (± 28.9)	64.7 (± 29.7)		
Role Functioning: C3D1 (n=154, 106)	74.4 (± 28.6)	65.3 (± 27.7)		
Role Functioning: C4D1 (n=134, 91)	77.9 (± 25.7)	67.2 (± 27.3)		
Role Functioning: C5D1 (n=123, 74)	78.2 (± 24.3)	69.6 (± 27.4)		
Role Functioning: C6D1 (n=120, 70)	80 (± 24.1)	69.5 (± 26.2)		
Role Functioning: C7D1 (n=115, 52)	81.7 (± 22.6)	72.1 (± 25.9)		
Role Functioning: C8D1 (n=111, 43)	80.4 (± 23.9)	75.2 (± 28.3)		
Role Functioning: C9D1 (n=101, 37)	80.9 (± 25.8)	76.6 (± 27.6)		
Role Functioning: C10D1 (n=94, 33)	81.6 (± 23.1)	75.3 (± 28.3)		
Role Functioning: C11D1 (n=84, 25)	81.3 (± 23.8)	75.3 (± 25.5)		
Role Functioning: C12D1 (n=76, 23)	81.6 (± 23.2)	72.5 (± 29.6)		
Role Functioning: C13D1 (n=74, 21)	80.2 (± 25.5)	68.3 (± 32)		
Role Functioning: C14D1 (n=66, 19)	83.8 (± 21.3)	68.4 (± 30.4)		
Role Functioning: C15D1 (n=62, 16)	80.6 (± 24)	77.1 (± 27.8)		
Role Functioning: C16D1 (n=53, 12)	84 (± 19)	69.4 (± 34)		
Role Functioning: C17D1 (n=47, 11)	77.7 (± 25.4)	71.2 (± 38.1)		
Role Functioning: C18D1 (n=45, 11)	80 (± 22.4)	71.2 (± 31.7)		
Role Functioning: C19D1 (n=40, 9)	82.1 (± 19.4)	74.1 (± 29)		
Role Functioning: C20D1 (n=35, 8)	81.9 (± 17.8)	70.8 (± 36.5)		
Role Functioning: C21D1 (n=30, 8)	80 (± 24.1)	66.7 (± 32.1)		
Role Functioning: C22D1 (n=24, 7)	84.7 (± 19)	67.9 (± 33.5)		

Role Functioning: C23D1 (n=23, 4)	76.8 (± 26.9)	37.5 (± 25)		
Role Functioning: C24D1 (n=20, 3)	80.8 (± 24.3)	44.4 (± 38.5)		
Role Functioning: C25D1 (n=18, 3)	87 (± 19.4)	44.4 (± 25.5)		
Role Functioning: C26D1 (n=14, 3)	75 (± 29.1)	33.3 (± 33.3)		
Role Functioning: C27D1 (n=14, 2)	69 (± 35.1)	25 (± 11.8)		
Role Functioning: C28D1 (n=11, 2)	77.3 (± 33.6)	25 (± 35.4)		
Role Functioning: C29D1 (n=8, 2)	77.1 (± 34.4)	25 (± 11.8)		
Role Functioning: C30D1 (n=8, 1)	77.1 (± 34.4)	0 (± 0)		
Role Functioning: C31D1 (n=7, 0)	71.4 (± 36.9)	0 (± 0)		
Role Functioning: C32D1 (n=6, 0)	86.1 (± 12.5)	0 (± 0)		
Role Functioning: C33D1 (n=6, 0)	88.9 (± 13.6)	0 (± 0)		
Role Functioning: C34D1 (n=5, 0)	96.7 (± 7.5)	0 (± 0)		
Role Functioning: C35D1 (n=4, 0)	91.7 (± 16.7)	0 (± 0)		
Role Functioning: C36D1 (n=1, 0)	100 (± 0)	0 (± 0)		
Role Functioning: C37D1 (n=1, 0)	100 (± 0)	0 (± 0)		
Emotional Functioning: Baseline (n=165, 162)	74.5 (± 21.3)	73.7 (± 20.7)		
Emotional Functioning: C2D1 (n=155, 133)	83.1 (± 18.7)	77.7 (± 19.3)		
Emotional Functioning: C3D1 (n=154, 106)	83.3 (± 16.7)	77.9 (± 21.5)		
Emotional Functioning: C4D1 (n=135, 90)	84.1 (± 17.3)	80.5 (± 18.9)		
Emotional Functioning: C5D1 (n=123, 74)	83 (± 19.1)	79.8 (± 19.9)		
Emotional Functioning: C6D1 (n=120, 70)	85.3 (± 17.8)	81.2 (± 19.4)		
Emotional Functioning: C7D1 (n=115, 52)	86.4 (± 16.5)	81.9 (± 17.6)		
Emotional Functioning: C8D1 (n=111, 43)	83.9 (± 19.8)	81.6 (± 20.7)		
Emotional Functioning: C9D1 (n=101, 37)	84.4 (± 19)	82.4 (± 19.6)		
Emotional Functioning: C10D1 (n=94, 33)	87.2 (± 16.8)	81.8 (± 21.2)		
Emotional Functioning: C11D1 (n=84,25)	86.1 (± 16.7)	85 (± 17.8)		
Emotional Functioning: C12D1 (n=76, 23)	85.3 (± 18.6)	84.8 (± 18.6)		
Emotional Functioning: C13D1 (n=74, 21)	84.9 (± 19)	80.6 (± 19.1)		
Emotional Functioning: C14D1 (n=66, 19)	84.5 (± 19.9)	81.6 (± 21.1)		
Emotional Functioning: C15D1 (n=62, 16)	86.3 (± 18)	82.3 (± 18.2)		
Emotional Functioning: C16D1 (n=53, 12)	85.8 (± 17.6)	77.8 (± 27.8)		
Emotional Functioning: C17D1 (n=47, 11)	85.6 (± 22)	79.5 (± 23.4)		
Emotional Functioning: C18D1 (n=44, 11)	86.4 (± 17.2)	75.8 (± 27.8)		
Emotional Functioning: C19D1 (n=40, 9)	87.3 (± 16)	81.5 (± 20.7)		
Emotional Functioning: C20D1 (n=35, 8)	83.8 (± 17.5)	82.3 (± 25)		
Emotional Functioning: C21D1 (n=30, 8)	84.5 (± 17.1)	80.2 (± 29.5)		
Emotional Functioning: C22D1 (n=24, 7)	83.7 (± 21.6)	78.6 (± 24.9)		

Emotional Functioning: C23D1 (n=23, 4)	84.1 (± 19.8)	70.8 (± 21)		
Emotional Functioning: C24D1 (n=20, 3)	87.9 (± 16.1)	66.7 (± 30)		
Emotional Functioning: C25D1 (n=18, 3)	81.5 (± 19.5)	72.2 (± 24.1)		
Emotional Functioning: C26D1 (n=14, 3)	73.2 (± 28.3)	72.2 (± 24.1)		
Emotional Functioning: C27D1 (n=14, 2)	70.8 (± 27.3)	58.3 (± 0)		
Emotional Functioning: C28D1 (n=11, 2)	81.1 (± 27.2)	58.3 (± 0)		
Emotional Functioning: C29D1 (n=8, 2)	86.5 (± 15.4)	54.2 (± 5.9)		
Emotional Functioning: C30D1 (n=8, 1)	84.4 (± 25)	58.3 (± 0)		
Emotional Functioning: C31D1 (n=7, 0)	76.2 (± 28.2)	0 (± 0)		
Emotional Functioning: C32D1 (n=6, 0)	87.5 (± 17.3)	0 (± 0)		
Emotional Functioning: C33D1 (n=6, 0)	90.3 (± 13.4)	0 (± 0)		
Emotional Functioning: C34D1 (n=5, 0)	91.7 (± 14.4)	0 (± 0)		
Emotional Functioning: C35D1 (n=4, 0)	83.3 (± 20.4)	0 (± 0)		
Emotional Functioning: C36D1 (n=1, 0)	58.3 (± 0)	0 (± 0)		
Emotional Functioning: C37D1 (n=1, 0)	58.3 (± 0)	0 (± 0)		
Cognitive Functioning: Baseline (n=165, 162)	85.6 (± 18.3)	83.6 (± 22.3)		
Cognitive Functioning: C2D1 (n=155, 133)	85.5 (± 18.9)	84.5 (± 20.6)		
Cognitive Functioning: C3D1 (n=154, 106)	87 (± 15.7)	83.8 (± 20.4)		
Cognitive Functioning: C4D1 (n=135, 90)	88.1 (± 15.6)	82.6 (± 20.4)		
Cognitive Functioning: C5D1 (n=123, 74)	88.9 (± 14.4)	82.7 (± 22)		
Cognitive Functioning: C6D1 (n=120, 70)	87.5 (± 15.3)	83.8 (± 19.2)		
Cognitive Functioning: C7D1 (n=115, 52)	86.7 (± 15.6)	85.3 (± 18.3)		
Cognitive Functioning: C8D1 (n=111, 43)	87.8 (± 14.7)	82.2 (± 23.4)		
Cognitive Functioning: C9D1 (n=101, 37)	88.3 (± 16.6)	84.7 (± 21.7)		
Cognitive Functioning: C10D1 (n=94, 33)	89.2 (± 16)	80.8 (± 22.1)		
Cognitive Functioning: C11D1 (n=84, 25)	87.9 (± 14.9)	85.3 (± 19.4)		
Cognitive Functioning: C12D1 (n=76, 23)	89.5 (± 14.4)	80.4 (± 22.8)		
Cognitive Functioning: C13D1 (n=74, 21)	88.5 (± 15.6)	79.4 (± 27.8)		
Cognitive Functioning: C14D1 (n=66, 19)	88.9 (± 14.7)	81.6 (± 24.1)		
Cognitive Functioning: C15D1 (n=62, 16)	87.6 (± 15.4)	84.4 (± 18.7)		
Cognitive Functioning: C16D1 (n=53, 12)	87.4 (± 14.2)	72.2 (± 25.9)		
Cognitive Functioning: C17D1 (n=47, 11)	85.1 (± 15.2)	75.8 (± 21.6)		
Cognitive Functioning: C18D1 (n=44, 11)	88.3 (± 14.6)	75.8 (± 25.1)		
Cognitive Functioning: C19D1 (n=40, 9)	87.5 (± 14.5)	70.4 (± 23.2)		
Cognitive Functioning: C20D1 (n=35, 8)	85.7 (± 15.2)	72.9 (± 23.5)		
Cognitive Functioning: C21D1 (n=30, 8)	85.6 (± 15)	72.9 (± 23.5)		

Cognitive Functioning: C22D1 (n=24, 7)	86.1 (± 15.3)	69 (± 24.4)		
Cognitive Functioning: C23D1 (n=23, 4)	85.5 (± 14.5)	58.3 (± 21.5)		
Cognitive Functioning: C24D1 (n=20, 3)	85.8 (± 19.7)	61.1 (± 34.7)		
Cognitive Functioning: C25D1 (n=18, 3)	86.1 (± 15.4)	55.6 (± 25.5)		
Cognitive Functioning: C26D1 (n=14, 3)	81 (± 26)	61.1 (± 34.7)		
Cognitive Functioning: C27D1 (n=14, 2)	76.2 (± 25.9)	41.7 (± 11.8)		
Cognitive Functioning: C28D1 (n=11, 2)	78.8 (± 21.2)	41.7 (± 11.8)		
Cognitive Functioning: C29D1 (n=8, 2)	87.5 (± 11.8)	33.3 (± 0)		
Cognitive Functioning: C30D1 (n=8, 1)	83.3 (± 23.6)	16.7 (± 0)		
Cognitive Functioning: C31D1 (n=7, 0)	81 (± 20.2)	0 (± 0)		
Cognitive Functioning: C32D1 (n=6, 0)	83.3 (± 18.3)	0 (± 0)		
Cognitive Functioning: C33D1 (n=6, 0)	86.1 (± 16.4)	0 (± 0)		
Cognitive Functioning: C34D1 (n=5, 0)	90 (± 9.1)	0 (± 0)		
Cognitive Functioning: C35D1 (n=4, 0)	95.8 (± 8.3)	0 (± 0)		
Cognitive Functioning: C36D1 (n=1, 0)	100 (± 0)	0 (± 0)		
Cognitive Functioning: C37D1 (n=1, 0)	83.3 (± 0)	0 (± 0)		
Social Functioning: Baseline (n=165, 162)	68 (± 27.7)	67.1 (± 29)		
Social Functioning: C2D1 (n=155, 133)	75.9 (± 25.1)	69.5 (± 28.1)		
Social Functioning: C3D1 (n=154, 106)	78.5 (± 24)	72.5 (± 26.7)		
Social Functioning: C4D1 (n=135, 90)	79.4 (± 23.9)	71.7 (± 26.3)		
Social Functioning: C5D1 (n=123, 74)	79.4 (± 23.8)	74.5 (± 27.1)		
Social Functioning: C6D1 (n=120, 70)	81.8 (± 22.1)	76.4 (± 27.3)		
Social Functioning: C7D1 (n=115, 52)	82.3 (± 21.8)	77.9 (± 24.6)		
Social Functioning: C8D1 (n=111, 43)	82 (± 21.3)	77.5 (± 24.4)		
Social Functioning: C9D1 (n=101, 37)	80.4 (± 24.7)	80.2 (± 21.8)		
Social Functioning: C10D1 (n=94, 33)	81.9 (± 25.1)	76.3 (± 27)		
Social Functioning: C11D1 (n=84, 25)	81.9 (± 23)	78.7 (± 24.8)		
Social Functioning: C12D1 (n=76, 23)	82 (± 23.5)	71 (± 31.9)		
Social Functioning: C13D1 (n=74, 21)	81.8 (± 24.7)	71.4 (± 28.9)		
Social Functioning: C14D1 (n=66, 19)	81.3 (± 23.8)	69.3 (± 34.8)		
Social Functioning: C15D1 (n=62, 16)	81.5 (± 25.6)	74 (± 28.5)		
Social Functioning: C16D1 (n=53, 12)	82.7 (± 21.9)	65.3 (± 35.9)		
Social Functioning: C17D1 (n=47, 11)	81.9 (± 24.8)	69.7 (± 33.2)		
Social Functioning: C18D1 (n=44, 11)	82.6 (± 22.7)	65.2 (± 35.3)		
Social Functioning: C19D1 (n=40, 9)	84.6 (± 22.8)	64.8 (± 31.7)		
Social Functioning: C20D1 (n=35, 8)	82.9 (± 23.7)	70.8 (± 33)		
Social Functioning: C21D1 (n=30, 8)	82.8 (± 24.2)	64.6 (± 36.1)		
Social Functioning: C22D1 (n=24, 7)	82.6 (± 23.8)	65.5 (± 39.8)		
Social Functioning: C23D1 (n=23, 4)	84.4 (± 23.9)	41.7 (± 50)		
Social Functioning: C24D1 (n=20, 3)	84.2 (± 27.3)	61.1 (± 53.6)		
Social Functioning: C25D1 (n=18, 3)	89.8 (± 19.1)	50 (± 50)		
Social Functioning: C26D1 (n=14, 3)	78.6 (± 28.8)	50 (± 50)		
Social Functioning: C27D1 (n=14, 2)	85.7 (± 15.8)	33.3 (± 47.1)		
Social Functioning: C28D1 (n=11, 2)	83.3 (± 26.9)	33.3 (± 47.1)		
Social Functioning: C29D1 (n=8, 2)	83.3 (± 25.2)	33.3 (± 47.1)		
Social Functioning: C30D1 (n=8, 1)	85.4 (± 24.3)	0 (± 0)		
Social Functioning: C31D1 (n=7, 0)	73.8 (± 38.3)	0 (± 0)		
Social Functioning: C32D1 (n=6, 0)	83.3 (± 18.3)	0 (± 0)		
Social Functioning: C33D1 (n=6, 0)	94.4 (± 13.6)	0 (± 0)		
Social Functioning: C34D1 (n=5, 0)	96.7 (± 7.5)	0 (± 0)		
Social Functioning: C35D1 (n=4, 0)	91.7 (± 16.7)	0 (± 0)		

Social Functioning: C36D1 (n=1, 0)	66.7 (± 0)	0 (± 0)		
Social Functioning: C37D1 (n=1, 0)	66.7 (± 0)	0 (± 0)		
Fatigue: Baseline (n=165, 163)	38.3 (± 24.4)	36.1 (± 25.3)		
Fatigue: C2D1 (n=155, 133)	31.4 (± 23.4)	39.5 (± 24.8)		
Fatigue: C3D1 (n=154, 106)	30.8 (± 24.1)	39.4 (± 24.5)		
Fatigue: C4D1 (n=135, 91)	27.1 (± 22.3)	34.1 (± 22.1)		
Fatigue: C5D1 (n=123, 74)	24.7 (± 19.8)	31.5 (± 25.2)		
Fatigue: C6D1 (n=120, 70)	24.6 (± 19.3)	31 (± 22.8)		
Fatigue: C7D1 (n=115, 52)	23.9 (± 19.8)	27.6 (± 23.1)		
Fatigue: C8D1 (n=111, 43)	23.2 (± 18.9)	26.6 (± 23.6)		
Fatigue: C9D1 (n=101, 37)	22.9 (± 21.7)	28.5 (± 26.6)		
Fatigue: C10D1 (n=94, 33)	21.4 (± 20)	28.6 (± 27.9)		
Fatigue: C11D1 (n=84, 25)	22.1 (± 19.6)	22.2 (± 22.9)		
Fatigue: C12D1 (n=76, 23)	21.9 (± 22.9)	26.1 (± 24.1)		
Fatigue: C13D1 (n=74, 21)	23.3 (± 21.3)	27.5 (± 25.2)		
Fatigue: C14D1 (n=66, 19)	21.7 (± 21.7)	28.1 (± 26.8)		
Fatigue: C15D1 (n=62, 16)	20.8 (± 22.5)	24.3 (± 24.8)		
Fatigue: C16D1 (n=53, 12)	22.2 (± 18)	24.1 (± 21.6)		
Fatigue: C17D1 (n=47, 11)	23.4 (± 20)	23.2 (± 23)		
Fatigue: C18D1 (n=45, 11)	21.5 (± 18.3)	27.3 (± 22.4)		
Fatigue: C19D1 (n=40, 9)	20.8 (± 18.7)	24.7 (± 20.6)		
Fatigue: C20D1 (n=35, 8)	24.4 (± 19.2)	27.8 (± 26.6)		
Fatigue: C21D1 (n=30, 8)	23.9 (± 17.8)	25.7 (± 27.7)		
Fatigue: C22D1 (n=24, 7)	23.6 (± 16.2)	27 (± 23.9)		
Fatigue: C23D1 (n=23, 4)	25.1 (± 19.3)	47.2 (± 14)		
Fatigue: C24D1 (n=20, 3)	24.4 (± 18.9)	40.7 (± 23.1)		
Fatigue: C25D1 (n=18, 3)	24.7 (± 16)	44.4 (± 19.2)		
Fatigue: C26D1 (n=14, 3)	30.2 (± 25.6)	44.4 (± 19.2)		
Fatigue: C27D1 (n=14, 2)	35.7 (± 25.1)	55.6 (± 15.7)		
Fatigue: C28D1 (n=11, 2)	28.3 (± 22.4)	38.9 (± 7.9)		
Fatigue: C29D1 (n=8, 2)	30.6 (± 22.8)	50 (± 23.6)		
Fatigue: C30D1 (n=8, 1)	26.4 (± 24.4)	55.6 (± 0)		
Fatigue: C31D1 (n=7, 0)	28.6 (± 16.8)	0 (± 0)		
Fatigue: C32D1 (n=6, 0)	25.9 (± 5.7)	0 (± 0)		
Fatigue: C33D1 (n=6, 0)	18.5 (± 11.5)	0 (± 0)		
Fatigue: C34D1 (n=5, 0)	15.6 (± 16.9)	0 (± 0)		
Fatigue: C35D1 (n=4, 0)	27.8 (± 14.3)	0 (± 0)		
Fatigue: C36D1 (n=1, 0)	33.3 (± 0)	0 (± 0)		
Fatigue: C37D1 (n=1, 0)	11.1 (± 0)	0 (± 0)		
Nausea and Vomiting: Baseline (n=165, 163)	8.4 (± 14.4)	11.7 (± 18)		
Nausea and Vomiting: C2D1 (n=155, 133)	15.2 (± 20.9)	12.7 (± 19)		
Nausea and Vomiting: C3D1 (n=154, 106)	13.9 (± 21.2)	9.9 (± 16.6)		
Nausea and Vomiting: C4D1 (n=135, 91)	9.9 (± 18.1)	8.1 (± 14.1)		
Nausea and Vomiting: C5D1 (n=123, 74)	9.2 (± 14.7)	9 (± 16.8)		
Nausea and Vomiting: C6D1 (n=120, 70)	10.1 (± 15.2)	6.9 (± 13.2)		
Nausea and Vomiting: C7D1 (n=115, 52)	7.1 (± 11.9)	7.7 (± 11.7)		

Nausea and Vomiting: C8D1 (n=111, 43)	8.8 (± 13.7)	8.9 (± 14.7)		
Nausea and Vomiting: C9D1 (n=101, 37)	6.9 (± 13)	9.5 (± 19.9)		
Nausea and Vomiting: C10D1 (n=94, 33)	8.5 (± 14.6)	8.1 (± 15.7)		
Nausea and Vomiting: C11D1 (n=84, 25)	8.3 (± 12.8)	8 (± 16)		
Nausea and Vomiting: C12D1 (n=76, 23)	6.4 (± 12.8)	7.2 (± 15.8)		
Nausea and Vomiting: C13D1 (n=74, 21)	8.6 (± 14.1)	7.1 (± 16.3)		
Nausea and Vomiting: C14D1 (n=66, 19)	5.8 (± 13.9)	7 (± 14)		
Nausea and Vomiting: C15D1 (n=62, 16)	5.9 (± 11.3)	6.2 (± 13.4)		
Nausea and Vomiting: C16D1 (n=53, 12)	5.3 (± 9.7)	6.9 (± 11.1)		
Nausea and Vomiting: C17D1 (n=47, 11)	7.8 (± 12.5)	10.6 (± 11.2)		
Nausea and Vomiting: C18D1 (n=45, 11)	7 (± 13.5)	3 (± 6.7)		
Nausea and Vomiting: C19D1 (n=40, 9)	8.8 (± 14.6)	9.3 (± 12.1)		
Nausea and Vomiting: C20D1 (n=35, 8)	7.4 (± 13.5)	10.4 (± 15.3)		
Nausea and Vomiting: C21D1 (n=30, 8)	7.8 (± 12.9)	8.3 (± 12.6)		
Nausea and Vomiting: C22D1 (n=24, 7)	2.8 (± 6.3)	14.3 (± 17.8)		
Nausea and Vomiting: C23D1 (n=23, 4)	5.4 (± 10.5)	45.8 (± 21)		
Nausea and Vomiting: C24D1 (n=20, 3)	7.5 (± 14.8)	33.3 (± 28.9)		
Nausea and Vomiting: C25D1 (n=18, 3)	3.7 (± 9.1)	27.8 (± 25.5)		
Nausea and Vomiting: C26D1 (n=14, 3)	10.7 (± 27.4)	33.3 (± 16.7)		
Nausea and Vomiting: C27D1 (n=14, 2)	11.9 (± 27.3)	33.3 (± 23.6)		
Nausea and Vomiting: C28D1 (n=11, 2)	3 (± 6.7)	25 (± 11.8)		
Nausea and Vomiting: C29D1 (n=8, 2)	10.4 (± 15.3)	25 (± 11.8)		
Nausea and Vomiting: C30D1 (n=8, 1)	6.3 (± 12.4)	33.3 (± 0)		
Nausea and Vomiting: C31D1 (n=7, 0)	14.3 (± 17.8)	0 (± 0)		
Nausea and Vomiting: C32D1 (n=6, 0)	11.1 (± 17.2)	0 (± 0)		
Nausea and Vomiting: C33D1 (n=6, 0)	11.1 (± 17.2)	0 (± 0)		
Nausea and Vomiting: C34D1 (n=5, 0)	13.3 (± 18.3)	0 (± 0)		
Nausea and Vomiting: C35D1 (n=4, 0)	12.5 (± 16)	0 (± 0)		
Nausea and Vomiting: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Nausea and Vomiting: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Pain: Baseline (n=165, 163)	23.9 (± 24.7)	28 (± 27.3)		
Pain: C2D1 (n=155, 133)	13.9 (± 19.8)	25.7 (± 25.3)		
Pain: C3D1 (n=154, 106)	13.7 (± 20.4)	23.3 (± 26.6)		
Pain: C4D1 (n=135, 91)	13 (± 19.5)	19 (± 21.5)		
Pain: C5D1 (n=123, 74)	11.5 (± 16.7)	20.5 (± 23)		
Pain: C6D1 (n=120, 70)	10.6 (± 15)	19.5 (± 23)		
Pain: C7D1 (n=115, 52)	9.6 (± 14.3)	21.5 (± 24.3)		
Pain: C8D1 (n=111, 43)	11.3 (± 18)	17.4 (± 23.6)		
Pain: C9D1 (n=101, 37)	11.8 (± 18.8)	23 (± 27.6)		
Pain: C10D1 (n=94, 33)	8.7 (± 14)	24.2 (± 28.6)		
Pain: C11D1 (n=84, 25)	10.5 (± 16.3)	22 (± 27.9)		
Pain: C12D1 (n=76, 23)	8.6 (± 14.3)	25.4 (± 29.7)		
Pain: C13D1 (n=74, 21)	10.1 (± 15.3)	27.8 (± 30.4)		
Pain: C14D1 (n=66, 19)	8.1 (± 12.8)	23.7 (± 26.2)		

Pain: C15D1 (n=62, 16)	9.4 (± 15.6)	22.9 (± 25.7)		
Pain: C16D1 (n=53, 12)	9.4 (± 14.4)	31.9 (± 28.8)		
Pain: C17D1 (n=47, 11)	10.6 (± 16.1)	24.2 (± 27.2)		
Pain: C18D1 (n=45, 11)	11.1 (± 18.1)	24.2 (± 29.2)		
Pain: C19D1 (n=40, 9)	11.3 (± 17)	24.1 (± 20.6)		
Pain: C20D1 (n=35, 8)	11.9 (± 18.8)	22.9 (± 28.1)		
Pain: C21D1 (n=30, 8)	11.7 (± 15.3)	29.2 (± 30.5)		
Pain: C22D1 (n=24, 7)	6.9 (± 12.9)	33.3 (± 28.9)		
Pain: C23D1 (n=23, 4)	9.1 (± 16.1)	33.3 (± 36)		
Pain: C24D1 (n=20, 3)	4.2 (± 11.9)	27.8 (± 48.1)		
Pain: C25D1 (n=18, 3)	4.6 (± 7.7)	38.9 (± 41.9)		
Pain: C26D1 (n=14, 3)	17.9 (± 27.3)	38.9 (± 41.9)		
Pain: C27D1 (n=14, 2)	13.1 (± 25.5)	58.3 (± 35.4)		
Pain: C28D1 (n=11, 2)	4.5 (± 7.8)	50 (± 47.1)		
Pain: C29D1 (n=8, 2)	2.1 (± 5.9)	41.7 (± 35.4)		
Pain: C30D1 (n=8, 1)	4.2 (± 7.7)	83.3 (± 0)		
Pain: C31D1 (n=7, 0)	4.8 (± 8.1)	0 (± 0)		
Pain: C32D1 (n=6, 0)	5.6 (± 8.6)	0 (± 0)		
Pain: C33D1 (n=6, 0)	2.8 (± 6.8)	0 (± 0)		
Pain: C34D1 (n=5, 0)	3.3 (± 7.5)	0 (± 0)		
Pain: C35D1 (n=4, 0)	8.3 (± 16.7)	0 (± 0)		
Pain: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Pain: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Dyspnea: Baseline (n=165, 163)	31.1 (± 28.3)	32.5 (± 28.2)		
Dyspnea: C2D1 (n=155, 133)	21.5 (± 21.4)	33.6 (± 27.7)		
Dyspnea: C3D1 (n=154, 106)	21.6 (± 23)	33.3 (± 28.4)		
Dyspnea: C4D1 (n=135, 91)	17.3 (± 20.7)	29.3 (± 26.2)		
Dyspnea: C5D1 (n=123, 74)	16 (± 20.6)	29.3 (± 24)		
Dyspnea: C6D1 (n=120, 70)	15.8 (± 22)	26.2 (± 24.7)		
Dyspnea: C7D1 (n=115, 52)	17.4 (± 20.9)	28.2 (± 22.3)		
Dyspnea: C8D1 (n=111, 43)	15.8 (± 19.7)	22.5 (± 28.8)		
Dyspnea: C9D1 (n=101, 37)	13.9 (± 19)	23.4 (± 24.7)		
Dyspnea: C10D1 (n=94, 33)	17.7 (± 20.6)	24.2 (± 22.5)		
Dyspnea: C11D1 (n=84, 25)	17.5 (± 22.8)	25.3 (± 22.1)		
Dyspnea: C12D1 (n=76, 23)	14.5 (± 19.9)	30.4 (± 28.3)		
Dyspnea: C13D1 (n=74, 21)	14 (± 20.6)	23.8 (± 23.9)		
Dyspnea: C14D1 (n=66, 19)	15.2 (± 21.2)	29.8 (± 24.6)		
Dyspnea: C15D1 (n=62, 16)	15.6 (± 21.5)	20.8 (± 20.6)		
Dyspnea: C16D1 (n=53, 12)	13.8 (± 17.8)	19.4 (± 22.3)		
Dyspnea: C17D1 (n=46, 11)	14.5 (± 20.7)	24.2 (± 21.6)		
Dyspnea: C18D1 (n=45, 11)	14.1 (± 16.6)	24.2 (± 26.2)		
Dyspnea: C19D1 (n=40, 9)	14.2 (± 18.3)	25.9 (± 22.2)		
Dyspnea: C20D1 (n=35, 8)	10.5 (± 17.7)	33.3 (± 25.2)		
Dyspnea: C21D1 (n=30, 8)	13.3 (± 16.6)	33.3 (± 17.8)		
Dyspnea: C22D1 (n=24, 7)	13.9 (± 19.5)	28.6 (± 23)		
Dyspnea: C23D1 (n=23, 4)	9.4 (± 14.9)	41.7 (± 16.7)		
Dyspnea: C24D1 (n=20, 3)	18.3 (± 20.2)	44.4 (± 19.2)		
Dyspnea: C25D1 (n=18, 3)	11.1 (± 16.2)	33.3 (± 33.3)		
Dyspnea: C26D1 (n=14, 3)	14.3 (± 28.4)	33.3 (± 33.3)		
Dyspnea: C27D1 (n=14, 2)	11.9 (± 16.6)	50 (± 23.6)		
Dyspnea: C28D1 (n=11, 2)	12.1 (± 16.8)	50 (± 23.6)		
Dyspnea: C29D1 (n=8, 2)	4.2 (± 11.8)	50 (± 23.6)		

Dyspnea: C30D1 (n=8, 1)	8.3 (± 15.4)	66.7 (± 0)		
Dyspnea: C31D1 (n=7, 0)	9.5 (± 16.3)	0 (± 0)		
Dyspnea: C32D1 (n=6, 0)	16.7 (± 18.3)	0 (± 0)		
Dyspnea: C33D1 (n=6, 0)	11.1 (± 17.2)	0 (± 0)		
Dyspnea: C34D1 (n=5, 0)	13.3 (± 18.3)	0 (± 0)		
Dyspnea: C35D1 (n=4, 0)	16.7 (± 19.2)	0 (± 0)		
Dyspnea: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Dyspnea: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Insomnia : Baseline (n=164, 163)	22.6 (± 26.4)	27.8 (± 27.3)		
Insomnia : C2D1 (n=155, 133)	15.3 (± 23.5)	27.1 (± 25.3)		
Insomnia : C3D1 (n=154, 106)	16.2 (± 26.2)	23.6 (± 26)		
Insomnia : C4D1 (n=135, 91)	13.3 (± 21.2)	23.8 (± 26.9)		
Insomnia : C5D1 (n=123, 74)	13.6 (± 21.3)	25.7 (± 26.8)		
Insomnia : C6D1 (n=120, 70)	14.2 (± 21.9)	23.3 (± 25)		
Insomnia : C7D1 (n=114, 52)	9.4 (± 17.5)	21.8 (± 25.5)		
Insomnia : C8D1 (n=111, 43)	12.5 (± 21.5)	21.7 (± 22.9)		
Insomnia : C9D1 (n=100, 37)	12.3 (± 21.5)	22.5 (± 24.9)		
Insomnia : C10D1 (n=94, 33)	13.5 (± 23.6)	24.2 (± 25.4)		
Insomnia : C11D1 (n=84, 25)	13.9 (± 22.1)	22.7 (± 24.9)		
Insomnia : C12D1 (n=76, 23)	13.6 (± 21.9)	23.2 (± 25.5)		
Insomnia : C13D1 (n=74, 21)	10.8 (± 19.2)	25.4 (± 25.6)		
Insomnia : C14D1 (n=66, 19)	11.1 (± 18.8)	24.6 (± 29.1)		
Insomnia : C15D1 (n=62, 16)	11.3 (± 20)	29.2 (± 26.9)		
Insomnia : C16D1 (n=53, 11)	13.8 (± 20.1)	21.2 (± 22.5)		
Insomnia : C17D1 (n=47, 11)	13.5 (± 21.6)	15.2 (± 22.9)		
Insomnia : C18D1 (n=45, 11)	12.6 (± 17.8)	21.2 (± 27)		
Insomnia : C19D1 (n=40, 9)	13.3 (± 19.7)	22.2 (± 28.9)		
Insomnia : C20D1 (n=35, 8)	15.2 (± 20.4)	20.8 (± 24.8)		
Insomnia : C21D1 (n=30, 8)	12.2 (± 18.5)	29.2 (± 27.8)		
Insomnia : C22D1 (n=24, 7)	12.5 (± 19.2)	31 (± 24.4)		
Insomnia : C23D1 (n=23, 4)	17.4 (± 26.3)	50 (± 19.2)		
Insomnia : C24D1 (n=20, 3)	11.7 (± 22.4)	22.2 (± 38.5)		
Insomnia : C25D1 (n=18, 3)	20.4 (± 30.5)	44.4 (± 19.2)		
Insomnia : C26D1 (n=14, 3)	21.4 (± 33.6)	22.2 (± 38.5)		
Insomnia : C27D1 (n=14, 2)	16.7 (± 21.7)	50 (± 23.6)		
Insomnia : C28D1 (n=11, 2)	9.1 (± 15.6)	50 (± 23.6)		
Insomnia : C29D1 (n=8, 2)	8.3 (± 15.4)	33 (± 0)		
Insomnia : C30D1 (n=8, 1)	12.5 (± 24.8)	33.3 (± 0)		
Insomnia : C31D1 (n=7, 0)	0 (± 0)	0 (± 0)		
Insomnia : C32D1 (n=6, 0)	5.6 (± 13.6)	0 (± 0)		
Insomnia : C33D1 (n=6, 0)	5.6 (± 13.6)	0 (± 0)		
Insomnia : C34D1 (n=5, 0)	13.3 (± 18.3)	0 (± 0)		
Insomnia : C35D1 (n=4, 0)	16.7 (± 19.2)	0 (± 0)		
Insomnia : C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Insomnia : C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Appetite loss : Baseline(n=165, 163)	24.4 (± 28.8)	23.3 (± 28.2)		
Appetite loss : C2/D1(n=155, 133)	21.1 (± 30.2)	24.3 (± 28.5)		
Appetite loss : C3/D1(n=154, 106)	18.4 (± 29)	21.7 (± 27.2)		
Appetite loss : C4/D1(n=135, 91)	14.6 (± 24.3)	19.4 (± 23.3)		
Appetite loss : C5/D1(n=123, 74)	12.7 (± 22.4)	19.4 (± 28.1)		
Appetite loss : C6/D1(n=120, 70)	13.6 (± 21.8)	12.9 (± 23.6)		
Appetite loss : C7/D1(n=115, 52)	10.4 (± 19.4)	12.8 (± 22)		

Appetite loss : C8/D1(n=111, 43)	12.8 (± 20.8)	10.9 (± 22.7)		
Appetite loss : C9/D1(n=101, 37)	12.2 (± 239)	14.4 (± 27.8)		
Appetite loss : C10/D1(n=94, 33)	12.4 (± 22.9)	14.1 (± 25)		
Appetite loss : C11/D1(n=84, 25)	13.5 (± 19.4)	14.7 (± 25.6)		
Appetite loss : C12/D1(n=76, 23)	11 (± 21.4)	14.5 (± 24.3)		
Appetite loss : C13/D1(n=74, 21)	9.5 (± 20.3)	17.5 (± 27.1)		
Appetite loss : C15/D1(n=62, 16)	8.6 (± 20.9)	12.5 (± 26.9)		
Appetite loss : C16/D1(n=53, 12)	8.8 (± 18.7)	16.7 (± 30.2)		
Appetite loss : C17/D1(n=47, 11)	8.5 (± 16.3)	15.2 (± 31.1)		
Appetite loss : C18/D1(n=45, 11)	11.1 (± 17.4)	12.1 (± 22.5)		
Appetite loss : C19/D1(n=40, 9)	8.3 (± 16.5)	18.5 (± 33.8)		
Appetite loss : C20/D1(n=35, 8)	7.6 (± 16.3)	20.8 (± 35.4)		
Appetite loss : C21/D1(n=30, 8)	11.1 (± 16)	25 (± 34.5)		
Appetite loss : C22/D1(n=24, 7)	6.9 (± 13.8)	14.3 (± 37.8)		
Appetite loss : C23/D1(n=23, 4)	9.4 (± 14.9)	50 (± 43)		
Appetite loss : C24/D1(n=20, 3)	5 (± 12.2)	33.3 (± 33.3)		
Appetite loss : C25/D1(n=18, 3)	1.9 (± 7.9)	44.4 (± 50.9)		
Appetite loss : C26/D1(n=14, 3)	11.9 (± 21.1)	33.3 (± 33.3)		
Appetite loss : C27/D1(n=14, 2)	7.1 (± 19.3)	33.3 (± 47.1)		
Appetite loss : C28/D1(n=11, 2)	15.2 (± 17.4)	33.3 (± 47.1)		
Appetite loss : C29/D1(n=8, 2)	12.5 (± 17.3)	33.3 (± 47.1)		
Appetite loss : C30/D1(n=8, 1)	8.3 (± 15.4)	100 (± 0)		
Appetite loss : C31/D1(n=7, 0)	14.3 (± 17.8)	0 (± 0)		
Constipation: Baseline (n=164, 162)	14.8 (± 25.1)	16.9 (± 25)		
Constipation: C2D1 (n=155, 133)	28.6 (± 30.5)	14 (± 24.3)		
Constipation: C3D1 (n=154, 106)	27.1 (± 30)	16 (± 22.2)		
Constipation: C4D1 (n=134, 90)	22.9 (± 26.6)	14.8 (± 25.5)		
Constipation: C5D1 (n=123, 74)	21.4 (± 25.7)	20.3 (± 29.6)		
Constipation: C6D1 (n=120, 70)	21.7 (± 23.9)	15.7 (± 23.2)		
Constipation: C7D1 (n=115, 52)	21.7 (± 26.1)	19.9 (± 26.6)		
Constipation: C8D1 (n=111, 43)	18.6 (± 24.1)	16.3 (± 24.5)		
Constipation: C9D1 (n=101, 37)	18.8 (± 22.3)	16.2 (± 21.7)		
Constipation: C10D1 (n=94, 33)	16 (± 22.8)	19.2 (± 25)		
Constipation: C11D1 (n=84, 25)	21 (± 25.8)	21.3 (± 19)		
Constipation: C12D1 (n=76, 23)	19.7 (± 24.5)	21.7 (± 23.8)		
Constipation: C13D1 (n=74, 21)	21.2 (± 26.2)	22.2 (± 26.5)		
Constipation: C14D1 (n=66, 19)	21.7 (± 27.1)	24.6 (± 31.1)		
Constipation: C15D1 (n=62, 16)	22.6 (± 27.5)	18.7 (± 21)		
Constipation: C16D1 (n=53, 12)	19.5 (± 26.5)	22.2 (± 25.9)		
Constipation: C17D1 (n=47, 11)	22 (± 27.2)	24.2 (± 30.2)		
Constipation: C18D1 (n=44, 11)	22.7 (± 25.7)	15.2 (± 22.9)		
Constipation: C19D1 (n=40, 9)	25 (± 25.9)	22.2 (± 23.6)		
Constipation: C20D1 (n=35, 8)	22.9 (± 26.5)	20.8 (± 24.8)		
Constipation: C21D1 (n=30, 8)	24.4 (± 28.9)	16.7 (± 25.2)		
Constipation: C22D1 (n=24, 7)	18.1 (± 24)	19 (± 26.2)		
Constipation: C23D1 (n=23, 4)	11.6 (± 19.1)	25 (± 31.9)		
Constipation: C24D1 (n=20, 3)	21.7 (± 24.8)	22.2 (± 19.2)		
Constipation: C25D1 (n=18, 3)	22.2 (± 32.3)	33.3 (± 33.3)		
Constipation: C26D1 (n=14, 3)	26.2 (± 32.5)	44.4 (± 50.9)		
Constipation: C27D1 (n=14, 2)	35.7 (± 40.2)	50 (± 23.6)		
Constipation: C28D1 (n=11, 2)	21.2 (± 16.8)	50 (± 23.6)		
Constipation: C29D1 (n=8, 2)	29.2 (± 21.4)	50 (± 23.6)		

Constipation: C30D1 (n=8, 1)	29.2 (± 27.8)	33.3 (± 0)		
Constipation: C31D1 (n=7, 0)	33.3 (± 27.2)	0 (± 0)		
Constipation: C32D1 (n=6, 0)	33.3 (± 42.2)	0 (± 0)		
Constipation: C33D1 (n=6, 0)	38.9 (± 25.1)	0 (± 0)		
Constipation: C34D1 (n=5, 0)	40 (± 43.5)	0 (± 0)		
Constipation: C35D1 (n=4, 0)	33.3 (± 27.2)	0 (± 0)		
Constipation: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Constipation: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Constipation: EOT (n=49, 90)	28.6 (± 27.2)	18.1 (± 25.6)		
Diarrhea: Baseline (n=165, 162)	9.7 (± 19.1)	7.8 (± 16)		
Diarrhea: C2D1 (n=155, 132)	18.1 (± 26.7)	11.1 (± 20.5)		
Diarrhea: C3D1 (n=153, 106)	21.6 (± 28.7)	7.9 (± 18.1)		
Diarrhea: C4D1 (n=134, 90)	23.1 (± 26.9)	8.5 (± 18.4)		
Diarrhea: C5D1 (n=123, 74)	24.4 (± 25.6)	5.9 (± 15)		
Diarrhea: C6D1 (n=120, 70)	22.2 (± 26.4)	7.1 (± 16.9)		
Diarrhea: C7D1 (n=115, 52)	20.6 (± 24.8)	9.6 (± 16.6)		
Diarrhea: C8D1 (n=111, 43)	18.6 (± 24.1)	9.3 (± 19.7)		
Diarrhea: C9D1 (n=101, 37)	17.3 (± 22.8)	7.2 (± 16)		
Diarrhea: C10D1 (n=94, 33)	17.7 (± 22.3)	7.1 (± 16.2)		
Diarrhea: C11D1 (n=84, 25)	21 (± 22.4)	8 (± 17.4)		
Diarrhea: C12D1 (n=76, 23)	17.5 (± 25.2)	8.7 (± 15)		
Diarrhea: C13D1 (n=74, 21)	17.6 (± 23.6)	12.7 (± 19.7)		
Diarrhea: C14D1 (n=66, 19)	17.7 (± 22.8)	8.8 (± 18.7)		
Diarrhea: C15D1 (n=62, 16)	16.1 (± 21.5)	4.2 (± 11.4)		
Diarrhea: C16D1 (n=52, 12)	16 (± 20.3)	5.6 (± 13)		
Diarrhea: C17D1 (n=47, 11)	19.9 (± 22.7)	12.1 (± 22.5)		
Diarrhea: C18D1 (n=44, 11)	22.7 (± 25.7)	12.1 (± 22.5)		
Diarrhea: C19D1 (n=40, 9)	21.7 (± 25.7)	7.4 (± 14.7)		
Diarrhea: C20D1 (n=35, 8)	21 (± 24.4)	4.2 (± 11.8)		
Diarrhea: C21D1 (n=30, 8)	22.2 (± 22)	8.3 (± 15.4)		
Diarrhea: C22D1 (n=24, 7)	23.6 (± 25)	11.9 (± 15.9)		
Diarrhea: C23D1 (n=23, 4)	15.9 (± 19.8)	25 (± 16.7)		
Diarrhea: C24D1 (n=20, 3)	21.7 (± 22.4)	11.1 (± 19.2)		
Diarrhea: C25D1 (n=18, 3)	20.4 (± 25.9)	22.2 (± 19.2)		
Diarrhea: C26D1 (n=14, 3)	19 (± 25.2)	11.1 (± 19.2)		
Diarrhea: C27D1 (n=14, 2)	23.8 (± 30.5)	16.7 (± 23.6)		
Diarrhea: C28D1 (n=11, 2)	15.2 (± 17.4)	16.7 (± 23.6)		
Diarrhea: C29D1 (n=8, 2)	20.8 (± 24.8)	16.7 (± 23.6)		
Diarrhea: C30D1 (n=8, 1)	12.5 (± 17.3)	0 (± 0)		
Diarrhea: C31D1 (n=7, 0)	14.3 (± 17.8)	0 (± 0)		
Diarrhea: C32D1 (n=6, 0)	11.1 (± 17.2)	0 (± 0)		
Diarrhea: C33D1 (n=6, 0)	11.1 (± 17.2)	0 (± 0)		
Diarrhea: C34D1 (n=5, 0)	6.7 (± 14.9)	0 (± 0)		
Diarrhea: C35D1 (n=4, 0)	16.7 (± 19.2)	0 (± 0)		
Diarrhea: C36D1 (n=1, 0)	33.3 (± 0)	0 (± 0)		
Diarrhea: C37D1 (n=1, 0)	33.3 (± 0)	0 (± 0)		
Diarrhea: EOT (n=49, 90)	18.4 (± 23.6)	10 (± 21.5)		
Financial Difficulties: Baseline (n=165, 161)	28.5 (± 33)	27.3 (± 30.7)		
Financial Difficulties: C2D1 (n=155, 133)	21.9 (± 27.2)	22.3 (± 28.9)		
Financial Difficulties: C3D1 (n=154, 105)	19 (± 26.6)	20.3 (± 27.9)		

Financial Difficulties: C4D1 (n=135, 90)	17.5 (± 26)	21.9 (± 26)		
Financial Difficulties: C5D1 (n=123, 74)	16.8 (± 25)	19.4 (± 23.4)		
Financial Difficulties: C6D1 (n=120, 70)	15.6 (± 24)	18.6 (± 25.1)		
Financial Difficulties: C7D1 (n=115, 52)	14.8 (± 21.3)	18.6 (± 25.9)		
Financial Difficulties: C8D1 (n=111, 43)	16.8 (± 25)	15.5 (± 23.4)		
Financial Difficulties: C9D1 (n=101, 36)	17.8 (± 26.1)	16.7 (± 23.2)		
Financial Difficulties: C10D1 (n=94, 33)	16.3 (± 26.2)	15.2 (± 23.7)		
Financial Difficulties: C11D1 (n=84, 25)	17.5 (± 25.1)	17.3 (± 21.8)		
Financial Difficulties: C12D1 (n=76, 23)	17.1 (± 24.6)	18.8 (± 28.1)		
Financial Difficulties: C13D1 (n=74, 21)	16.2 (± 24.2)	17.5 (± 27.1)		
Financial Difficulties: C14D1 (n=66, 19)	14.1 (± 20.3)	17.5 (± 32.1)		
Financial Difficulties: C15D1 (n=62, 16)	14 (± 23)	16.7 (± 27.2)		
Financial Difficulties: C16D1 (n=53, 12)	15.7 (± 25)	30.6 (± 36.1)		
Financial Difficulties: C17D1 (n=47, 11)	17.7 (± 29.4)	33.3 (± 36.5)		
Financial Difficulties: C18D1 (n=44, 11)	18.9 (± 30)	15.2 (± 31.1)		
Financial Difficulties: C19D1 (n=40, 9)	17.5 (± 31.1)	25.9 (± 32.4)		
Financial Difficulties: C20D1 (n=35, 8)	16.2 (± 27.3)	25 (± 34.5)		
Financial Difficulties: C21D1 (n=30, 8)	13.3 (± 27.1)	29.2 (± 33)		
Financial Difficulties: C22D1 (n=24, 7)	18.1 (± 31.1)	28.6 (± 35.6)		
Financial Difficulties: C23D1 (n=23, 4)	17.4 (± 31.6)	33.3 (± 47.1)		
Financial Difficulties: C24D1 (n=20, 3)	20 (± 33.2)	33.3 (± 57.7)		
Financial Difficulties: C25D1 (n=18, 3)	11.1 (± 16.2)	44.4 (± 50.9)		
Financial Difficulties: C26D1 (n=14, 3)	14.3 (± 17.1)	44.4 (± 50.9)		
Financial Difficulties: C27D1 (n=14, 2)	14.3 (± 17.1)	66.7 (± 47.1)		
Financial Difficulties: C28D1 (n=11, 2)	15.2 (± 22.9)	66.7 (± 47.1)		
Financial Difficulties: C29D1 (n=8, 2)	8.3 (± 15.4)	66.7 (± 47.1)		
Financial Difficulties: C30D1 (n=8, 1)	4.2 (± 11.8)	100 (± 0)		
Financial Difficulties: C31D1 (n=7, 0)	9.5 (± 16.3)	0 (± 0)		
Financial Difficulties: C32D1 (n=6, 0)	22.2 (± 27.2)	0 (± 0)		
Financial Difficulties: C33D1 (n=6, 0)	16.7 (± 27.9)	0 (± 0)		
Financial Difficulties: C34D1 (n=5, 0)	13.3 (± 18.3)	0 (± 0)		
Financial Difficulties: C35D1 (n=4, 0)	8.3 (± 16.7)	0 (± 0)		
Financial Difficulties: C36D1 (n=1, 0)	33.3 (± 0)	0 (± 0)		
Financial Difficulties: C37D1 (n=1, 0)	66.7 (± 0)	0 (± 0)		
Financial Difficulties: EOT (n=49, 90)	17 (± 27.3)	24.1 (± 30)		
Appetite loss: C32D1 (n=6, 0)	11.1 (± 17.2)	0 (± 0)		
Appetite loss: C33D1 (n=6, 0)	11.1 (± 17.2)	0 (± 0)		
Appetite loss: C34D1 (n=5, 0)	13.3 (± 18.3)	0 (± 0)		
Appetite loss: C35D1 (n=4, 0)	16.7 (± 19.2)	0 (± 0)		
Appetite loss: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Appetite loss: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Appetite loss: EOT (n=49, 90)	21.8 (± 26)	28.1 (± 30.4)		
Global QoI: EOT (n=49, 90)	56.1 (± 24.5)	46.4 (± 25.4)		
Physical Functioning: EOT (n=49, 90)	80.7 (± 23)	66.2 (± 27.7)		
Role Functioning: EOT (n=49, 90)	71.8 (± 27.7)	54.1 (± 34.7)		
Emotional Functioning: EOT (n=49, 90)	75.2 (± 25.1)	74.5 (± 25.2)		
Cognitive Functioning: EOT (n=49, 90)	83.7 (± 20.3)	80 (± 24)		
Social Function: EOT (n=49, 90)	78.2 (± 27.9)	59.4 (± 33.5)		
Fatigue: EOT (n=49, 90)	32 (± 28.2)	46.9 (± 26.9)		
Nausea and Vomiting: EOT (n=49, 90)	16.3 (± 22.9)	15.7 (± 20.4)		
Pain: EOT (n=49, 90)	23.8 (± 30.4)	33.7 (± 31.3)		
Dyspnea: EOT (n=49, 90)	23.8 (± 28.1)	40 (± 30.1)		

Insomnia: EOT (n=49, 90)	18.4 (± 24.6)	30.4 (± 27.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Supplement Module for Lung Cancer (EORTC QLQ-LC13)

End point title	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Supplement Module for Lung Cancer (EORTC QLQ-LC13)

End point description:

QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy. The 13 questions comprised 1 multi-item scale for dyspnea and 10 single-item symptoms and side effects (coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, chest pain, arm pain, other pain, and medicine for pain). Recall period: past week; response range: 1 'Not at All' to 4 'Very Much'. Scores averaged, transformed to 0-100 scale; higher symptom score = greater degree of symptoms.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each cycle until disease progression, end of treatment (up to 112 weeks)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	162		
Units: units on a scale				
arithmetic mean (standard deviation)				
Dyspnea: Baseline (n=164, 162)	27.2 (± 21.7)	26.9 (± 23.4)		
Dyspnea: C2D1 (n=155, 132)	17.6 (± 18.1)	28.6 (± 22.3)		
Dyspnea: C3D1 (n=153, 106)	17.9 (± 17.8)	28 (± 25.4)		
Dyspnea: C4D1 (n=135, 91)	16.2 (± 17.5)	27.5 (± 22.8)		
Dyspnea: C5D1 (n=123, 74)	16.9 (± 16.7)	24.8 (± 22.9)		
Dyspnea: C6D1 (n=119, 70)	15.2 (± 15.8)	25.2 (± 23)		
Dyspnea: C7D1 (n=115, 52)	15.6 (± 16.5)	24.4 (± 20.3)		
Dyspnea: C8D1 (n=111, 43)	14.7 (± 16)	22 (± 22.8)		
Dyspnea: C9D1 (n=101, 37)	13.9 (± 15.8)	19.5 (± 19)		
Dyspnea: C10D1 (n=94, 33)	15.4 (± 17)	21.5 (± 21)		
Dyspnea: C11D1 (n=84, 25)	15.1 (± 17.5)	20.4 (± 24.1)		
Dyspnea: C12D1 (n=76, 23)	13.7 (± 15.5)	22.7 (± 22.1)		
Dyspnea: C13D1 (n=74, 21)	12.8 (± 14)	26.5 (± 25.9)		
Dyspnea: C14D1 (n=66, 19)	14.8 (± 16.9)	26.3 (± 26.8)		
Dyspnea: C15D1 (n=62, 16)	13.2 (± 15.4)	22.9 (± 18.4)		
Dyspnea: C16D1 (n=53, 12)	12.6 (± 11.7)	22.2 (± 18.3)		
Dyspnea: C17D1 (n=46, 11)	12.3 (± 11.5)	30.3 (± 23.9)		
Dyspnea: C18D1 (n=45, 11)	14.1 (± 13.5)	26.3 (± 20.7)		

Dyspnea: C19D1 (n=40, 9)	14.4 (± 13.8)	23.5 (± 15.2)		
Dyspnea: C20D1 (n=35, 8)	13.7 (± 12.9)	34.7 (± 24.1)		
Dyspnea: C21D1 (n=30, 8)	12.6 (± 13)	25 (± 14.2)		
Dyspnea: C22D1 (n=24, 7)	10.6 (± 11.1)	27 (± 21.1)		
Dyspnea: C23D1 (n=23, 4)	13.8 (± 14.2)	52.8 (± 19)		
Dyspnea: C24D1 (n=20, 3)	14.4 (± 14.9)	48.1 (± 23.1)		
Dyspnea: C25D1 (n=18, 3)	15.4 (± 12.1)	40.7 (± 23.1)		
Dyspnea: C26D1 (n=14, 3)	14.3 (± 10.2)	44.4 (± 22.2)		
Dyspnea: C27D1 (n=14, 2)	15.1 (± 11.2)	55.6 (± 0)		
Dyspnea: C28D1 (n=11, 2)	11.1 (± 8.6)	61.1 (± 7.9)		
Dyspnea: C29D1 (n=8, 2)	12.5 (± 11)	50 (± 7.9)		
Dyspnea: C30D1 (n=8, 1)	9.7 (± 7.1)	77.8 (± 0)		
Dyspnea: C31D1 (n=7, 0)	15.9 (± 8.7)	0 (± 0)		
Dyspnea: C32D1 (n=6, 0)	18.5 (± 9.1)	0 (± 0)		
Dyspnea: C33D1 (n=6, 0)	18.5 (± 9.1)	0 (± 0)		
Dyspnea: C34D1 (n=5, 0)	20 (± 5)	0 (± 0)		
Dyspnea: C35D1 (n=4, 0)	16.7 (± 6.4)	0 (± 0)		
Dyspnea: C36D1 (n=1, 0)	22.2 (± 0)	0 (± 0)		
Dyspnea: C37D1 (n=1, 0)	11.1 (± 0)	0 (± 0)		
Dyspnea: EOT (n=49, 90)	21.8 (± 19)	35.6 (± 26.7)		
Coughing: Baseline (n=164, 162)	38.2 (± 27.4)	42.2 (± 31.3)		
Coughing: C2D1 (n=155, 132)	23 (± 19.6)	34.8 (± 26.3)		
Coughing: C3D1 (n=153, 106)	23.5 (± 21.6)	32.4 (± 27.4)		
Coughing: C4D1 (n=135, 91)	19.8 (± 22.4)	27.1 (± 24.8)		
Coughing: C5D1 (n=123, 74)	18.4 (± 21)	25.7 (± 25)		
Coughing: C6D1 (n=119, 70)	14.6 (± 18.2)	30 (± 25.5)		
Coughing: C7D1 (n=115, 52)	15.9 (± 18.4)	26.3 (± 23.2)		
Coughing: C8D1 (n=111, 43)	13.2 (± 18.7)	22.5 (± 23.8)		
Coughing: C9D1 (n=101, 37)	13.5 (± 18.4)	25.2 (± 28.8)		
Coughing: C10D1 (n=94, 33)	14.2 (± 19.2)	20.2 (± 26.3)		
Coughing: C11D1 (n=83, 25)	12.9 (± 20.7)	18.7 (± 25.6)		
Coughing: C12D1 (n=76, 23)	14.5 (± 20.6)	23.2 (± 25.5)		
Coughing: C13D1 (n=74, 21)	14 (± 21.4)	27 (± 27.1)		
Coughing: C14D1 (n=66, 19)	13.1 (± 19.3)	24.6 (± 31.1)		
Coughing: C15D1 (n=62, 16)	11.8 (± 21)	20.8 (± 20.6)		
Coughing: C16D1 (n=53, 12)	13.8 (± 19)	22.2 (± 21.7)		
Coughing: C17D1 (n=47, 11)	6.4 (± 15)	27.3 (± 25)		
Coughing: C18D1 (n=45, 11)	13.3 (± 18)	18.2 (± 17.4)		
Coughing: C19D1 (n=40, 9)	12.5 (± 18)	14.8 (± 17.6)		
Coughing: C20D1 (n=35, 8)	10.5 (± 15.7)	29.2 (± 21.4)		
Coughing: C21D1 (n=30, 8)	13.3 (± 24.1)	33.3 (± 25.2)		
Coughing: C22D1 (n=24, 7)	8.3 (± 14.7)	28.6 (± 23)		
Coughing: C23D1 (n=23, 4)	11.6 (± 19.1)	33.3 (± 0)		
Coughing: C24D1 (n=20, 3)	8.3 (± 14.8)	44.4 (± 19.2)		
Coughing: C25D1 (n=18, 3)	5.6 (± 12.8)	44.4 (± 19.2)		
Coughing: C26D1 (n=14, 3)	2.4 (± 8.9)	33.3 (± 0)		
Coughing: C27D1 (n=14, 2)	7.1 (± 14.2)	50 (± 23.6)		
Coughing: C28D1 (n=11, 2)	18.2 (± 31.1)	50 (± 23.6)		
Coughing: C29D1 (n=8, 2)	8.3 (± 15.4)	33.3 (± 0)		
Coughing: C30D1 (n=8, 1)	20.8 (± 24.8)	33.3 (± 0)		
Coughing: C31D1 (n=7, 0)	19 (± 17.8)	0 (± 0)		
Coughing: C32D1 (n=6, 0)	16.7 (± 27.9)	0 (± 0)		

Coughing: C33D1 (n=6, 0)	11.1 (± 17.2)	0 (± 0)		
Coughing: C34D1 (n=5, 0)	20 (± 29.8)	0 (± 0)		
Coughing: C35D1 (n=4, 0)	33.3 (± 47.1)	0 (± 0)		
Coughing: C36D1 (n=1, 0)	33.3 (± 0)	0 (± 0)		
Coughing: C37D1 (n=1, 0)	33.3 (± 0)	0 (± 0)		
Coughing: EOT (n=49, 90)	25.9 (± 23.8)	37.4 (± 29.1)		
Hemoptysis: Baseline (n=164, 162)	2.4 (± 9.5)	3.7 (± 12.3)		
Hemoptysis: C2D1 (n=155, 132)	1.7 (± 7.4)	3.5 (± 12.5)		
Hemoptysis: C3D1 (n=153, 106)	0.9 (± 5.3)	2.2 (± 8.3)		
Hemoptysis: C4D1 (n=135, 91)	1 (± 5.7)	1.5 (± 6.9)		
Hemoptysis: C5D1 (n=123, 74)	0.3 (± 3)	0.9 (± 5.4)		
Hemoptysis: C6D1 (n=119, 70)	0.6 (± 4.3)	3.8 (± 14.5)		
Hemoptysis: C7D1 (n=115, 52)	0 (± 0)	1.3 (± 9.2)		
Hemoptysis: C8D1 (n=111, 43)	0.9 (± 7)	2.3 (± 11.3)		
Hemoptysis: C9D1 (n=101, 37)	0.3 (± 3.3)	2.7 (± 12.1)		
Hemoptysis: C10D1 (n=94, 33)	0.4 (± 3.4)	3 (± 17.4)		
Hemoptysis: C11D1 (n=83, 25)	2.4 (± 11.4)	4 (± 14.7)		
Hemoptysis: C12D1 (n=76, 23)	0.9 (± 5.4)	5.8 (± 21.7)		
Hemoptysis: C13D1 (n=74, 21)	2.3 (± 10.1)	4.8 (± 15.9)		
Hemoptysis: C14D1 (n=66, 19)	0.5 (± 4.1)	0 (± 0)		
Hemoptysis: C15D1 (n=62, 16)	1.1 (± 5.9)	0 (± 0)		
Hemoptysis: C16D1 (n=53, 12)	0.6 (± 4.6)	5.6 (± 13)		
Hemoptysis: C17D1 (n=47, 11)	0 (± 0)	9.1 (± 21.6)		
Hemoptysis: C18D1 (n=45, 11)	1.5 (± 6.9)	3 (± 10.1)		
Hemoptysis: C19D1 (n=40, 9)	0 (± 0)	3.7 (± 11.1)		
Hemoptysis: C20D1 (n=35, 8)	1 (± 5.6)	8.3 (± 15.4)		
Hemoptysis: C21D1 (n=30, 8)	0 (± 0)	4.2 (± 11.8)		
Hemoptysis: C22D1 (n=24, 7)	0 (± 0)	9.5 (± 16.3)		
Hemoptysis: C23D1 (n=23, 4)	1.4 (± 7)	0 (± 0)		
Hemoptysis: C24D1 (n=20, 3)	0 (± 0)	0 (± 0)		
Hemoptysis: C25D1 (n=18, 3)	0 (± 0)	0 (± 0)		
Hemoptysis: C26D1 (n=14, 3)	0 (± 0)	0 (± 0)		
Hemoptysis: C27D1 (n=14, 2)	0 (± 0)	0 (± 0)		
Hemoptysis: C28D1 (n=11, 2)	0 (± 0)	0 (± 0)		
Hemoptysis: C29D1 (n=8, 2)	0 (± 0)	0 (± 0)		
Hemoptysis: C30D1 (n=8, 1)	0 (± 0)	0 (± 0)		
Hemoptysis: C31D1 (n=7, 0)	0 (± 0)	0 (± 0)		
Hemoptysis: C32D1 (n=6, 0)	0 (± 0)	0 (± 0)		
Hemoptysis: C33D1 (n=6, 0)	0 (± 0)	0 (± 0)		
Hemoptysis: C34D1 (n=5, 0)	0 (± 0)	0 (± 0)		
Hemoptysis: C35D1 (n=4, 0)	0 (± 0)	0 (± 0)		
Hemoptysis: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Hemoptysis: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Hemoptysis: EOT (n=49, 90)	0.7 (± 4.8)	4.8 (± 13.7)		
Sore Mouth: Baseline (n=164, 162)	5.5 (± 15.3)	6.4 (± 18.4)		
Sore Mouth: C2D1 (n=155, 132)	8 (± 17.9)	9.1 (± 18.5)		
Sore Mouth: C3D1 (n=153, 106)	7 (± 14.6)	9.4 (± 21)		
Sore Mouth: C4D1 (n=135, 91)	8.1 (± 16.5)	10.3 (± 21.5)		
Sore Mouth: C5D1 (n=123, 73)	5.1 (± 12.1)	9.6 (± 20.4)		
Sore Mouth: C6D1 (n=119, 70)	4.8 (± 13.9)	10.5 (± 19.3)		
Sore Mouth: C7D1 (n=115, 52)	5.2 (± 15)	7.7 (± 15.6)		
Sore Mouth: C8D1 (n=111, 43)	3 (± 9.6)	10.9 (± 18.9)		

Sore Mouth: C9D1 (n=101, 37)	4.8 (± 12.5)	10.8 (± 22.3)		
Sore Mouth: C10D1 (n=94, 33)	6.4 (± 14.9)	12.1 (± 23.3)		
Sore Mouth: C11D1 (n=84, 25)	4.8 (± 14.8)	9.3 (± 18.1)		
Sore Mouth: C12D1 (n=76, 23)	3.9 (± 12.1)	8.7 (± 18)		
Sore Mouth: C13D1 (n=74, 21)	4.5 (± 12.7)	9.5 (± 15.4)		
Sore Mouth: C14D1 (n=66, 19)	4.5 (± 12.9)	7 (± 14)		
Sore Mouth: C15D1 (n=62, 16)	5.4 (± 12.4)	14.6 (± 29.7)		
Sore Mouth: C16D1 (n=53, 12)	6.3 (± 14.7)	8.3 (± 15.1)		
Sore Mouth: C17D1 (n=47, 11)	3.5 (± 10.4)	6.1 (± 13.5)		
Sore Mouth: C18D1 (n=45, 11)	5.2 (± 12.2)	12.1 (± 16.8)		
Sore Mouth: C19D1 (n=40, 9)	4.2 (± 11.2)	7.4 (± 14.7)		
Sore Mouth: C20D1 (n=35, 8)	7.6 (± 16.3)	12.5 (± 24.8)		
Sore Mouth: C21D1 (n=30, 8)	4.4 (± 11.5)	4.2 (± 11.8)		
Sore Mouth: C22D1 (n=24, 7)	5.6 (± 12.7)	7.1 (± 13.1)		
Sore Mouth: C23D1 (n=23, 4)	5.1 (± 11.7)	16.7 (± 19.2)		
Sore Mouth: C24D1 (n=20, 3)	6.7 (± 17.4)	0 (± 0)		
Sore Mouth: C25D1 (n=18, 3)	0 (± 0)	0 (± 0)		
Sore Mouth: C26D1 (n=14, 3)	4.8 (± 17.8)	11.1 (± 19.2)		
Sore Mouth: C27D1 (n=14, 2)	7.1 (± 19.3)	16.7 (± 23.6)		
Sore Mouth: C28D1 (n=11, 2)	6.1 (± 20.1)	0 (± 0)		
Sore Mouth: C29D1 (n=8, 2)	8.3 (± 15.4)	16.7 (± 23.6)		
Sore Mouth: C30D1 (n=8, 1)	8.3 (± 23.6)	0 (± 0)		
Sore Mouth: C31D1 (n=7, 0)	9.5 (± 25.2)	0 (± 0)		
Sore Mouth: C32D1 (n=6, 0)	0 (± 0)	0 (± 0)		
Sore Mouth: C33D1 (n=6, 0)	0 (± 0)	0 (± 0)		
Sore Mouth: C34D1 (n=5, 0)	0 (± 0)	0 (± 0)		
Sore Mouth: C35D1 (n=4, 0)	0 (± 0)	0 (± 0)		
Sore Mouth: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Sore Mouth: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Sore Mouth: EOT (n=49, 90)	3.4 (± 10.2)	8.1 (± 18.2)		
Dysphagia: Baseline (n=164, 162)	7.1 (± 16.4)	8.6 (± 20.9)		
Dysphagia: C2D1 (n=155, 132)	8.2 (± 15.4)	9.8 (± 19.2)		
Dysphagia: C3D1 (n=153, 106)	7.6 (± 16.4)	9.7 (± 20.6)		
Dysphagia: C4D1 (n=135, 91)	6.2 (± 15.3)	8.1 (± 19.5)		
Dysphagia: C5D1 (n=123, 74)	6 (± 14.8)	7.7 (± 17)		
Dysphagia: C6D1 (n=119, 70)	7 (± 15)	10 (± 16.4)		
Dysphagia: C7D1 (n=115, 52)	4.1 (± 11.8)	5.1 (± 13.8)		
Dysphagia: C8D1 (n=111, 43)	3.2 (± 11.1)	6.2 (± 15)		
Dysphagia: C9D1 (n=101, 37)	5 (± 11.9)	7.2 (± 16)		
Dysphagia: C10D1 (n=94, 33)	4.3 (± 12.2)	6.1 (± 13.1)		
Dysphagia: C11D1 (n=84, 25)	3.2 (± 9.8)	4 (± 11.1)		
Dysphagia: C12D1 (n=76, 23)	3.5 (± 10.3)	7.2 (± 17.3)		
Dysphagia: C13D1 (n=74, 21)	4.1 (± 11)	6.3 (± 13.4)		
Dysphagia: C14D1 (n=66, 19)	3 (± 11.3)	7 (± 14)		
Dysphagia: C15D1 (n=62, 16)	3.8 (± 13.6)	4.2 (± 16.7)		
Dysphagia: C16D1 (n=53, 12)	4.4 (± 11.4)	2.8 (± 9.6)		
Dysphagia: C17D1 (n=47, 11)	2.8 (± 9.4)	6.1 (± 13.5)		
Dysphagia: C18D1 (n=45, 11)	3.7 (± 10.6)	3 (± 10.1)		
Dysphagia: C19D1 (n=40, 9)	4.2 (± 11.2)	0 (± 0)		
Dysphagia: C20D1 (n=35, 8)	4.8 (± 14.3)	8.3 (± 15.4)		
Dysphagia: C21D1 (n=30, 8)	3.3 (± 10.2)	8.3 (± 15.4)		
Dysphagia: C22D1 (n=24, 7)	2.8 (± 9.4)	0 (± 0)		

Dysphagia: C23D1 (n=23, 4)	2.9 (± 9.6)	8.3 (± 16.7)		
Dysphagia: C24D1 (n=20, 3)	5 (± 22.4)	0 (± 0)		
Dysphagia: C25D1 (n=18, 3)	0 (± 0)	11.1 (± 19.2)		
Dysphagia: C26D1 (n=14, 3)	9.5 (± 27.5)	11.1 (± 19.2)		
Dysphagia: C27D1 (n=14, 2)	2.4 (± 8.9)	16.7 (± 23.6)		
Dysphagia: C28D1 (n=11, 2)	6.1 (± 13.5)	16.7 (± 23.6)		
Dysphagia: C29D1 (n=8, 2)	8.3 (± 15.4)	16.7 (± 23.6)		
Dysphagia: C30D1 (n=8, 1)	0 (± 0)	33.3 (± 0)		
Dysphagia: C31D1 (n=7, 0)	4.8 (± 12.6)	0 (± 0)		
Dysphagia: C32D1 (n=6, 0)	5.6 (± 13.6)	0 (± 0)		
Dysphagia: C33D1 (n=6, 0)	0 (± 0)	0 (± 0)		
Dysphagia: C34D1 (n=5, 0)	6.7 (± 14.9)	0 (± 0)		
Dysphagia: C35D1 (n=4, 0)	8.3 (± 16.7)	0 (± 0)		
Dysphagia: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Dysphagia: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Dysphagia: EOT (n=49, 90)	4.8 (± 13.6)	8.5 (± 19.7)		
Peripheral Neuropathy: Baseline (n=164, 162)	14 (± 22.1)	17.7 (± 27.3)		
Peripheral Neuropathy: C2D1 (n=155, 132)	18.1 (± 24.1)	21.5 (± 29.2)		
Peripheral Neuropathy: C3D1 (n=153, 106)	17.6 (± 26.2)	18.2 (± 29.1)		
Peripheral Neuropathy: C4D1 (n=134, 91)	15.9 (± 23)	21.6 (± 27.8)		
Peripheral Neuropathy: C5D1 (n=123, 74)	15.2 (± 21)	21.2 (± 28.4)		
Peripheral Neuropathy: C6D1 (n=119, 70)	13.7 (± 21.9)	18.1 (± 27)		
Peripheral Neuropathy: C7D1 (n=115, 52)	13 (± 21)	21.8 (± 28.7)		
Peripheral Neuropathy: C8D1 (n=111, 43)	10.8 (± 20.2)	24 (± 32.8)		
Peripheral Neuropathy: C9D1 (n=101, 37)	11.2 (± 19.6)	29.7 (± 34.1)		
Peripheral Neuropathy: C10D1 (n=94, 33)	11.3 (± 21.1)	27.3 (± 29.4)		
Peripheral Neuropathy: C11D1 (n=84, 25)	11.1 (± 21.5)	24 (± 31.2)		
Peripheral Neuropathy: C12D1 (n=76, 23)	11.4 (± 22.1)	33.3 (± 36.2)		
Peripheral Neuropathy: C13D1 (n=74, 21)	10.4 (± 19.1)	33.3 (± 35)		
Peripheral Neuropathy: C14D1 (n=66, 19)	10.6 (± 21.2)	29.8 (± 35)		
Peripheral Neuropathy: C15D1 (n=62, 16)	8.6 (± 18)	25 (± 31)		
Peripheral Neuropathy: C16D1 (n=52, 12)	10.3 (± 19.3)	25 (± 20.7)		
Peripheral Neuropathy: C17D1 (n=47, 11)	12.1 (± 23.5)	27.3 (± 29.1)		
Peripheral Neuropathy: C18D1 (n=45, 11)	11.9 (± 22.6)	30.3 (± 31.5)		
Peripheral Neuropathy: C19D1 (n=40, 9)	9.2 (± 20)	22.2 (± 16.7)		
Peripheral Neuropathy: C20D1 (n=35, 8)	12.4 (± 25.7)	33.3 (± 30.9)		
Peripheral Neuropathy: C21D1 (n=30, 8)	11.1 (± 18.2)	29.2 (± 21.4)		

Peripheral Neuropathy: C22D1 (n=24, 7)	8.3 (± 20.3)	28.6 (± 23)		
Peripheral Neuropathy: C23D1 (n=23, 4)	8.7 (± 20.6)	41.7 (± 31.9)		
Peripheral Neuropathy: C24D1 (n=20, 3)	3.3 (± 14.9)	44.4 (± 38.5)		
Peripheral Neuropathy: C25D1 (n=18, 3)	9.3 (± 19.2)	44.4 (± 38.5)		
Peripheral Neuropathy: C26D1 (n=14, 3)	16.7 (± 36.4)	22.2 (± 19.2)		
Peripheral Neuropathy: C27D1 (n=14, 2)	9.5 (± 20.4)	66.7 (± 0)		
Peripheral Neuropathy: C28D1 (n=11, 2)	15.2 (± 22.9)	33.3 (± 0)		
Peripheral Neuropathy: C29D1 (n=8, 2)	12.5 (± 24.8)	50 (± 23.6)		
Peripheral Neuropathy: C30D1 (n=8, 1)	16.7 (± 30.9)	33.3 (± 0)		
Peripheral Neuropathy: C31D1 (n=7, 0)	19 (± 32.5)	0 (± 0)		
Peripheral Neuropathy: C32D1 (n=6, 0)	11.1 (± 27.2)	0 (± 0)		
Peripheral Neuropathy: C33D1 (n=6, 0)	11.1 (± 27.2)	0 (± 0)		
Peripheral Neuropathy: C34D1 (n=5, 0)	20 (± 44.7)	0 (± 0)		
Peripheral Neuropathy: C35D1 (n=4, 0)	25 (± 50)	0 (± 0)		
Peripheral Neuropathy: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Peripheral Neuropathy: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Peripheral Neuropathy: EOT (n=49, 90)	10.2 (± 16.9)	21.9 (± 29.6)		
Alopecia: Baseline (n=163, 162)	17.4 (± 30.6)	16.9 (± 29.8)		
Alopecia: C2D1 (n=155, 132)	9.5 (± 21.4)	36.6 (± 39.7)		
Alopecia: C3D1 (n=153, 106)	7.6 (± 18.1)	30.5 (± 36.5)		
Alopecia: C4D1 (n=135, 91)	8.9 (± 22)	24.9 (± 32)		
Alopecia: C5D1 (n=123, 74)	6 (± 17.1)	23.9 (± 31)		
Alopecia: C6D1 (n=118, 70)	4.2 (± 14.8)	23.3 (± 32.8)		
Alopecia: C7D1 (n=115, 52)	4.9 (± 14.1)	19.9 (± 30.4)		
Alopecia: C8D1 (n=111, 43)	3.9 (± 11.7)	18.6 (± 28.5)		
Alopecia: C9D1 (n=101, 37)	4 (± 11.8)	16.2 (± 23.1)		
Alopecia: C10D1 (n=94, 33)	4.6 (± 14.3)	14.1 (± 22.1)		
Alopecia: C11D1 (n=84, 25)	4 (± 15)	16 (± 21.8)		
Alopecia: C12D1 (n=76, 23)	4.4 (± 14.7)	20.3 (± 26.1)		
Alopecia: C13D1 (n=74, 21)	6.3 (± 18)	12.7 (± 19.7)		
Alopecia: C14D1 (n=65, 19)	3.6 (± 14.6)	15.8 (± 23.2)		
Alopecia: C15D1 (n=62, 16)	4.8 (± 16.9)	8.3 (± 19.2)		
Alopecia: C16D1 (n=53, 12)	6.3 (± 18.6)	13.9 (± 22.3)		
Alopecia: C17D1 (n=46, 11)	5.1 (± 17.2)	18.2 (± 22.9)		
Alopecia: C18D1 (n=45, 11)	3.7 (± 12.8)	18.2 (± 22.9)		
Alopecia: C19D1 (n=40, 9)	5.8 (± 19.8)	18.5 (± 24.2)		
Alopecia: C20D1 (n=35, 8)	3.8 (± 13.5)	25 (± 23.6)		
Alopecia: C21D1 (n=30, 8)	7.8 (± 22.6)	16.7 (± 25.2)		
Alopecia: C22D1 (n=24, 7)	2.8 (± 9.4)	14.3 (± 17.8)		
Alopecia: C23D1 (n=23, 3)	1.4 (± 7)	22.2 (± 19.2)		
Alopecia: C24D1 (n=20, 3)	6.7 (± 23.2)	33.3 (± 33.3)		
Alopecia: C25D1 (n=18, 3)	9.3 (± 27.5)	33.3 (± 33.3)		
Alopecia: C26D1 (n=14, 3)	7.1 (± 26.7)	44.4 (± 38.5)		
Alopecia: C27D1 (n=14, 2)	16.7 (± 36.4)	33.3 (± 0)		
Alopecia: C28D1 (n=11, 2)	6.1 (± 20.1)	50 (± 23.6)		
Alopecia: C29D1 (n=8, 2)	16.7 (± 35.6)	33.3 (± 0)		
Alopecia: C30D1 (n=8, 1)	12.5 (± 35.4)	33.3 (± 0)		

Alopecia: C31D1 (n=7, 0)	9.5 (± 25.2)	0 (± 0)		
Alopecia: C32D1 (n=6, 0)	0 (± 0)	0 (± 0)		
Alopecia: C33D1 (n=6, 0)	0 (± 0)	0 (± 0)		
Alopecia: C34D1 (n=5, 0)	0 (± 0)	0 (± 0)		
Alopecia: C35D1 (n=4, 0)	0 (± 0)	0 (± 0)		
Alopecia: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Alopecia: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Alopecia: EOT (n=49, 90)	6.8 (± 18)	33.3 (± 37.7)		
Pain in Chest: Baseline (n=163, 160)	18.8 (± 22.8)	24 (± 27.5)		
Pain in Chest: C2D1 (n=155, 132)	9.5 (± 17.7)	23.7 (± 25.9)		
Pain in Chest: C3D1 (n=153, 106)	7 (± 13.6)	23.3 (± 26.5)		
Pain in Chest: C4D1 (n=135, 91)	7.4 (± 13.9)	19.8 (± 22.8)		
Pain in Chest: C5D1 (n=123, 74)	6.8 (± 14.1)	17.1 (± 21.5)		
Pain in Chest: C6D1 (n=119, 70)	6.2 (± 13)	16.2 (± 22.5)		
Pain in Chest: C7D1 (n=115, 52)	7.5 (± 14.7)	16.7 (± 22.4)		
Pain in Chest: C8D1 (n=111, 43)	5.1 (± 14.4)	14 (± 20.9)		
Pain in Chest: C9D1 (n=101, 37)	5.9 (± 12.8)	17.1 (± 23.1)		
Pain in Chest: C10D1 (n=94, 33)	6.7 (± 14.3)	18.2 (± 31.3)		
Pain in Chest: C11D1 (n=84, 25)	6.3 (± 13.2)	20 (± 25.5)		
Pain in Chest: C12D1 (n=76, 23)	5.3 (± 12.2)	23.2 (± 30.9)		
Pain in Chest: C13D1 (n=74, 21)	6.3 (± 13.1)	23.8 (± 30.1)		
Pain in Chest: C14D1 (n=66, 19)	7.6 (± 16.3)	22.8 (± 22.4)		
Pain in Chest: C15D1 (n=62, 16)	5.9 (± 14.2)	18.7 (± 24.2)		
Pain in Chest: C16D1 (n=53, 12)	3.8 (± 10.7)	16.7 (± 17.4)		
Pain in Chest: C17D1 (n=46, 11)	7.2 (± 15.6)	21.2 (± 22.5)		
Pain in Chest: C18D1 (n=45, 11)	5.9 (± 16.3)	24.2 (± 33.6)		
Pain in Chest: C19D1 (n=40, 9)	5 (± 14.2)	18.5 (± 24.2)		
Pain in Chest: C20D1 (n=35, 8)	5.7 (± 15.1)	29.2 (± 21.4)		
Pain in Chest: C21D1 (n=30, 8)	5.6 (± 15.4)	25 (± 23.6)		
Pain in Chest: C22D1 (n=24, 7)	4.2 (± 11.3)	26.2 (± 30.2)		
Pain in Chest: C23D1 (n=23, 4)	3.6 (± 10)	41.7 (± 31.9)		
Pain in Chest: C24D1 (n=20, 3)	1.7 (± 7.5)	33.3 (± 33.3)		
Pain in Chest: C25D1 (n=18, 3)	5.6 (± 12.8)	33.3 (± 33.3)		
Pain in Chest: C26D1 (n=14, 3)	7.1 (± 19.3)	33.3 (± 33.3)		
Pain in Chest: C27D1 (n=14, 2)	4.8 (± 12.1)	50 (± 23.6)		
Pain in Chest: C28D1 (n=11, 2)	9.1 (± 15.6)	50 (± 23.6)		
Pain in Chest: C29D1 (n=8, 2)	0 (± 0)	50 (± 23.6)		
Pain in Chest: C30D1 (n=8, 1)	4.2 (± 11.8)	66.7 (± 0)		
Pain in Chest: C31D1 (n=7, 0)	9.5 (± 16.3)	0 (± 0)		
Pain in Chest: C32D1 (n=6, 0)	0 (± 0)	0 (± 0)		
Pain in Chest: C33D1 (n=6, 0)	0 (± 0)	0 (± 0)		
Pain in Chest: C34D1 (n=5, 0)	6.7 (± 14.9)	0 (± 0)		
Pain in Chest: C35D1 (n=4, 0)	8.3 (± 16.7)	0 (± 0)		
Pain in Chest: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Pain in Chest: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Pain in Chest: EOT (n=49, 90)	17 (± 24.6)	28.5 (± 29.4)		
Pain in Arm or Shoulder: Baseline (n=164, 161)	16.3 (± 24.1)	19.5 (± 28)		
Pain in Arm or Shoulder: C2D1 (n=155, 132)	9 (± 18.3)	19.9 (± 27)		
Pain in Arm or Shoulder: C3D1 (n=153, 105)	8.1 (± 14.8)	17.5 (± 24.5)		

Pain in Arm or Shoulder: C4D1 (n=135, 91)	6.9 (± 15.3)	14.3 (± 22.3)		
Pain in Arm or Shoulder: C5D1 (n=123, 74)	6.2 (± 15)	13.1 (± 21.9)		
Pain in Arm or Shoulder: C6D1 (n=119, 70)	6.7 (± 14.1)	17.1 (± 25.8)		
Pain in Arm or Shoulder: C7D1 (n=115, 52)	6.4 (± 13.2)	17.3 (± 23.3)		
Pain in Arm or Shoulder: C8D1 (n=111, 43)	6.9 (± 14.3)	20.2 (± 28.3)		
Pain in Arm or Shoulder: C9D1 (n=101, 37)	5.6 (± 12.5)	23.4 (± 28.2)		
Pain in Arm or Shoulder: C10D1 (n=94, 33)	7.4 (± 17)	25.3 (± 32.3)		
Pain in Arm or Shoulder: C11D1 (n=84, 25)	6 (± 14.8)	24 (± 26.4)		
Pain in Arm or Shoulder: C12D1 (n=76, 23)	6.6 (± 15.4)	29 (± 35.3)		
Pain in Arm or Shoulder: C13D1 (n=74, 21)	5.9 (± 12.8)	25.4 (± 34.8)		
Pain in Arm or Shoulder: C14D1 (n=66, 19)	7.6 (± 18.3)	29.8 (± 31.2)		
Pain in Arm or Shoulder: C15D1 (n=62, 16)	5.4 (± 13.8)	25 (± 25.8)		
Pain in Arm or Shoulder: C16D1 (n=53, 12)	5 (± 12)	16.7 (± 22.5)		
Pain in Arm or Shoulder: C17D1 (n=47, 11)	3.5 (± 10.4)	21.2 (± 22.5)		
Pain in Arm or Shoulder: C18D1 (n=45, 11)	8.1 (± 20.3)	30.3 (± 34.8)		
Pain in Arm or Shoulder: C19D1 (n=40, 9)	6.7 (± 15.5)	18.5 (± 24.2)		
Pain in Arm or Shoulder: C20D1 (n=35, 8)	9.5 (± 22.2)	25 (± 23.6)		
Pain in Arm or Shoulder: C21D1 (n=30, 8)	7.8 (± 16.8)	29.2 (± 27.8)		
Pain in Arm or Shoulder: C22D1 (n=24, 7)	2.8 (± 9.4)	21.4 (± 24.9)		
Pain in Arm or Shoulder: C23D1 (n=23, 4)	0.7 (± 3.5)	33.3 (± 38.5)		
Pain in Arm or Shoulder: C24D1 (n=20, 3)	3.3 (± 10.3)	44.4 (± 38.5)		
Pain in Arm or Shoulder: C25D1 (n=18, 3)	1.9 (± 7.9)	33.3 (± 33.3)		
Pain in Arm or Shoulder: C26D1 (n=14, 3)	7.1 (± 19.3)	22.2 (± 19.2)		
Pain in Arm or Shoulder: C27D1 (n=14, 2)	4.8 (± 12.1)	50 (± 23.6)		
Pain in Arm or Shoulder: C28D1 (n=11, 2)	0 (± 0)	33.3 (± 0)		
Pain in Arm or Shoulder: C29D1 (n=8, 2)	0 (± 0)	66.7 (± 0)		
Pain in Arm or Shoulder: C30D1 (n=8, 1)	0 (± 0)	33.3 (± 0)		
Pain in Arm or Shoulder: C31D1 (n=7, 0)	0 (± 0)	0 (± 0)		
Pain in Arm or Shoulder: C32D1 (n=6, 0)	11.1 (± 17.2)	0 (± 0)		
Pain in Arm or Shoulder: C33D1 (n=6, 0)	0 (± 0)	0 (± 0)		
Pain in Arm or Shoulder: C34D1 (n=5, 0)	0 (± 0)	0 (± 0)		

Pain in Arm or Shoulder: C35D1 (n=4, 0)	0 (± 0)	0 (± 0)		
Pain in Arm or Shoulder: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Pain in Arm or Shoulder: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Pain in Arm or Shoulder: EOT (n=48, 90)	11.1 (± 21)	21.9 (± 28.8)		
Pain in Other Parts: Baseline (n=163, 158)	23.1 (± 27.3)	31.4 (± 30.4)		
Pain in Other Parts: C2D1 (n=153, 125)	15 (± 23.2)	25.9 (± 28)		
Pain in Other Parts: C3D1 (n=152, 104)	11.4 (± 20.7)	21.2 (± 27.1)		
Pain in Other Parts: C4D1 (n=134, 90)	12.7 (± 22.7)	21.5 (± 24.6)		
Pain in Other Parts: C5D1 (n=123, 73)	14.4 (± 23)	20.5 (± 27.6)		
Pain in Other Parts: C6D1 (n=118, 68)	10.7 (± 18.9)	18.1 (± 26)		
Pain in Other Parts: C7D1 (n=115, 51)	11.3 (± 20.7)	16.3 (± 26.1)		
Pain in Other Parts: C8D1 (n=111, 42)	10.5 (± 20.6)	22.2 (± 30.9)		
Pain in Other Parts: C9D1 (n=100, 37)	10.7 (± 21.1)	24.3 (± 31.1)		
Pain in Other Parts: C10D1 (n=92, 33)	9.8 (± 18.8)	28.3 (± 35.5)		
Pain in Other Parts: C11D1 (n=83, 25)	12.4 (± 21.3)	24 (± 29.7)		
Pain in Other Parts: C12D1 (n=74, 23)	12.2 (± 20.3)	24.6 (± 30.5)		
Pain in Other Parts: C13D1 (n=74, 21)	10.8 (± 19.2)	31.7 (± 34.1)		
Pain in Other Parts: C14D1 (n=66, 19)	11.6 (± 18)	24.6 (± 29.1)		
Pain in Other Parts: C15D1 (n=61, 16)	9.8 (± 15.3)	25 (± 22.8)		
Pain in Other Parts: C16D1 (n=53, 12)	10.7 (± 19.4)	38.9 (± 34.3)		
Pain in Other Parts: C17D1 (n=46, 11)	13.8 (± 19.3)	24.2 (± 21.6)		
Pain in Other Parts: C18D1 (n=45, 11)	10.4 (± 19.9)	33.3 (± 39.4)		
Pain in Other Parts: C19D1 (n=40, 9)	14.2 (± 22.5)	25.9 (± 14.7)		
Pain in Other Parts: C20D1 (n=35, 8)	13.3 (± 20.1)	29.2 (± 21.4)		
Pain in Other Parts: C21D1 (n=30, 8)	21.1 (± 27)	29.2 (± 37.5)		
Pain in Other Parts: C22D1 (n=24, 7)	12.5 (± 21.6)	40.5 (± 30.2)		
Pain in Other Parts: C23D1 (n=23, 4)	5.1 (± 11.7)	41.7 (± 31.9)		
Pain in Other Parts: C24D1 (n=20, 3)	6.7 (± 17.4)	11.1 (± 19.2)		
Pain in Other Parts: C25D1 (n=18, 3)	9.3 (± 15.4)	44.4 (± 38.5)		
Pain in Other Parts: C26D1 (n=14, 3)	23.8 (± 30.5)	33.3 (± 33.3)		
Pain in Other Parts: C27D1 (n=14, 2)	16.7 (± 31.4)	50 (± 23.6)		
Pain in Other Parts: C28D1 (n=11, 2)	6.1 (± 13.5)	33.3 (± 0)		
Pain in Other Parts: C29D1 (n=8, 2)	4.2 (± 11.8)	16.7 (± 23.6)		
Pain in Other Parts: C30D1 (n=8, 1)	12.5 (± 17.3)	33.3 (± 0)		
Pain in Other Parts: C31D1 (n=7, 0)	9.5 (± 16.3)	0 (± 0)		
Pain in Other Parts: C32D1 (n=6, 0)	5.6 (± 13.6)	0 (± 0)		
Pain in Other Parts: C33D1 (n=6, 0)	0 (± 0)	0 (± 0)		
Pain in Other Parts: C34D1 (n=5, 0)	6.7 (± 14.9)	0 (± 0)		
Pain in Other Parts: C35D1 (n=4, 0)	0 (± 0)	0 (± 0)		
Pain in Other Parts: C36D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Pain in Other Parts: C37D1 (n=1, 0)	0 (± 0)	0 (± 0)		
Pain in Other Parts: EOT (n=49, 90)	18.4 (± 29.7)	29.6 (± 34.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: European Quality of Life - 5 Dimensional (EQ-5D) Visual Analog Scale (VAS)

End point title	European Quality of Life - 5 Dimensional (EQ-5D) Visual Analog Scale (VAS)

End point description:

EQ-5D: participant rated questionnaire to assess health-related quality of life in terms of a single index value. The VAS component rates current health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state); higher scores indicate a better health state.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of each cycle until disease progression, end of treatment (up to 112 weeks)

End point values	Crizotinib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	161		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=164, 161)	64.09 (± 21.04)	66.76 (± 20.74)		
C2D1 (n=153, 131)	69.19 (± 19.42)	66.33 (± 20.3)		
C3D1 (n=153, 105)	73.13 (± 18.97)	65.84 (± 20.8)		
C4D1 (n=135, 90)	73.78 (± 18.25)	69.13 (± 18.14)		
C5D1 (n=122, 74)	75.27 (± 17.99)	68.12 (± 23.19)		
C6D1 (n=120, 70)	75.79 (± 18.67)	69.71 (± 22.46)		
C7D1 (n=115, 52)	77.02 (± 17.34)	70.63 (± 24.31)		
C8D1 (n=110, 43)	74.72 (± 18.09)	72.3 (± 23.54)		
C9D1 (n=101, 37)	74.45 (± 18.32)	72.27 (± 25.85)		
C10D1 (n=94, 33)	75.49 (± 18.18)	74.27 (± 24.88)		
C11D1 (n=84, 25)	76.32 (± 17)	77.24 (± 20.31)		
C12D1 (n=77, 23)	76.95 (± 17.63)	74.83 (± 22.6)		
C13D1 (n=73, 21)	76.38 (± 17.5)	73 (± 23.54)		
C14D1 (n=66, 19)	78.77 (± 15.54)	74.11 (± 22.56)		
C15D1 (n=62, 16)	77.71 (± 16.78)	77.44 (± 19.52)		
C16D1 (n=53, 12)	75.32 (± 16.21)	79 (± 13.28)		
C17D1 (n=47, 11)	75.09 (± 17.68)	81.73 (± 15.98)		
C18D1 (n=45, 11)	75.87 (± 16.63)	78.91 (± 16.25)		

C19D1 (n=40, 9)	76.85 (± 16.39)	78 (± 14.04)		
C20D1 (n=35, 8)	72.66 (± 19.81)	76.75 (± 17.65)		
C21D1 (n=30, 8)	74.13 (± 16.19)	73.63 (± 19.41)		
C22D1 (n=24, 7)	77.54 (± 17.54)	72.21 (± 19.79)		
C23D1 (n=23, 4)	75.48 (± 17.75)	54 (± 16.35)		
C24D1 (n=20, 3)	71.4 (± 23.15)	62 (± 20.3)		
C25D1 (n=18, 3)	75.61 (± 15.97)	63.67 (± 22.59)		
C26D1 (n=14, 3)	72.14 (± 20.71)	63 (± 17.52)		
C27D1 (n=14, 2)	66.57 (± 16.96)	50 (± 14.14)		
C28D1 (n=11, 2)	72.36 (± 12.72)	55 (± 21.21)		
C29D1 (n=8, 2)	71.38 (± 12.28)	45 (± 14.14)		
C30D1 (n=8, 1)	69.5 (± 17)	40 (± 0)		
C31D1 (n=7, 0)	68.57 (± 16.76)	0 (± 0)		
C32D1 (n=6, 0)	65.83 (± 19.41)	0 (± 0)		
C33D1 (n=6, 0)	67.5 (± 20.34)	0 (± 0)		
C34D1 (n=5, 0)	68 (± 20.8)	0 (± 0)		
C35D1 (n=4, 0)	72.25 (± 14.84)	0 (± 0)		
C36D1 (n=1, 0)	90 (± 0)	0 (± 0)		
C37D1 (n=1, 0)	85 (± 0)	0 (± 0)		
EOT (n=49, 90)	68.33 (± 21.25)	58.34 (± 23.71)		

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 the last dose of study treatment.

Adverse event reporting additional description:

All causality (serious and non-serious) AEs have been reported. Non-serious AEs above the 5% threshold are reported herein. All causality deaths include deaths not related to the trial. Deaths resulting from AEs include all deaths considered to be causally related to AEs. All information are taken from the safety database.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Chemotherapy

Reporting group description:

Pemetrexed 500 mg/m^2 intravenous infusion over 10 minutes or docetaxel 75 mg/m^2 intravenous infusion over 1 hour on Day 1 of 21-day cycle, as per investigator discretion. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent occurred.

Reporting group title	Crizotinib

Reporting group description:

Crizotinib (PF-02341066) 250 mg (administered as two 100-mg tablets and one 50-mg tablet) orally twice daily continuously in 21-day cycles. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent occurred.

Serious adverse events	Chemotherapy	Crizotinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 171 (24.56%)	80 / 172 (46.51%)	
number of deaths (all causes)	7	30	
number of deaths resulting from adverse events	1	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer recurrent			

subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 171 (1.17%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cancer surgery			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Product contamination microbial			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 171 (1.17%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 171 (0.00%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Disease progression			
subjects affected / exposed	3 / 171 (1.75%)	18 / 172 (10.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 18	
deaths causally related to treatment / all	0 / 3	0 / 16	

Fatigue			
subjects affected / exposed	1 / 171 (0.58%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	2 / 171 (1.17%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 171 (0.58%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Malaise			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute respiratory failure			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 171 (1.17%)	6 / 172 (3.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 2	
Organising pneumonia			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 171 (0.00%)	3 / 172 (1.74%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonitis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleural effusion			
subjects affected / exposed	3 / 171 (1.75%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 171 (1.75%)	7 / 172 (4.07%)	
occurrences causally related to treatment / all	1 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			

subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 171 (0.00%)	3 / 172 (1.74%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 171 (0.00%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	2 / 171 (1.17%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 171 (0.58%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac arrest			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac tamponade			
subjects affected / exposed	1 / 171 (0.58%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 171 (1.17%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 171 (1.17%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			

subjects affected / exposed	0 / 171 (0.00%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral cyst			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 171 (0.58%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 171 (1.17%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	12 / 171 (7.02%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	15 / 15	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 171 (1.17%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 171 (1.17%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 171 (0.00%)	3 / 172 (1.74%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatitis			

subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 171 (1.17%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Empyema			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 171 (1.17%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 171 (0.00%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 171 (0.58%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 171 (1.75%)	8 / 172 (4.65%)	
occurrences causally related to treatment / all	1 / 3	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 171 (0.58%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Urinary tract infection			

subjects affected / exposed	1 / 171 (0.58%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 171 (0.00%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 171 (0.58%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 171 (0.58%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 171 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Chemotherapy	Crizotinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	169 / 171 (98.83%)	172 / 172 (100.00%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	32 / 171 (18.71%)	31 / 172 (18.02%)	
occurrences (all)	38	78	
Chest pain			
subjects affected / exposed	13 / 171 (7.60%)	15 / 172 (8.72%)	
occurrences (all)	17	18	
Fatigue			
subjects affected / exposed	60 / 171 (35.09%)	51 / 172 (29.65%)	
occurrences (all)	106	83	
Oedema			
subjects affected / exposed	6 / 171 (3.51%)	15 / 172 (8.72%)	
occurrences (all)	6	25	
Oedema peripheral			
subjects affected / exposed	15 / 171 (8.77%)	59 / 172 (34.30%)	
occurrences (all)	16	105	
Pyrexia			
subjects affected / exposed	33 / 171 (19.30%)	41 / 172 (23.84%)	
occurrences (all)	43	51	
Pain			
subjects affected / exposed	9 / 171 (5.26%)	10 / 172 (5.81%)	
occurrences (all)	10	11	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	35 / 171 (20.47%)	37 / 172 (21.51%)	
occurrences (all)	42	56	
Dyspnoea			
subjects affected / exposed	29 / 171 (16.96%)	27 / 172 (15.70%)	
occurrences (all)	43	39	
Epistaxis			
subjects affected / exposed	10 / 171 (5.85%)	3 / 172 (1.74%)	
occurrences (all)	11	3	
Haemoptysis			
subjects affected / exposed	11 / 171 (6.43%)	9 / 172 (5.23%)	
occurrences (all)	12	10	
Oropharyngeal pain			
subjects affected / exposed	7 / 171 (4.09%)	20 / 172 (11.63%)	
occurrences (all)	10	24	
Rhinorrhoea			
subjects affected / exposed	9 / 171 (5.26%)	4 / 172 (2.33%)	
occurrences (all)	10	5	
Productive cough			
subjects affected / exposed	8 / 171 (4.68%)	12 / 172 (6.98%)	
occurrences (all)	10	15	
Pulmonary embolism			
subjects affected / exposed	2 / 171 (1.17%)	9 / 172 (5.23%)	
occurrences (all)	2	10	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 171 (7.60%)	19 / 172 (11.05%)	
occurrences (all)	14	21	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	21 / 171 (12.28%)	72 / 172 (41.86%)	
occurrences (all)	36	195	
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 171 (9.94%)	55 / 172 (31.98%)	
occurrences (all)	25	127	
Blood alkaline phosphatase increased			

subjects affected / exposed	6 / 171 (3.51%)	18 / 172 (10.47%)	
occurrences (all)	8	27	
Blood creatinine increased			
subjects affected / exposed	3 / 171 (1.75%)	13 / 172 (7.56%)	
occurrences (all)	3	27	
Neutrophil count decreased			
subjects affected / exposed	9 / 171 (5.26%)	15 / 172 (8.72%)	
occurrences (all)	11	73	
Weight decreased			
subjects affected / exposed	8 / 171 (4.68%)	21 / 172 (12.21%)	
occurrences (all)	9	29	
White blood cell count decreased			
subjects affected / exposed	13 / 171 (7.60%)	16 / 172 (9.30%)	
occurrences (all)	15	66	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 171 (0.00%)	9 / 172 (5.23%)	
occurrences (all)	0	20	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 171 (1.75%)	11 / 172 (6.40%)	
occurrences (all)	3	15	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 171 (0.00%)	9 / 172 (5.23%)	
occurrences (all)	0	10	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 171 (7.60%)	34 / 172 (19.77%)	
occurrences (all)	15	49	
Dysgeusia			
subjects affected / exposed	17 / 171 (9.94%)	45 / 172 (26.16%)	
occurrences (all)	20	66	
Headache			
subjects affected / exposed	26 / 171 (15.20%)	46 / 172 (26.74%)	
occurrences (all)	29	85	
Paraesthesia			

subjects affected / exposed	7 / 171 (4.09%)	13 / 172 (7.56%)	
occurrences (all)	10	18	
Neuropathy peripheral			
subjects affected / exposed	10 / 171 (5.85%)	5 / 172 (2.91%)	
occurrences (all)	10	7	
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 171 (3.51%)	9 / 172 (5.23%)	
occurrences (all)	9	12	
Visual perseveration			
subjects affected / exposed	0 / 171 (0.00%)	12 / 172 (6.98%)	
occurrences (all)	0	18	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 171 (15.79%)	36 / 172 (20.93%)	
occurrences (all)	46	81	
Leukopenia			
subjects affected / exposed	9 / 171 (5.26%)	24 / 172 (13.95%)	
occurrences (all)	16	110	
Neutropenia			
subjects affected / exposed	18 / 171 (10.53%)	41 / 172 (23.84%)	
occurrences (all)	28	222	
Eye disorders			
Photopsia			
subjects affected / exposed	1 / 171 (0.58%)	21 / 172 (12.21%)	
occurrences (all)	2	27	
Vision blurred			
subjects affected / exposed	5 / 171 (2.92%)	13 / 172 (7.56%)	
occurrences (all)	7	19	
Visual impairment			
subjects affected / exposed	8 / 171 (4.68%)	74 / 172 (43.02%)	
occurrences (all)	8	106	
Lacrimation increased			
subjects affected / exposed	9 / 171 (5.26%)	1 / 172 (0.58%)	
occurrences (all)	10	1	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	8 / 171 (4.68%)	18 / 172 (10.47%)	
occurrences (all)	9	22	
Abdominal pain upper			
subjects affected / exposed	13 / 171 (7.60%)	17 / 172 (9.88%)	
occurrences (all)	13	17	
Constipation			
subjects affected / exposed	39 / 171 (22.81%)	83 / 172 (48.26%)	
occurrences (all)	61	150	
Diarrhoea			
subjects affected / exposed	34 / 171 (19.88%)	106 / 172 (61.63%)	
occurrences (all)	44	332	
Dyspepsia			
subjects affected / exposed	6 / 171 (3.51%)	18 / 172 (10.47%)	
occurrences (all)	9	22	
Nausea			
subjects affected / exposed	60 / 171 (35.09%)	104 / 172 (60.47%)	
occurrences (all)	125	249	
Stomatitis			
subjects affected / exposed	13 / 171 (7.60%)	9 / 172 (5.23%)	
occurrences (all)	16	16	
Vomiting			
subjects affected / exposed	32 / 171 (18.71%)	88 / 172 (51.16%)	
occurrences (all)	51	311	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 171 (0.00%)	12 / 172 (6.98%)	
occurrences (all)	0	14	
Dysphagia			
subjects affected / exposed	2 / 171 (1.17%)	9 / 172 (5.23%)	
occurrences (all)	2	11	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	35 / 171 (20.47%)	21 / 172 (12.21%)	
occurrences (all)	39	26	
Dry skin			

subjects affected / exposed	2 / 171 (1.17%)	10 / 172 (5.81%)	
occurrences (all)	2	13	
Pruritus			
subjects affected / exposed	7 / 171 (4.09%)	12 / 172 (6.98%)	
occurrences (all)	7	17	
Rash			
subjects affected / exposed	30 / 171 (17.54%)	23 / 172 (13.37%)	
occurrences (all)	36	34	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 171 (11.70%)	15 / 172 (8.72%)	
occurrences (all)	36	16	
Back pain			
subjects affected / exposed	11 / 171 (6.43%)	30 / 172 (17.44%)	
occurrences (all)	12	37	
Musculoskeletal pain			
subjects affected / exposed	6 / 171 (3.51%)	14 / 172 (8.14%)	
occurrences (all)	6	18	
Myalgia			
subjects affected / exposed	19 / 171 (11.11%)	5 / 172 (2.91%)	
occurrences (all)	25	6	
Pain in extremity			
subjects affected / exposed	10 / 171 (5.85%)	20 / 172 (11.63%)	
occurrences (all)	12	28	
Muscle spasms			
subjects affected / exposed	4 / 171 (2.34%)	9 / 172 (5.23%)	
occurrences (all)	4	10	
Neck pain			
subjects affected / exposed	5 / 171 (2.92%)	11 / 172 (6.40%)	
occurrences (all)	5	12	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 171 (4.09%)	32 / 172 (18.60%)	
occurrences (all)	10	63	
Upper respiratory tract infection			

subjects affected / exposed	14 / 171 (8.19%)	24 / 172 (13.95%)	
occurrences (all)	18	33	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	46 / 171 (26.90%)	56 / 172 (32.56%)	
occurrences (all)	67	151	
Hyperglycaemia			
subjects affected / exposed	9 / 171 (5.26%)	12 / 172 (6.98%)	
occurrences (all)	13	26	
Hypoalbuminaemia			
subjects affected / exposed	1 / 171 (0.58%)	16 / 172 (9.30%)	
occurrences (all)	1	34	
Hypokalaemia			
subjects affected / exposed	5 / 171 (2.92%)	15 / 172 (8.72%)	
occurrences (all)	5	24	
Hypocalcaemia			
subjects affected / exposed	0 / 171 (0.00%)	13 / 172 (7.56%)	
occurrences (all)	0	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2009	Protocol was updated based on feedback from a Special Protocol Assessment completed by the Federal Drug Administration (FDA). Specific changes were to central laboratory requirements for ALK testing; entry criteria modifications; survival analysis modifications; PK requirements were updated; sample size for ECG substudy and independent radiology review requirements were modified.
23 November 2009	RECIST version 1.0 changed to version 1.1; CTCAE criteria changed from version 3.0 to version 4.0; primary endpoint changed from ORR to PFS, interim analysis timelines were updated; randomization block design updated; survival follow up period revised; tumor assessments were updated to be based on calendar and not cycle; toxicity management for pemetrexed and docetaxel updated; wound healing timelines was added; administration for PF 02341066 was updated to be with or without food; dose modification section for PF 02341066 updated based on safety database.
21 December 2009	Japan specific amendment: Modifications were made for Japanese sites only regarding eligibility criteria.
26 January 2010	Update to pemetrexed dosing administration and contraception requirements based on approved packet insert.
18 February 2010	France specific amendment: Modifications were made for French sites only to require all patients in France to have both MUGA scans (or echocardiograms) and ophthalmology examinations at scheduled times during the study.
08 March 2010	Ireland specific amendment: Modifications were made for Ireland sites only to require all patients for Irish sites to have a MUGA test at scheduled times during the study
22 June 2010	The patient reported VSAQ ALK was included, additional ECG monitoring was added for patients 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 required review by a third party radiology laboratory, a treatment delay to up to 42 days without requiring discontinuation was allowed; and metabolites of crizotinib were 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	Dose modifications for crizotinib updated; dose administration guidelines for docetaxel and pemetrexed updated; safety guidelines for potential cases of drug induced liver injury added; washout for palliative radiation changed.
09 November 2011	Sample size requirement was updated after planned interim analysis removed and study design assumptions revised post consultation and approval by the US FDA. Time to tumor response was added as a secondary endpoint. Duration of survival evaluation period was extended. Revised monitoring guidance for Hy's Law and new safety and monitoring guidance for complex renal cysts development was added. Language was added regarding the Internal Oncology Business Unit Safety Data Monitoring Committee. Text modified in some sections to ensure compliance with the Sponsor protocol template.

21 March 2012	France specific amendment: Modifications were made for French sites only: safety information about Hy's Law cases provided and dose modification rules were revised for patients with drug-related ALT increases.
31 December 2012	Modifications based on the country specific amendment for France regarding updated safety information about Hy's Law cases and such. A reduced schedule of assessments for ongoing patients in Arm A was provided. The total number of OS events required to conduct the final OS analysis was revised. Detailed description of patients of child bearing potential language as an inclusion criteria and detailed contraception guidelines were introduced to ensure consistency with updated Sponsor protocol. Text was added or replaced to ensure consistency with updated Pfizer protocol template language especially regarding medication error, and SAE reporting for Oncology studies after the active safety reporting period was clarified. Use of prophylactic antiemetics and concomitant acetaminophen/paracetamol was clarified. Prohibited medications use by topical administration was added. Pregnancy testing in response to IRBs/IECs and/or local regulations was clarified. Reporting of local cardiologist manual ECG overread was clarified. Corrections of typographical errors/omissions and other administrative inconsistencies were made throughout the protocol.
03 December 2014	Blood sample collection for hematology and blood chemistries will now be during non visit cycles. Survival follow up data collection text clarified to be collected until the required number of Overall Survival events has been reached or until death, whichever is earlier. Reduced Schedule of Activities was introduced for patients still ongoing after Secondary Overall Survival endpoint is reached. Dose modification and adverse event management guidance were revised for bradycardia and pneumonitis, based on the updated safety information. Some text was revised to ensure consistency with updated Sponsor protocol template language especially regarding contraception guidelines, pregnancy testing, and serious adverse event reporting for Oncology studies after permanent discontinuation of study 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.

No analyses of ALK fusion variants or protein expression were done due to limited slide stability of unstained tissue sections required for immunohistochemistry and no nucleic acid based assay was available to identify specific ALK gene fusion.

Notes: