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GENERIC DRUG NAME: Crizotinib

COMPOUND NUMBER: PF-02341066

PROTOCOL NO.: A8081007

PROTOCOL TITLE: Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of PF-02341066 Versus Standard-of-Care Chemotherapy (Pemetrexed or Docetaxel) in Subjects With Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus.

Study Centers: A total of 106 centers participated in the study in 21 countries: Australia (2 centers), Brazil (5 centers), Canada (3 centers), China (8 centers), France (6 centers), Germany (9 centers), Greece (1 center), Hong Kong (2 centers), Hungary (2 centers), Ireland (2 centers), Italy (11 centers), Japan (10 centers), Republic of Korea (3 centers), Netherlands (1 center), Poland (3 centers), Russian Federation (2 centers), Spain [8 centers], Sweden [1 center], Taiwan [1 center], United Kingdom [4 centers], and United States (US; 22 centers). An additional 59 centers received study drug, but did not enroll subjects.

Study Initiation Date and Final Completion Dates:

Study initiation date: 18 September 2009

Study completion date: 05 January 2016

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- To demonstrate that crizotinib (Arm A) was superior to standard-of-care chemotherapy, pemetrexed or docetaxel (Arm B), in prolonging progression-free survival (PFS) in subjects with advanced NSCLC whose tumors harbor a translocation or inversion event involving the ALK gene locus and who had received only 1 prior chemotherapy regimen for advanced NSCLC and this regimen must have been platinum-based.

Secondary Objectives:

- To compare secondary measures of clinical efficacy including overall survival (OS), objective response rate (ORR), and disease control rate (DCR) between the 2 treatment arms, and evaluate duration of response (DR) and time to tumor response (TTR).

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- To assess the safety and tolerability of crizotinib compared to chemotherapy (pemetrexed or docetaxel).

- To compare patient-reported outcomes of health-related quality of life (QoL), disease/treatment-related symptoms of lung cancer, and general health status in both treatment arms.

- To characterize the effects of crizotinib at therapeutic doses on QT interval in this subject population.

- To determine pharmacokinetics (PK) in this subject population using population PK (popPK) method and explore correlations between PK, response, and/or safety findings.

- To explore the relationship of ALK gene fusion to the presence of ALK protein and fusion transcript.

- To correlate modulation of soluble biomarkers to PK and outcome measures.

METHODS

Study Design:

This was a multinational, multicenter, randomized, open-label Phase 3 efficacy and safety study of crizotinib vs standard-of-care chemotherapy (pemetrexed or docetaxel) in subjects with previously treated NSCLC (with 1 prior platinum-based chemotherapy regimen) whose tumors harbor ALK fusions.

The ALK break-apart fluorescence in-situ hybridization (FISH) assay was used to determine ALK-positivity.

A total of 318 subjects were planned for randomization in a 1:1 ratio (2 arms) and to receive crizotinib (Arm A) or chemotherapy (pemetrexed or docetaxel) (Arm B). Each treatment cycle was defined as 21 days. Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0-1, 2), brain metastases (present, absent), and previous treatment with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) (yes or no).

After starting study drug, subjects were to continue with the assigned treatment until Response Evaluation Criteria in Solid Tumors (RECIST, version [v] 1.1) - defined progression of disease as assessed by the independent radiology review (IRR), unacceptable toxicity, or consent withdrawal. Subjects continued treatment as assigned beyond the time of RECIST-defined progression, as assessed by the IRR, at the discretion of the investigator if the subject was perceived to be experiencing clinical benefit. In addition, subjects in the chemotherapy arm, who had RECIST defined progression of disease, as assessed by the IRR, had the option to enroll in A8081005 to receive crizotinib treatment if they met the safety screening inclusion/exclusion criteria for crizotinib.

The complete schedule of events for all subjects is shown in Table 1. A reduced schedule of events for subjects in the crizotinib arm is shown in Table 2.

Table 1   Schedule of Activities

Protocol Activities	Screening	Study Treatment[1]			End of Treatment	
		Cycle 1		Cycles ≥ 2		
	≤28 Days Prior to Randomization	Day 1 (±2)[2]	Day 15 (±2)	Day 1 (±2; except as noted below)	End of Treatment/ Withdrawal[3]	Post Treatment Follow-up
Baseline Documentation						
Informed Consent[4]	X					
Medical/ Oncological History[5]	X					
Baseline Signs/Symptoms		X				
Mandatory Tumor Tissue for Molecular Profiling[6]	X					
Physical Examination[7]	X	(X)		X	X	
ECOG Performance Status	X	X		X	X	
Ophthalmologic Examination[8]	X			Cycle 5, then every 4 cycles (France only)		
Laboratory Studies						
Hematology[9]	X	(X)	X	X	X	
Blood Chemistry[9]	X	(X)	X	X	X	
Coagulation[9]	X					
Dipstick Urinalysis and Urine Reflex Microscopy[10]	X (Korea only)	X (Korea only)		X (Korea only)	X (Korea only)	
12-lead ECG[11]	X	X		Cycle 2		
Pregnancy Test (as appropriate)[12]	X				X	
Disease Assessments						
Tumor Assessments (including scans)[13]	X			every 6 weeks (±1 week)	X	X
Other Clinical Assessments						
Adverse Events and Hospitalizations[14]	X	X	X	X	X	X
Concomitant Medications/Treatments[15]	X	X	X	X	X	X
EORTC QLQ-C30, QLQ-LC13, EQ-5D and VSAQ-ALK[16]		X		X	X	
Multiple Gate Acquisition (MUGA) Scan or Echocardiogram[17] (France, Ireland and any substudy site)	X			Cycle 3, then every 4 cycles		
Contraception Check				X[12]	X[12]	
Survival Follow-up[18]						X

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| Protocol Activities | Screening | Study Treatment[1] | | | End of Treatment | |
| | | Cycle 1 | | Cycles ≥ 2 | | |
	≤28 Days Prior to Randomization	Day 1 (±2)[2]	Day 15 (±2)	Day 1 (±2; except as noted below)	End of Treatment/ Withdrawal[3]	Post Treatment Follow-up
Study Treatment						
PF-02341066 (Crizotinib) (ie, Arm A only)		Daily				
Pemetrexed or Docetaxel (ie, Arm B only)[19]		X		X		
Special Laboratory Studies						
Optional Blood Sample for Biomarkers and Optional Tumor Tissue for Molecular Profiling (crizotinib arm only)[20]		X		Cycle 2	X	
Pharmacokinetics (PK) (crizotinib arm only)[21]		X		Cycles 2, 3, 5		

( ) – if not performed within 7 days of study treatment.

Abbreviations: AE=adverse event; ALK=anaplastic lymphoma kinase; ALT=alanine aminotransferase; c-Met=hepatocyte growth factor receptor; CT=computed tomography; ECG=electrocardiogram; EORTC=European Organization for the Research and Treatment of Cancer; EQ-5D=EuroQOL-5D; ECOG=Eastern Cooperative Oncology Group; FISH=fluorescence in-situ hybridization; HGF=hepatocyte growth factor; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition; OS=overall survival; PK=pharmacokinetic; QLQ-C30= Quality of Life Questionnaire – Core 30 Questionnaire; QLQ-LC13=Quality of Life Questionnaire – Lung Cancer 13; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse events; VSAQ-ALK=Visual Symptom Assessment Questionnaire-ALK

1. **Study Treatment**: All cycles were 21 days in duration.
2. **Cycle 1/Day 1**: Blood chemistry, hematology, and physical examination were not to be required if acceptable screening assessment was performed within 7 days prior to the start of study treatment.
3. **End of Treatment/Withdrawal**: These assessments were obtained if not completed during the previous 4 weeks on study (during the last 6 weeks for disease assessments).
4. **Informed Consent**: Was obtained prior to undergoing any trial specific procedure.
5. **Medical/Oncological History**: Included information on prior regimens.
6. **Mandatory Tumor Tissue for Molecular Profiling**: Paraffin block(s) of adequate size to allow if possible for at least 10 slides with cuts that were 5-microns thick. These samples were used for the assessment of ALK gene fusion by FISH by the central laboratory.
7. **Physical Examination**: Examination of major body systems, height (at screening only); weight, blood pressure, and pulse rate (at baseline and on Day 1 of each cycle).
8. **Ophthalmologic Examination**: Visual acuity, slit lamp and fundoscopy were performed by an ophthalmologist. The ophthalmologic examination was repeated during the study when visual disturbances were observed and when there was an increase in the grade for visual disturbances. For all subjects enrolled in France, ophthalmology exams were performed after the completion of every 4 cycles.
9. **Hematology, Blood Chemistry and Coagulation**: For crizotinib arm only: If ALT or AST ≥ Grade 3 and total bilirubin ≥ Grade 2, then liver function tests were repeated within 48 hours and then repeated every 48-72 hours until ALT or AST ≤ Grade 1. A 4 mL serum sample obtained just prior to the first dose of study medication was stored frozen on-site through completion of the study for possible use as a baseline reference if additional laboratory tests were indicated, for example, additional testing to exclude other causes of liver injury.
10. **Dipstick urinalysis and Urine Reflex Microscopy**: Urine reflex microscopy was performed if urine dipstick was positive for blood or protein.
11. **12-lead ECG.**
12. **Pregnancy Test**.

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Protocol Activities	Screening	Study Treatment[1]			End of Treatment	
		Cycle 1		Cycles ≥ 2		
	≤28 Days Prior to Randomization	Day 1 (±2)[2]	Day 15 (±2)	Day 1 (±2; except as noted below)	End of Treatment/ Withdrawal[3]	Post Treatment Follow-up
[13] **Tumor Assessments**: CT or MRI was to include chest, brain, abdomen and pelvis at screening. Bone scan was performed at screening. Scans performed 6 weeks after randomization had a +1 week allowance; all subsequent scans were performed at 6 week intervals (±1 week). Tumor Assessments should have continued every 6 weeks until RECIST-defined disease progression confirmed by an independent radiology laboratory. If study drug was discontinued in the absence of confirmed RECIST-defined disease progression, subjects remained on study until confirmation was received by the independent radiology laboratory.						
[14] **Adverse Events and Hospitalizations**: Subjects were followed for AEs from the time they signed the protocol-specific informed consent until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities were resolved or were determined to be "chronic" or "stable", whichever was later. Hospitalizations were recorded from 28 days prior to the start of study treatment until the last day of study drug administration.						
[15] **Concomitant Medications/Treatments**: Concomitant medications and treatments were recorded from 28 days prior to the start of study treatment and up to 28 days post the last dose of study treatment.						
[16] **EORTC QLQ-C30, QLQ-LC13 EQ-5D, and VSAQ-ALK**: Subjects were to complete the EORTC QLQ-C30, the QLQ-LC13, the EQ-5D, and the VSAQ-ALK questionnaires at the clinic prior to any study or medical procedure. Subjects with visual disturbances ongoing at the End of Treatment visit were also to complete the VSAQ-ALK at the 28 day follow-up visit after last dose. All self-assessment questionnaires were completed by the subjects while in the clinic and could not be taken home. The VSAQ-ALK has been translated into different languages; however, if the VSAQ-ALK was not available in the subject's preferred language, the subject did not need to complete this assessment.						
[17] **MUGA Scan or Echocardiogram**: MUGA scans or echocardiograms were required from selected sites for a total of 30 subjects/treatment arm.						
[18] **Survival Follow-Up**: After discontinuation of study treatment, post-study survival status was collected every 2 months until death or until the required number of OS events had been reached, whichever was earlier. Included collection of information on subsequent anti-cancer therapies. Telephone contact was acceptable.						
[19] **Pemetrexed or Docetaxel (ie, Arm B Only)**.						
[20] **Optional Blood Sample for Biomarkers and Optional Tumor Tissue for Molecular Profiling (Crizotinib Arm Only)**: An optional blood sample was collected for soluble biomarkers including c-Met ectodomain and HGF scatter factors, prior to dosing on Cycle 1 Day 1, Cycle 2 Day 1 (corresponding to the 2-6 hour post-dose PK sample) and end of treatment if a subject discontinued due to disease progression. An optional fresh tumor sample was collected at the end of treatment if a subject discontinued due to disease progression.						
[21] **Pharmacokinetics** (Crizotinib Arm Only).						

Table 2   Reduced Schedule of Activities for Subjects in the Crizotinib Arm

Protocol Activities	Study Treatment/Each Cycle[1]	End of Treatment/ Withdrawal[2]	Post Treatment Follow-up
	Day 1 (±2; Except as Noted Below)		
Baseline Documentation			
Physical Examination[3]	X	X	
ECOG Performance Status	X	X	
Ophthalmologic Examination[4]	Cycle 5, then every 4 cycles (France only)		
Laboratory Studies			
Hematology[5]	X	X	
Blood Chemistry[5]	X	X	
Dipstick Urinalysis and Urine Reflex Microscopy[6]	X (Korea only, other countries as clinically indicated)	X (Korea only, other countries as clinically indicated)	
12-lead ECG[7]	Cycles 1 and 2 only		
Female Subjects: Pregnancy Test (as appropriate)[8]	(X)	X	
Disease Assessments			
Tumor Assessments (including scans)[9]	As per local clinical practice		
Other Clinical Assessments			
Adverse Events and Hospitalizations[10]	X	X	X
Concomitant Medications/Treatments[11]	X	X	X
EORTC QLQ-C30, QLQ-LC13, EQ-5D and VSAQ-ALK[12]	X	X	
Multiple Gate Acquisition (MUGA) Scan or Echocardiogram[13] (France and Ireland)	Cycle 3, then every 4 cycles		
Contraception Check	X	X	
Survival Follow-up[14]			X
Study Treatment			
PF-02341066	Twice daily		
Special Laboratory Studies			
Optional Blood Sample for Biomarkers and Optional Tumor Tissue for Molecular Profiling[15]	Cycle 2 (if applicable)	X	
Pharmacokinetics (PK)[16]	Cycles 2, 3, 5 (If applicable)		
Abbreviations: ALT=alanine aminotransferase; c-Met=hepatocyte growth factor receptor; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organization for the Research and Treatment of Cancer; EQ-5D=EuroQol-5D; MUGA=Multiple Gated Acquisition; OS=overall survival; QLQ-PK: Pharmacokinetics; C30=Quality of Life Questionnaire – Core 30 Questionnaire; QLQ-LC13=Quality of Life Questionnaire – Lung Cancer 13; SAE=serious adverse event; VSAQ-ALK=Visual Symptom Assessment Questionnaire-Anaplastic Lymphoma Kinase.			

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[1]	**Study Treatment:** Enough study drug for 2 cycles of treatment was dispensed at each clinic visit.
[2]	**End of Treatment/Withdrawal:** These assessments were obtained if not completed during the previous 4 weeks on study.
[3]	**Physical Examination:** Included an examination of major body systems, weight, blood pressure, and pulse rate (at each cycle visit, ie, Day 1 of that cycle).
[4]	**Ophthalmologic Examination:** Included visual acuity, slit lamp, and fundoscopy and should be performed by an ophthalmologist. The ophthalmologic examination was repeated during the study when visual disturbances had been observed and when there was an increase in the grade for visual disturbances.
[5]	**Hematology and Blood Chemistry:** For subjects in the crizotinib arm only: If ALT ≥ Grade 3 and total bilirubin ≥ Grade 2, then liver function tests needed to be repeated every 48-72 hours until ALT ≤ Grade 2.
[6]	**Dipstick Urinalysis and Urine Reflex Microscopy:** Urine reflex microscopy was required if urine dipstick was positive for blood or protein.
[7]	**12-lead ECG.**
[8]	**Pregnancy Test.**
[9]	**Tumor Assessments:** The timing for tumor imaging could be completed per standard of care while receiving study treatment.
[10]	**Adverse Events and Hospitalizations:** Subjects were follow for adverse events from the time they signed the protocol-specific informed consent until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities had resolved or were determined to be "chronic" or "stable", whichever was later.
[11]	**Concomitant Medications/Treatments:** Concomitant medications and treatments were recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment.
[12]	**EORTC QLQ-C30, QLQ-LC13; EQ-5D, and VSAQ-ALK:** Subjects were to complete the EORTC QLQ-C30, the QLQ-LC13, the EQ-5D, and the VSAQ-ALK questionnaires at the clinic prior to any study or medical procedure. Subjects with visual disturbances ongoing at the End of Treatment visit were also to complete the VSAQ-ALK at the 28 day follow-up visit after last dose. All self-assessment questionnaires were completed by the subjects while in the clinic and could not be taken home. The VSAQ-ALK was translated into different languages. However, if the VSAQ-ALK was not available in the subject's preferred language, the subject did not need to complete this assessment.
[13]	**MUGA Scan or Echocardiogram:** MUGA scans or echocardiograms were required from selected sites for a total of 30 subjects/treatment arm.
[14]	**Survival Follow-Up:** After discontinuation of study treatment, post-study survival status was collected every 2 months until death or until the required number of OS events had been reached, whichever was earlier. Included collection of information on subsequent anti-cancer therapies. Telephone contact was acceptable.
[15]	**Optional Blood Sample for Biomarkers and Optional Tumor Tissue for Molecular Profiling (Crizotinib arm only):** An optional blood sample was collected for soluble biomarkers including c-Met ectodomain and HGF scatter factors, prior to dosing on Cycle 1 Day 1, Cycle 2 Day 1 (corresponding to the 2-6 hour post-dose PK sample) and at end of treatment if a subject discontinued due to disease progression. An optional fresh tumor sample was collected at the end of treatment if a subject discontinued due to disease progression.
[16]	**Pharmacokinetics (Crizotinib arm only).**

Number of Subjects (Planned and Analyzed):

Planned: 318 subjects.

Randomized and analyzed: 347 subjects and included in the Full Analysis (FA) population: 347 subjects (173 subjects in the crizotinib arm and 174 subjects in the chemotherapy arm).

Safety Analysis (SA) population: 343 treated subjects (172 treated with crizotinib and 171 treated with chemotherapy).

Diagnosis and Main Criteria for Inclusion and Exclusion:

Subjects with histologically or cytologically proven diagnosis of NSCLC (locally advanced or metastatic) with measurable tumors, who were positive for the ALK fusion gene and whose disease had progressed after only 1 prior chemotherapy that included one platinum drug, were included in the study.

Study Treatment:

Subjects were randomized in a 1:1 ratio to receive crizotinib (Arm A) or chemotherapy (pemetrexed or docetaxel; Arm B).

Test Product, Dose and Mode of Administration:

Crizotinib tablets, 250 mg twice daily (BID), were administered orally at approximately the same times each day on a continuous daily dosing schedule (i.e. no break in dosing). Cycles were defined in 21-day periods to facilitate scheduling of visits and assessments. Subjects were monitored closely for toxicity and the dose of crizotinib could have been reduced by 1 and, if needed, 2 dose levels depending on the type and severity of toxicity encountered (Dose Level -1 was 200 mg BID; Dose Level -2 was 250 mg once daily).

Reference Therapy, Dose and Mode of Administration:

Standard doses of chemotherapy (pemetrexed or docetaxel) were administered by intravenous (IV) infusion:

- Pemetrexed (500 mg/m^2) was administered by IV infusion over 10 minutes or according to institutional practices on Day 1 of a 21-day cycle.

- Docetaxel (75 mg/m^2) was administered by IV infusion over 1 hour or according to institutional practices on Day 1 of a 21-day cycle.

Efficacy, Pharmacokinetic and Pharmacodynamic Evaluations or Outcome Research Endpoints:

Primary Endpoint:

- PFS based on RECIST v1.1 (confirmed by the IRR assessment).

Secondary Endpoints:

- OS and survival probabilities at 6 and 12 months.

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- ORR.

- DCR at 6 and 12 weeks.

- DR.

- TTR.

- Type, incidence, severity, seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities.

- Plasma concentrations of PF-02341066.

- QTc.

- Types of EML4-ALK fusion variants and ALK protein expression.

- Plasma concentrations of soluble c-Met ectodomain and HGF scatter proteins.

- TTD in patient reported pain, dyspnea, and cough.

- HRQoL, lung cancer disease/treatment-related symptoms, and general health status.

Safety Evaluations:

Safety evaluations included clinical monitoring, physical examinations, vital signs, ECOG PS, ophthalmologic examinations, laboratory parameters (hematology, blood chemistry, coagulation [screening only], urinalysis [introduced in Protocol Amendment 10: for subjects enrolled in Korea, urinalysis was obtained at Day 1 of every cycle and at the End of Treatment (EOT); for subjects enrolled in all other countries, urinalysis was repeated as clinically indicated – at the time of the initial diagnosis of a renal cyst], and pregnancy tests), 12-lead ECGs, AEs, concomitant medications/treatments, and multiple gated acquisition (MUGA) scans or echocardiograms. The safety evaluations were done as per the schedule mentioned in Table 1 and Table 2.

Statistical Methods:

The full analysis (FA) population included all subjects who were randomized with study drug assignment designated according to initial randomization. The FA population was the primary population for evaluating time-to-event efficacy endpoints (ie, PFS and OS), ORR, DCR, PROs, and subject characteristics.

The SA population included all subjects who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. The SA population was the primary population for evaluating safety and treatment.

The PRO evaluable population was defined as the subjects from the FA population who completed a baseline and at least 1 post baseline PRO assessment.

The PK concentration population was defined as all subjects in the SA population who had at least 1 concentration following treatment with at least 1 dose of crizotinib.

Analysis of Efficacy Parameters:

Primary Endpoint: PFS was defined as the time from the date of randomization to the date of the first documentation of objective tumor progression or death on study due to any cause, whichever occurred first. PFS was summarized using the FA population based on the IRR of the tumor imaging data. Differences in PFS between treatment arms were analyzed by 1-sided log-rank test stratified for baseline factors of ECOG PS (0-1 or 2), brain metastases (present or absent), and prior EGFR inhibitor treatment (yes or no). Estimates of the PFS curves obtained from the Kaplan-Meier method were presented and displayed graphically. The median event time (and other quartiles) and corresponding 2-sided 95% confidence interval (CI) were provided for each treatment arm. Additionally, for each treatment arm, the median PFS and a 2-sided 95% CI were provided for each level of the stratification variables and for subgroups of other relevant subject baseline characteristics. Cox regression models, adjusted for baseline stratification factors and other subject baseline characteristics, were fitted. The estimated hazard ratio (HR) and 2-sided 95% CI were provided. PFS was also analyzed by an unstratified log-rank test.

Secondary Endpoints: OS was defined as the time from randomization to the date of death due to any cause. Upon confirmation of progressive disease by the IRR, subjects in Arm B had the opportunity to receive crizotinib by enrolling in a previous open-label, multicenter, single arm study (Phase 2, Open-Label Single Arm Study of the Efficacy And Safety of PF-02341066 in subjects With Advanced Non-Small Cell Lung Cancer [NSCLC] Harboring a Translocation or Inversion Involving the ALK Gene Locus [NCT00932451]). For these subjects, survival follow-up data and follow-up systemic therapies were collected in the previous study. Data from both study databases were used for analysis of OS and reported under this study.

Differences in OS between treatment arms were analyzed by the 1-sided log-rank test stratified for baseline factors. Estimates of the OS curves obtained from the Kaplan-Meier method were presented. OS curves were also displayed graphically. The median event time (and other quartiles) and corresponding 2-sided 95% CI for the event times were provided for each treatment arm.

Cox regression models, adjusted for baseline stratification factors and other subject baseline characteristics, were fitted. The estimated HR and 2-sided 95% CI were provided. Six-month and 1-year survival probabilities were estimated using the Kaplan-Meier method together with the 2-sided 95% CI.

Subgroup analyses were provided for major baseline subject characteristics and for the baseline stratification factors: median OS (and other quartiles) and 2-sided 95% CI were estimated.

ORR was defined as the percent of subjects with complete response (CR) or partial response (PR) according to RECIST version 1.1 as assessed by the IRR, relative to the FA population. The ORR was summarized for each treatment arm along with the corresponding exact 2-sided 95% CI using a method based on the F-distribution. ORR between the 2 treatment arms was compared using a 2-sided Cochran-Mantel-Haenszel test stratified for baseline stratification factors and an unstratified test (2-sided Pearson). An analysis of ORR in the SA population was performed with chemotherapy arm separated for pemetrexed and

docetaxel. Disagreement rates between ORR based on IRR and Investigator assessments of tumor responses were presented.

DR was defined as the time from the first documentation of objective tumor response (CR or PR), as assessed by the IRR, to the first documentation of objective tumor progression, or to death due to any cause, whichever occurred first. DR was summarized in the subgroup of subjects with objective response from the FA population using the Kaplan-Meier method and was graphically displayed. The median event time (and other quartiles) and 2-sided 95% CI for the event times for each treatment arm were provided.

TTR was defined as the time from randomization to first documentation of objective tumor response (CR or PR) as assessed by the IRR. For subjects proceeding from PR to CR, the onset of PR was taken as the onset of response. TTR was calculated for the subgroup of subjects with objective tumor response. Descriptive statistics were provided.

DCR at 6 and 12 weeks was defined as the percent of subjects with CR, PR or stable disease (SD) at 6 and 12 weeks as assessed by the IRR, relative to the FA population. The best response of SD could have been assigned if SD criteria were met at least once after randomization at a minimum interval of 6 weeks. DCR was summarized for each treatment arm along with the corresponding exact 2-sided 95% CI using a method based on the F-distribution.

TTD in pain (pain in chest from quality of life questionnaire supplement module for Lung Cancer [QLQ-LC13]), dyspnea (from QLQ-LC13), or cough (from QLQ-LC13) symptoms was a composite endpoint and defined as the time from randomization to the earliest time the subject's scale scores showed a 10 point or greater increase after baseline in any of the 3 symptoms and was summarized using Kaplan-Meier methods. The median event time (and other quartiles) and corresponding 2-sided 95% CI for the event times were provided for each treatment arm. Treatment group comparison was performed using the unstratified log-rank test. Descriptive statistics by treatment group were reported for the change from baseline for each quality of life questionnaire-core 30 (QLQ-C30) and QLQ-LC13 domains and single item scores, and European quality of life 5-dimensional (EuroQoL 5D) - visual analog scale (EQ-5D VAS). Change from baseline scores were compared between treatment arms using repeated measures mixed effects modeling, with the baseline scores included as a covariate.

Safety data were analyzed using descriptive statistics.

RESULTS

Subject Disposition:

Based on the FA population, of the 347 subjects randomized into the study 172 subjects were treated with crizotinib, 99 subjects were treated with pemetrexed, and 72 subjects were treated with docetaxel.

End of Treatment (EOT):

All crizotinib- or chemotherapy-treated subjects permanently discontinued from study treatment. The most frequent reasons for permanent discontinuation of study treatment in either treatment arm were objective progression or relapse and global deterioration of health status (Table 3).

Table 3   Subject Disposition at End of Treatment by Treatment Arm - Full Analysis

Number (%) of Subjects	Crizotinib (N=173) n (%)	Chemotherapy (N=174) n (%)	Total (N=347) n (%)
Ongoing treatment	0	0	0
Randomized but not treated	1 (<1.0)	3 (1.7)	4 (1.2)
Discontinued treatment			
Reason for discontinuation from treatment:			
Completed	0	0	0
Adverse event	17 (9.8)	19 (10.9)	36 (10.4)
Global deterioration of health status	57 (32.9)	25 (14.4)	82 (23.6)
Lost to follow-up	0	0	0
Objective progression or relapse	57 (32.9)	105 (60.3)	162 (46.7)
Protocol violation	0	1 (<1.0)	1 (<1.0)
Study terminated by sponsor	0	0	0
Subject died	12 (6.9)	4 (2.3)	16 (4.6)
Subject refused continued treatment for reason other than adverse event[a]	9 (5.2)	2 (1.1)	11 (3.2)
Other	20 (11.6)	15 (8.6)	35 (10.1)
Total	172 (99.4)	171 (98.3)	343 (98.8)

Abbreviations: AE=adverse event; CRF=case report form; CSR=clinical study report; N/n=number of subjects.
[a]   End of Treatment CRF reason "Subject No Longer Willing to Continue Treatment for Reason Other Than AE" was mapped to "Subject Refused Continued Treatment for Reason Other Than Adverse Event".

End of Study:

All subjects discontinued from the study. The most common reason for discontinuation from the study was subject death (115 [66.5%] subjects) in the crizotinib arm and "other" reasons (mainly crossover to Study 1005) (144 [82.8%] subjects) in the chemotherapy arm (Table 4).

Table 4   Subject Disposition at End of Study by Treatment Arm - Full Analysis

Number (%) of Subjects	Crizotinib (N=173) n (%)	Chemotherapy (N=174) n (%)	Total (N=347) n (%)
Reason for discontinuation from study			
Completed[a]	40 (23.1)	4 (2.3)	44 (12.7)
Subject died	115 (66.5)	24 (13.8)	139 (40.1)
Study terminated by sponsor	0	0	0
Lost to follow-up	8 (4.6)	0	8 (2.3)
Subject refused further follow-up	5 (2.9)	2 (1.1)	7 (2.0)
Other	5 (2.9)	144 (82.8)	149 (42.9)
Total	173 (100)	174 (100)	347 (100)
Reason for Discontinuation was based on the Subject Summary at End of Study page. Abbreviations: CSR=clinical study report; N/n=number of subjects. [a] "Completed study follow-up" was only applicable when the required number of events for overall survival had been reported. At that time, the sponsor sent written notification to the clinical sites.			

Data Sets Analyzed:

A summary of data sets analyzed is provided in Table 5.

Table 5   Data Sets Analyzed

	Crizotinib	Chemotherapy	Total
Number randomized	173	174	347
Full analysis	173	174	347
Safety analysis	172	171	343
PRO evaluable	162	151	313
EORTC QLQ-C30	165	163	328
QLQ LC13	164	162	326
EQ-5D VAS	164	161	325
VSAQ-ALK evaluable population	101	104	205
PK evaluable	152	NA	152
Abbreviations: N=number of subjects; EORTC QLQ LC13 = European organization for the research and treatment of cancer quality of life questionnaire–supplement module for Lung Cancer (LC13); EORTC QLQ C30 = European organization for the research and treatment of cancer quality of life questionnaire-core 30; EQ-5D VAS = EuroQol 5D visual analog scale; VSAQ-ALK=Visual Symptom Assessment Questionnaire–ALK, EuroQol = European quality of life; NA = not applicable; PK = pharmacokinetic; PRO = patient-reported outcomes.			

Demographic Characteristics:

A summary of demographic characteristics by treatment arm in the FA population is provided in Table 6. Demographics were comparable between the 2 treatment arms.

Table 6   **Summary of Demographics by Treatment Arm – Full Analysis**

	Crizotinib (N=173)	Chemotherapy (N=174)	Total (N=347)
Sex, n (%)			
Male	75 (43.4)	79 (45.4)	154 (44.4)
Female	98 (56.6)	95 (54.6)	193(55.6)
Age (years)			
Mean (standard deviation)	50.3 (13.09)	49.8 (13.03)	50.0 (13.04)
Median	51.0	49.0	50.0
Range	22 – 81	24 – 85	22 – 85
Age category, n (%)			
<45 years	64 (37.0)	63 (36.2)	127 (36.6)
45-<55 years	40 (23.1)	47 (27.0)	87 (25.1)
55-<65 years	42 (24.3)	41(23.6)	93 (23.9)
≥65 years	27 (15.6)	23 (13.2)	50 (14.4)
Race, n (%)			
White	90 (52.0)	91(52.3)	181 (52.2)
Black	2 (1.2)	3 (1.7)	5 (1.4)
Asian	79 (45.7)	78 (44.8)	157 (45.2)
Racial designation for Asian			
Japanese	40 (23.1)	29 (16.7)	69 (19.9)
Korean	22 (12.7)	28 (16.1)	50 (14.4)
Chinese	14 (8.1)	18 (10.3)	32 (9.2)
Other	3 (1.7)	3 (1.7)	6 (1.7)
Other	2 (1.2)	2 (1.1)	4 (1.2)
Smoking classification, n (%)			
Never smoked	108 (62.4)	110 (63.2)	218 (62.8)
Ex-smoker	59 (34.1)	55 (31.6)	114 (32.9)
Smoker	5 (2.9)	9 (5.2)	14 (4.0)
Not reported[a]	1 (<1.0)	0	1 (<1.0)

Abbreviation: N/n=number of subjects.
[a] Smoking status for 1 subject was not reported; the subject was randomized but not treated and some, but not all, baseline information was collected.

Efficacy Results:

Primary Endpoints:

Progression-Free Survival:

A summary of PFS based on the IRR assessment by treatment arm is provided in Table 7.
Crizotinib more than doubled median PFS compared to chemotherapy, with a median PFS of
7.7 months for 173 subjects randomized to crizotinib and 3.0 months for 174 subjects
randomized to chemotherapy. The HR comparing crizotinib with chemotherapy was 0.487
(95% CI: 0.371, 0.638) with a p-value of <0.0001 (1-sided stratified log-rank test).

**Table 7   Summary of Progression-Free Survival Based on the Independent Radiology
Review Assessment by Treatment Arm – Full Analysis**

	Crizotinib (N=173)	Chemotherapy (N=174)
Number with event, n (%)	100 (57.8)	127 (73.0)
Objective progression	84 (48.6)	119 (68.4)
Death without objective progression	16 (9.2)	8 (4.6)
Number censored, n (%)	73 (42.2)	47 (27.0)
No adequate baseline assessments	0	0
No on-study disease assessments	3 (1.7)	2 (1.1)
Given new anti-cancer treatment prior to tumor progression	13 (7.5)	13 (7.5)
Withdrew consent for follow-up	2 (1.2)	0
Lost to follow-up	0	0
Unacceptable gap (>14 weeks) between PD or death to the most recent prior adequate assessment	1 (<1.0)	2 (1.1)
In follow-up for progression	51 (29.5)	30 (17.2)
No scans/data available	3 (1.7)	0
Probability of being event free at Month 6[a]	58.2	30.0
95% CI[b]	49.7, 65.8	22.7, 37.6
Kaplan-Meier estimate of time to event (months)		
25% percentile (95% CI)[c]	4.0 (2.9, 5.3)	1.4 (1.4, 1.6)
50% percentile (95% CI)[c]	7.7 (6.0, 8.8)	3.0 (2.6, 4.3)
75% percentile (95% CI)[c]	13.9 (11.1, 18.0)	7.0 (5.7, 9.8)
Vs chemotherapy		
Hazard ratio[d]	0.487	
95% CI of hazard ratio	0.371-0.638	
p-value[e]	<0.0001	

Abbreviations: PD=progressive disease; CI=confidence interval; EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitor; ECOG PS=Eastern Cooperative Oncology Group performance status; n/N=number of subjects; vs=versus.

[a.]   Estimated from the Kaplan-Meier curve.
[b.]   Calculated using the normal approximation to the log transformed cumulative hazard rate.
[c.]   Based on the Brookmeyer and Crowley method.
[d.]   Based on the Cox proportional hazards model stratified by ECOG PS score, brain metastases, prior EGFR-TKI treatment. Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favor of crizotinib.
[e.]   1-sided p-value from the log-rank test stratified by ECOG PS score, brain metastases, and prior EGFR-TKI treatment.

A summary of PFS based on the IRR assessment by study treatment (crizotinib vs pemetrexed and crizotinib vs docetaxel) is provided in Table 8. Subgroup analysis of crizotinib vs pemetrexed and crizotinib vs docetaxel demonstrated superior PFS in the crizotinib arm. The median PFS was 7.7 months for 172 subjects treated with crizotinib and 4.2 months for 99 subjects treated with pemetrexed and 2.6 months for 72 subjects treated with docetaxel.

Table 8   Summary of Progression-Free Survival Based on the Independent Radiology Review Assessment by Study Treatment (Crizotinib Versus Pemetrexed and Crizotinib Versus Docetaxel) – Safety Analysis

	Crizotinib (N=172)	Pemetrexed (N=99)	Docetaxel (N=72)
Number with event, n (%)	100 (58.1)	72 (72.7)	54 (75.0)
Objective progression	84 (48.8)	67 (67.7)	52 (72.2)
Death without objective progression	16 (9.3)	5 (5.1)	2 (2.8)
Kaplan-Meier estimate of time to event (months)			
Quartiles (95% CI)[a]			
25% percentile (95% CI)[c]	4.0 (2.9, 5.3)	1.5 (1.4, 2.5)	1.4 (1.3, 1.6)
50% percentile (95% CI)[c]	7.7 (6.0, 8.8)	4.2 (2.8, 5.7)	2.6 (1.6, 4.0)
75% percentile (95% CI)[c]	13.9 (11.1, 18.0)	9.5 (6.7, 11.3)	5.5 (4.0, 7.0)
Vs pemetrexed or docetaxel			
Hazard ratio[b]		0.589	
Hazard ratio[b]			0.298
95% CI of hazard ratio		0.431-0.804	0.207-0.428
p-value[c]		0.0004	<0.0001

Abbreviations: CI=confidence interval; EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitor; ECOG PS=Eastern Cooperative Oncology Group performance status; n/N=number of subjects; vs=versus.
[a.] Based on the Brookmeyer and Crowley method.
[b.] Based on the Cox proportional hazards model stratified by ECOG PS score, brain metastases, and prior EGFR-TKI treatment. Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favor of crizotinib.
[c.] 1-sided p-value from the log-rank test stratified by ECOG PS score, brain metastases, prior EGFR-TKI treatment.

Secondary endpoints:

Overall Survival:

A summary of OS by treatment arm is provided in Table 9. A total of 116 (67.1%) subjects in the crizotinib arm and 126 (72.4%) subjects in the chemotherapy arm were known to have died. Data of subjects not known to have died were censored at the time they were last known to be alive. Among these, a total of 41 (23.7%) subjects in the crizotinib arm and 32 (18.4%) subjects in the chemotherapy arm were in the follow-up for survival at the data cutoff. There was no statistically significant improvement in OS for crizotinib vs chemotherapy. There was, however, a numerical improvement in OS in the crizotinib arm (HR: 0.854; 95% CI: 0.661, 1.104 with a p-value of 0.1145; 1-sided stratified log-rank test). The median OS was 21.7 months for crizotinib and 21.9 months for chemotherapy.

The survival probabilities at 6 months and 12 months were comparable in the 2 treatment arms. The survival probabilities at 6 months were 86.6% (95% CI: 80.5%, 90.9%) and 83.8% (95% CI: 77.4%, 88.5%) for the crizotinib arm and the chemotherapy arm,

respectively; and the survival probabilities at 12 months were 70.4% (95% CI: 62.9%, 76.7%) and 66.7% (95% CI: 59.1%, 73.2%) for the crizotinib arm and the chemotherapy arm, respectively.

Table 9   Summary of Overall Survival by Treatment Arm- Full Analysis

	Crizotinib (N=173)	Chemotherapy (N=174)
Number of deaths, n (%)	116 (67.1)	126 (72.4)
Number censored, n (%)	57 (32.9)	48 (27.6)
Subject remains in follow-up	41 (23.7)	32 (18.4)
Subject no longer being followed for survival	3 (1.7)	5 (2.9)
Withdrew consent for follow-up	5 (2.9)	8 (4.6)
Lost to follow-up	8 (4.6)	3 (1.7)
Survival probability:[a]		
at 6 months (95% CI)[b]	86.6 (80.5, 90.9)	83.8 (77.4, 88.5)
at 12 months (95% CI)[b]	70.4 (62.9, 76.7)	66.7 (59.1, 73.2)
Kaplan-Meier estimate of time to event (month)		
25% percentile (95% CI)[c]	10.4 (8.0, 13.1)	9.8 (7.8, 11.5)
50% percentile (95% CI)[c]	21.7 (18.9, 30.5)	21.9 (16.8, 26.0)
75% percentile (95% CI)[c]	58.0 (47.4, NR)	51.3 (35.6, NR)
Versus chemotherapy		
Hazard ratio[d]	0.854	
95% CI of hazard ratio	0.661-1.104	
p-value[e]	0.1145	

Abbreviations: CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR-TKI=Epidermal growth factor receptor tyrosine kinase inhibitor; HR=hazard ratio; N/n=number of subjects; NR=not reached.
[a]   Estimated from the Kaplan-Meier curve.
[b]   Calculated using the normal approximation to the log transformed cumulative hazard rate.
[c]   Based on the Brookmeyer and Crowley Method.
[d]   Based on the Cox Proportional hazards model stratified by ECOG PS, brain metastases, prior EGFR-TKI treatment. Assuming proportional hazards, a HR less than 1 indicates a reduction in hazard rate in favor of crizotinib.
[e]   1-sided p-value from the log-rank test stratified by ECOG PS, brain metastases, prior EGFR-TKI treatment.

Objective Response Rate:

This study demonstrated a statistically significant improvement in ORR for crizotinib as assessed by the IRR. Crizotinib more than tripled ORR compared to chemotherapy with ORRs of 65% (95% CI: 58%, 72%) for crizotinib and 20% (95% CI: 14%, 26%) for chemotherapy with p<0.0001 (2-sided stratified Cochran-Mantel-Haenszel [CMH] test). A summary of best overall response based on the IRR by treatment arm is provided in Table 10.

Table 10. Summary of Best Overall Response Based on the Independent Radiology Review Assessment by Treatment Arm – Full Analysis

	Crizotinib (N=173)	Chemotherapy (N=174)
Best overall response, n (%)		
Complete response	1 (<1.0)	0
Partial response	112 (64.7)	34 (19.5)
Stable disease for at least 6 weeks	32 (18.5)	63 (36.2)
Objective progression	11 (6.4)	60 (34.5)
Early death	4 (2.3)	4 (2.3)
Indeterminate	13 (7.5)	13 (7.5)
Objective response rate (CR+PR), n (%)	113 (65.3)	34 (19.5)
95% Exact CI[a]	57.7, 72.4	13.9, 26.2
SD duration (months)[b], n (%)		
0 to <3 months	13 (40.6)	23 (36.5)
3 to <6 months	9 (28.1)	24 (38.1)
6 to <9 months	8 (25.0)	10 (15.9)
9 to <12 months	2 (6.3)	1 (1.6)
≥12 months	0	5 (7.9)
Treatment comparison (vs chemotherapy)		
Treatment difference in ORR rate[c]	45.8	
95% CI of difference[c]	36.6, 55.0	
p-value[d]	<0.0001	
Treatment comparison (vs chemotherapy)		
Risk ratio[e]	3.4	
95% CI of risk ratio[e]	2.5, 4.7	
p-value[e]	<0.0001	

Best overall response was based on the independent radiology review.
Early death was death within 6 weeks (42 days) from randomization.
Abbreviations: CR=complete response; PR=partial response; CI=confidence interval; ORR=objective response rate; EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitor; ECOG PS=Eastern Cooperative Oncology Group performance status; SD=stable disease; vs=versus; N/n=number of subjects.
[a.] Using exact method based on F-distribution.
[b.] % was based on the number of SD subjects.
[c.] Calculated based on a normal distribution.
[d.] p-value was from a Pearson chi-square test.
[e.] Calculated from Cochran-Mantel-Haenszel (CMH) test stratified by ECOG-PS score, brain metastases, and prior EGFR-TKI treatment.

Disease Control Rate:

Summary of Disease Control Rate at Week 6 and Week 12 Based on the Independent Radiology Review Assessment by Treatment Arm is provided in Table 11.

Table 11   Summary of Disease Control Rate at Week 6 and Week 12 Based on the Independent Radiology Review Assessment by Treatment Arm – Full Analysis

	Crizotinib (N=173)	Chemotherapy (N=174)
Disease control rate at Week 6, n (%)	141 (81.5)	96 (55.2)
95% exact CI[a]	74.9, 87.0	47.5, 62.7
Treatment comparison (vs chemotherapy)		
Treatment difference in DCR rate[b]	26.3	
95% CI of difference[b]	16.9, 35.7	
p-value[c]	<0.0001	
Treatment comparison (vs chemotherapy)		
Risk ratio[d]	1.5	
95% CI of risk ratio[d]	1.3, 1.7	
p-value[e]	<0.0001	
Disease control rate at Week 12, n (%)	111 (64.2)	67 (38.5)
95% exact CI[a]	56.5, 71.3	31.2, 46.2
Treatment comparison (vs chemotherapy)		
Treatment difference in DCR rate[b]	25.7	
95% CI of difference[b]	15.5, 35.8	
P value[c]	<0.0001	
Treatment comparison (vs chemotherapy)		
Risk ratio[d]	1.7	
95% CI of risk ratio[d]	1.4, 2.1	
p-value[d]	<0.0001	

Abbreviations: CI=confidence interval; EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitor; ECOG PS=Eastern Cooperative Oncology Group performance status; DCR=disease control rate; n/N=number of subjects.
[a]   Using exact method based on F-distribution.
[b]   Calculated based on a normal distribution.
[c]   P-value was from a Pearson chi-square test.
[d]   Calculated from Cochran-Mantel-Haenszel (CMH) test stratified by ECOG PS score, brain metastases, and prior EGFR-TKI treatment.

Duration of Response:

Summary of Duration of Response Based on the Independent Radiology Review Assessment by Treatment Arm is provided in Table 12.

Table 12   Summary of Duration of Response Based on the Independent Radiology Review Assessment by Treatment Arm – Full Analysis (Objective Responders Only)

	Crizotinib (N=173)	Chemotherapy (N=174)
Number of subjects with objective response (CR or PR), n (%)	113 (65.3)	34 (19.5)
Objective response (CR or PR) status[a], n (%)		
With subsequent progression or death	61 (54.0)	20 (58.8)
Duration of response (weeks)[b]		
Mean (standard deviation)	25.4 (16.3)	17.3 (10.9)
Median	19	14.2
Range	2.1-72.4	3.0-43.6
Without subsequent progression or death	52 (46.0)	14 (41.2)
Kaplan-Meier estimates of duration of response (weeks)		
25% percentile (95% CI)[c]	17.7 (12.9, 23.1)	12.1 (7.0, 19.1)
50% percentile (95% CI)[c]	32.1 (26.4, 42.3)	24.4 (15.0, 36.0)
75% percentile (95% CI)[c]	61.4 (43.6, NR)	43.6 (25.1, 43.6)

Duration of response was the time from the date of first documentation of CR or PR to the date of first documentation of objective disease progression or death due to any cause.

Abbreviations: CR=complete response; PR=partial response; CI=confidence interval; NR=not reached; N/n=number of subjects.

[a].   % based on the number of subjects with objective response (CR or PR).
[b].   Descriptive statistics are presented for subjects with subsequent progression or death.
[c].   Based on the Brookmeyer and Crowley method.

Time to Tumor Response:

Summary of Time to Tumor Response Based on the Independent Radiology Review Assessment by Treatment Arm is provided in Table 13.

Table 13   Summary of Time to Tumor Response Based on the Independent Radiology Review Assessment by Treatment Arm – Full Analysis (Objective Responders Only)

	Crizotinib (N=173)	Chemotherapy (N=174)
Time to response (weeks)[a]		
N	113	34
Mean (standard deviation)	8.6 (6.2)	16.9 (10.1)
Median	6.3	12.6
Range	4.4-48.4	5.0-37.1
Category (weeks)[b]		
0 to <6	15 (13.3)	5 (14.7)
6 to <12	76 (67.3)	9 (26.5)
12 to <18	17 (15.0)	5 (14.7)
18 to <24	1 (0.9)	5 (14.7)
≥24	4 (3.5)	10 (29.4)

Time to response was the time from the randomization date to the first documentation of objective tumor response (CR or PR).

Abbreviations: N=number of subjects; CR=complete response; PR=partial response.

[a].   Descriptive statistics are presented for subjects with an event.
[b].   Category was presented for subjects with an event.

Time to Deterioration:

Summary of Time to Deterioration in Pain (in Chest), Dyspnea, or Cough (Composite Endpoint) by Arm is provided in Table 14.

Table 14   Summary of Time to Deterioration in Pain (in Chest), Dyspnea, or Cough (Composite Endpoint) by Arm – PRO Evaluable

	Crizotinib (N=162)	Chemotherapy (N=151)
Number with event, n (%)	91 (56.5)	111 (74.0)
Deterioration of symptom	91 (56.5)	111 (74.0)
Number censored, n (%)	70 (43.5)	39 (26.0)
No deterioration	70 (43.5)	39 (26.0)
Probability of being event free at Month 6[a] (95% CI [b])	46.2 (37.6, 54.4)	18.3 (11.5, 26.4)
Kaplan-Meier estimate of time to event (months)		
25% percentile (95% CI)[c]	1.3 (0.8, 1.6)	0.8 (0.8, 0.9)
50% percentile (95% CI)[c]	4.5 (3.0, 6.9)	1.4 (1.0, 1.6)
75% percentile (95% CI)[c]	18.7 (12.5, NR)	3.9 (2.4, 8.3)
Vs chemotherapy		
Hazard ratio[d]	0.497	
95% CI of hazard ratio	0.373, 0.661	
p-value[e]	<0.0001	

Time to deterioration was defined as the first occurrence of a 10-point or more increase in scores from baseline in symptoms of pain in chest (EORTC QLQ-LC13 pain in chest), cough (EORTC QLQ-LC13 cough), or dyspnea (EORTC QLQ-LC13 dyspnea); otherwise censored at date of last questionnaire. PRO evaluable subjects with either a missing baseline or follow-up symptom values are not included in summary.

Abbreviations: PRO=subject-reported outcomes; n/N=number of subjects; CI=confidence interval; NR=not reached; Vs=versus; EORTC QLQ-LC13=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire–supplement module for Lung Cancer (LC13).

[a.]   Estimated from the Kaplan-Meier curve.
[b.]   Calculated using the normal approximation to the log transformed cumulative hazard rate.
[c.]   Based on the Brookmeyer and Crowley Method.
[d.]   Based on the Cox Proportional hazards model. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of crizotinib.
[e.]   2-sided p-value from the unstratified log-rank test.

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

The change from baseline scores were found to be significantly different between the 2 treatment arms, with a significantly greater improvement observed in the crizotinib arm compared to the chemotherapy arm in global quality of life (p<0.0001), emotional functioning (p<0.05), physical functioning (p<0.0001), role functioning (p<0.05), and social functioning (p<0.05). The change from baseline scores for cognitive functioning between the crizotinib and chemotherapy arms were not significantly different.

The change from baseline was found to be significantly different between the 2 treatment arms, with a significantly greater improvement observed in the crizotinib arm compared to the chemotherapy arm in appetite loss (p<0.05), dyspnea (p<0.0001), fatigue (p<0.0001), insomnia (p<0.0001), and pain (p<0.0001). The change from baseline was found to be statistically significantly different between the 2 treatment arms, with a significantly greater

deterioration observed in the crizotinib arm compared to the chemotherapy arm for constipation (p<0.05) and diarrhea (p<0.0001). The difference in change from baseline scores between the crizotinib and chemotherapy arms was not statistically significant for nausea/vomiting.

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

The change from baseline was found to be significantly different between the 2 treatment arms, with a significantly greater improvement observed in the crizotinib arm compared to the chemotherapy arm in alopecia (p<0.0001), coughing (p<0.0001), dyspnea (p<0.0001), haemoptysis (p<0.05), pain in arm or shoulder (p<0.0001), pain in chest (p<0.0001), and pain in other parts (p<0.0001). Significantly greater deterioration from baseline was observed in the chemotherapy arm compared to crizotinib for the symptoms of peripheral neuropathy (p<0.05), dysphagia (p<0.05), and sore mouth (p<0.001).

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

The EQ-5D VAS records the subjects self-rated general health status on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). The results of the within subjects analyses showed a statistically significant (p<0.05) improvement from baseline in EQ-5D VAS scores in the crizotinib arm (Cycles 2 to 15) and no statistically significant change from baseline in the chemotherapy arm. The change from baseline in EQ-5D VAS scores was found to be statistically significantly different (p<0.001) between the 2 treatment arms, with a statistically significantly greater improvement observed in the crizotinib arm compared to the chemotherapy arm.

Visual Symptom Assessment Questionnaire

Subjects were instructed to complete Questions 2-7 of the VSAQ-ALK only if they indicated that they had a visual disturbance in Question 1 ("Have you experienced any visual disturbances?"). The number of chemotherapy-treated subjects who had completed Questions 2-7 of the VSAQ-ALK were much lower (n<20) than crizotinib-treated subjects as the majority reported not having a visual disturbance on the first question. Completion rates of all questions of the VSAQ-ALK questionnaire ranged from 59.6% to 93.1% for subjects treated with crizotinib over the first 30 cycles and 62.8% to 84.2% for subjects treated with chemotherapy over the first 10 cycles.

A total of 31.3% to 63.4% of crizotinib-treated subjects (up to Cycle 30) and 16.7% to 26.7% of chemotherapy-treated subjects (up to Cycle 10) had experienced visual disturbance. Among crizotinib-treated subjects who reported experiencing a visual disturbance in the first 30 cycles, the majority (range: 73.9% to 100%) had event frequency of >1 day per week; a total of 39.1% to 72.7%, 4.4% to 60.0% and 60.0% to 87.0% subjects had reported occurrence of visual disturbances in the morning, afternoon and evening within the first 30 cycles, respectively.

Among chemotherapy-treated subjects, based on the first 10 cycles, the majority (range: 58.3% to 100%) of subjects had event frequency of >1 day per week; a total of 41.7%

to 80.0%, 60.0% to 100% and 40.0% to 80.0% subjects had reported visual disturbances in the morning, afternoon, and evening within the first 10 cycles, respectively.

Most crizotinib-treated and chemotherapy-treated subjects had reported that each event had lasted for about ≤1 minute. The most commonly experienced visual disturbances in crizotinib-treated subjects were appearance of shimmering/flashing/trailing lights, streamers/strings/floaters, and overlapping shadows/after images and in chemotherapy-treated subjects was hazy/blurry vision.

In crizotinib-treated subjects, the occurrence of visual disturbance had produced not at all or little bothersome and most subjects indicated no or minimal impact (score 0 to 3) on daily activities at each cycle.

Pharmacokinetic endpoints:

Summary of Predose Concentrations (C_{trough}) of Crizotinib and its Metabolite, PF-06260182, and PF-06260182 to Crizotinib Ratio, Following 250 mg BID Oral Dosing of Crizotinib is provided in Table 15.

Table 15   Summary of Predose Concentrations (C_{trough}) of Crizotinib and its Metabolite, PF-06260182, and PF-06260182 to Crizotinib Ratio, Following 250 mg BID Oral Dosing of Crizotinib

Parameter	C_{trough}^{a} (ng/mL)			
	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 5 Day 1
N/n	15/13	62/55	61/59	47/46
Crizotinib	BLQ	293 (47)	306 (41)	291 (49)
PF-06260182	BLQ	81.3 (54)	85.7 (54)	87.1 (50)
PF-06260182 to crizotinib ratio	NA	0.267 (23)	0.267 (28)	0.291 (22)

Note: N=number of observations for crizotinib and n=number of observations for PF-06260182 and PF-06260182 to crizotinib ratio. The PF-06260182 to crizotinib ratio for plasma concentrations was calculated by ([concentration of PF-06260182]/[concentration of crizotinib])*([molecular weight of crizotinib (450.34)/molecular weight of PF-06260182 (464.33)]).
Abbreviations: C_{trough}=trough concentration; BID=twice daily; BLQ=below the lower limit of quantification; CV=coefficient of variation; NA=not applicable.
a.   Geometric mean (%CV).

Electrocardiograms:

The majority (88.4%) of crizotinib-treated subjects had maximum post-dose QTcF <450 msec (Table 16). Eight crizotinib-treated subjects (5.2%) had QTcF ≥500 msec.

Table 16   Categorization of Electrocardiogram Data, Maximum Postdose (Crizotinib Arm) - Safety Analysis

	Crizotinib	
	N	**n (%)**
Maximum QTcF		
<450 msec	155	137 (88.4)
450 to <480 msec	155	9 (5.8)
480 to <500 msec	155	1 (0.6)
≥500 msec	155	8 (5.2)
Table does not include subjects who participated in the ECG substudy. Abbreviations: N=number of subjects with a postbaseline assessment; n=number of subjects; QTcF=corrected QT interval using Fridericia's correction; ECG=electrocardiogram.		

Pharmacodynamic Results

Molecular Profiling (ALK status)

Subjects NSCLC were determined to be ALK-positive by an investigational-use only (IUO) diagnostic test from Abbott Molecular.

A summary of descriptive statistics for percentage of ALK-positive cells by the central laboratory IUO test (Abbott Molecular) is provided in Table 17.

Mean and median percentages of ALK-positive cells were similar between the 2 treatment arms.

Table 17   Descriptive Statistics for ALK Percentage of Positive Cells by Central Laboratory Test by Treatment Arm – Full Analysis

	Crizotinib (N=173)	Chemotherapy (N=174)
ALK percentage of positive cells (%)		
N	173	173[a]
Mean (standard deviation)	57.4 (21.80)	59.5 (20.05)
Median	58.0	58.0
Range	15.0-98.0	15.0-98.0
ALK+ by IUO includes all enrolled subjects with IOU data and ALK+. Abbreviations: N/n=number of subjects; ALK= anaplastic lymphoma kinase; IUO=investigational-use only; FISH=fluorescence in-situ hybridization. [a]. One subject on chemotherapy was ALK+ identified by local laboratory only, using FISH.		

Molecular Profiling Outcomes

Analyses investigating the relationship of ALK gene fusion to the presence of ALK protein and fusion transcript have not been performed for technical reasons, including limited sample stability.

Biomarkers

Plasma concentrations of soluble c-Met ectodomain protein are provided in Table 18. No statistically significant differences were observed in comparisons of on-treatment to baseline values or between objective response categories.

Table 18   Plasma Concentration of Soluble c-Met Ectodomain Protein in the Crizotinib Treatment Arm

	Plasma concentration (ng/ml)	
Number of samples analyzed (N)	172	
	Mean	Standard Deviation
Baseline (N=81)	1428.3	363.9
Cycle 2 Day 1 6 hour post dose (N=69)	1683.0	325.6
End of treatment (N=40)	1751.8	327.9

Safety Results:

Treatment-emergent adverse events due to all-causality and treatment-related are summarized in Table 19. Almost all subjects experienced treatment-related AEs (95.3% crizotinib-treated subjects, 83.8% pemetrexed -treated subjects and 95.8% docetaxel-treated subjects). A total of 13.4% of crizotinib-treated subjects, 9.1% of pemetrexed-treated subjects and 20.8% of docetaxel-treated subjects had treatment-related SAEs. None of the safety analyses was adjusted for the longer duration of crizotinib treatment than the duration of chemotherapy treatment (median 48 and 13 weeks, respectively).

Table 19   Treatment-Emergent Adverse Events by Treatment (All-Causality and Treatment-Related) – Safety Analysis

	Crizotinib (N=172) n (%)		Chemotherapy	
	All-Causality	Treatment-Related	All-Causality	Treatment-Related
Number of AEs	2741	1499	1430	845
Subjects with AEs	172 (100.0)	164 (95.3)	169 (98.8)	152 (88.9)
Subjects with SAEs	80 (46.5)	23 (13.4)	42 (24.6)	24 (14.0)
Subjects with Grade 3 or 4 AEs	111 (64.5)	67 (39.0)	82 (48.0)	58 (33.9)
Subjects with Grade 5 AEs	30 (17.4)	3 (1.7)	7 (4.1)	1 (0.6)
Subjects discontinued due to AEs	34 (19.8)	11 (6.4)	34 (19.9)	21 (12.3)
Subjects with dose reduced due to AEs	29 (16.9)	26 (15.1)	24 (14.0)	23 (13.5)
Subjects with temporary discontinuation due to AEs	83 (48.3)	64 (37.2)	28 (16.4)	17 (9.9)

Includes all AE data captured in the database.
Except for the Number of AEs, subjects counted only once per treatment group in each row.
SAEs - according to the investigator's assessment.
MedDRA (v18.1) coding dictionary applied.
Abbreviations: AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of subjects; SAE=serious adverse event; v=version.

Non-Serious adverse events (NSAEs):

NSAEs above the 5% threshold are summarized in Table 20.

Table 20   Non-Serious adverse events (NSAEs):

	Crizotinib n (%)		Chemotherapy n (%)	
Number (%) of Subjects:	**All-Causality**	**Treatment-Related**	**All-Causality**	**Treatment-Related**
Evaluable for adverse events	172		171	
With adverse events	171 (99.42)	162 (94.19)	157 (91.81)	136 (79.53)
Number (%) of Subjects with Adverse Events by System Organ Class and MedDRA (v18.1) Preferred Term				
BLOOD AND LYMPHATIC SYSTEM DISORDERS	65 (37.79)	55 (31.98)	43 (25.15)	38 (22.22)
Anaemia	36 (20.93)	20 (11.63)	27 (15.79)	23 (13.45)
Leukopenia	24 (13.95)	24 (13.95)	9 (5.26)	9 (5.26)
Neutropenia	41 (23.84)	39 (22.67)	18 (10.53)	16 (9.36)
CARDIAC DISORDERS	9 (5.23)	9 (5.23)	0	0
Bradycardia	9 (5.23)	9 (5.23)	0	0
EYE DISORDERS	98 (56.98)	96 (55.81)	22 (12.87)	6 (3.51)
Lacrimation increased	1 (0.58)		9 (5.26)	
Photopsia	21 (12.21)	21 (12.21)	1 (0.58)	1 (0.58)
Vision blurred	13 (7.56)	10 (5.81)	5 (2.92)	4 (2.34)
Visual impairment	74 (43.02)	73 (42.44)	8 (4.68)	2 (1.17)
GASTROINTESTINAL DISORDERS	158 (91.86)	145 (84.30)	101 (59.06)	88 (51.46)
Abdominal pain	18 (10.47)		8 (4.68)	
Abdominal pain upper	17 (9.88)	10 (5.81)	13 (7.60)	5 (2.92)
Constipation	83 (48.26)	62 (36.05)	39 (22.81)	32 (18.71)
Diarrhoea	106 (61.63)	94 (54.65)	34 (19.88)	29 (16.96)
Dyspepsia	18 (10.47)	11 (6.40)	6 (3.51)	4 (2.34)
Dysphagia	9 (5.23)		2 (1.17)	
Gastrooesophageal reflux disease	12 (6.98)		0	
Nausea	104 (60.47)	94 (54.65)	60 (35.09)	57 (33.33)

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	Crizotinib n (%)		Chemotherapy n (%)	
Stomatitis	9 (5.23)	8 (4.65)	13 (7.60)	12 (7.02)
Vomiting	88 (51.16)	79 (45.93)	32 (18.71)	24 (14.04)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	132 (76.74)	92 (53.49)	112 (65.50)	81 (47.37)
Asthenia	31 (18.02)	18 (10.47)	32 (18.71)	22 (12.87)
Chest pain	15 (8.72)		13 (7.60)	
Fatigue	51 (29.65)	31 (18.02)	60 (35.09)	51 (29.82)
Oedema	15 (8.72)	11 (6.40)	6 (3.51)	2 (1.17)
Oedema peripheral	59 (34.30)	50 (29.07)	15 (8.77)	7 (4.09)
Pain	10 (5.81)		9 (5.26)	
Pyrexia	41 (23.84)	9 (5.23)	33 (19.30)	19 (11.11)
INFECTIONS AND INFESTATIONS	50 (29.07)		20 (11.70)	
Nasopharyngitis	32 (18.60)		7 (4.09)	
Upper respiratory tract infection	24 (13.95)		14 (8.19)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11 (6.40)		3 (1.75)	
Fall	11 (6.40)		3 (1.75)	
INVESTIGATIONS	103 (59.88)	88 (51.16)	46 (26.90)	37 (21.64)
Alanine aminotransferase increased	72 (41.86)	68 (39.53)	21 (12.28)	19 (11.11)
Aspartate aminotransferase increased	55 (31.98)	51 (29.65)	17 (9.94)	14 (8.19)
Blood alkaline phosphatase increased	18 (10.47)	12 (6.98)	6 (3.51)	4 (2.34)
Blood creatinine increased	13 (7.56)	10 (5.81)	3 (1.75)	1 (0.58)
Electrocardiogram QT prolonged	9 (5.23)		0	
Neutrophil count decreased	15 (8.72)	14 (8.14)	9 (5.26)	9 (5.26)
Weight decreased	21 (12.21)	12 (6.98)	8 (4.68)	4 (2.34)
White blood cell count decreased	16 (9.30)	15 (8.72)	13 (7.60)	12 (7.02)
METABOLISM AND NUTRITION DISORDERS	79 (45.93)	46 (26.74)	56 (32.75)	37 (21.64)
Decreased appetite	56 (32.56)	37 (21.51)	46 (26.90)	37 (21.64)
Hyperglycaemia	12 (6.98)		9 (5.26)	
Hypoalbuminaemia	16 (9.30)	10 (5.81)	1 (0.58)	0
Hypocalcaemia	13 (7.56)		0	

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	Crizotinib n (%)		Chemotherapy n (%)	
Hypokalaemia	15 (8.72)		5 (2.92)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	63 (36.63)	5 (2.91)	54 (31.58)	24 (14.04)
Arthralgia	15 (8.72)	3 (1.74)	20 (11.70)	12 (7.02)
Back pain	30 (17.44)		11 (6.43)	
Muscle spasms	9 (5.23)		4 (2.34)	
Musculoskeletal pain	14 (8.14)		6 (3.51)	
Myalgia	5 (2.91)	2 (1.16)	19 (11.11)	18 (10.53)
Neck pain	11 (6.40)		5 (2.92)	
Pain in extremity	20 (11.63)		10 (5.85)	
NERVOUS SYSTEM DISORDERS	100 (58.14)	62 (36.05)	55 (32.16)	31 (18.13)
Dizziness	34 (19.77)	16 (9.30)	13 (7.60)	8 (4.68)
Dysgeusia	45 (26.16)	43 (25.00)	17 (9.94)	17 (9.94)
Headache	46 (26.74)	11 (6.40)	26 (15.20)	11 (6.43)
Neuropathy peripheral	5 (2.91)		10 (5.85)	
Paraesthesia	13 (7.56)		7 (4.09)	
Peripheral sensory neuropathy	9 (5.23)		6 (3.51)	
Visual perseveration	12 (6.98)	12 (6.98)	0	0
PSYCHIATRIC DISORDERS	19 (11.05)		13 (7.60)	
Insomnia	19 (11.05)		13 (7.60)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	72 (41.86)		75 (43.86)	
Cough	37 (21.51)		35 (20.47)	
Dyspnoea	27 (15.70)		29 (16.96)	
Epistaxis	3 (1.74)		10 (5.85)	
Haemoptysis	9 (5.23)		11 (6.43)	
Oropharyngeal pain	20 (11.63)		7 (4.09)	
Productive cough	12 (6.98)		8 (4.68)	
Pulmonary embolism	9 (5.23)		2 (1.17)	
Rhinorrhoea	4 (2.33)		9 (5.26)	
SKIN AND SUBCUTANEOUS TISSUE	47 (27.33)	22 (12.79)	62 (36.26)	57 (33.33)

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	Crizotinib n (%)		Chemotherapy n (%)	
DISORDERS				
Alopecia	21 (12.21)	5 (2.91)	35 (20.47)	34 (19.88)
Dry skin	10 (5.81)		2 (1.17)	
Pruritus	12 (6.98)		7 (4.09)	
Rash	23 (13.37)	18 (10.47)	30 (17.54)	29 (16.96)

Subjects are only counted once per treatment for each row.
MedDRA (v18.1) coding dictionary applied.

Serious Adverse Events (SAEs):

SAEs are summarized in Table 21.

Table 21   Serious Adverse Events (SAEs):

	Crizotinib n (%)		Chemotherapy n (%)	
Number (%) of Subjects:	**All-Causality**	**Treatment-Related**	**All-Causality**	**Treatment-Related**
Evaluable for adverse events	172		171	
With adverse events	80 (46.51)	23 (13.37)	42 (24.56)	24 (14.04)
Number (%) of Subjects with Adverse Events by System Organ Class and MedDRA (v18.1) Preferred Term				
BLOOD AND LYMPHATIC SYSTEM DISORDERS	6 (3.49)	2 (1.16)	14 (8.19)	14 (8.19)
Anaemia	2 (1.16)	0	2 (1.17)	2 (1.17)
Febrile neutropenia	1 (0.58)	1 (0.58)	12 (7.02)	12 (7.02)
Lymphadenopathy	1 (0.58)		0	
Neutropenia	2 (1.16)	1 (0.58)	2 (1.17)	2 (1.17)
Thrombocytopenia	0	0	1 (0.58)	1 (0.58)
CARDIAC DISORDERS	6 (3.49)	3 (1.74)	3 (1.75)	1 (0.58)
Arrhythmia	1 (0.58)	1 (0.58)	0	0
Cardiac arrest	1 (0.58)	1 (0.58)	0	0
Cardiac tamponade	1 (0.58)	0	1 (0.58)	1 (0.58)
Coronary artery disease	1 (0.58)		0	
Myocardial ischaemia	1 (0.58)		0	
Pericardial effusion	1 (0.58)	0	2 (1.17)	1 (0.58)
Supraventricular tachycardia	0		1 (0.58)	
Syncope	1 (0.58)	1 (0.58)	0	0
GASTROINTESTINAL DISORDERS	7 (4.07)	2 (1.16)	4 (2.34)	2 (1.17)
Abdominal pain upper	1 (0.58)	1 (0.58)	0	0
Diarrhoea	1 (0.58)	1 (0.58)	0	0
Food poisoning	1 (0.58)		0	
Haematemesis	1 (0.58)		0	

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	Crizotinib n (%)		Chemotherapy n (%)	
Ileus paralytic	1 (0.58)		0	
Intestinal perforation	1 (0.58)		0	
Melaena	0		1 (0.58)	
Nausea	1 (0.58)	1 (0.58)	2 (1.17)	1 (0.58)
Oesophageal stenosis	1 (0.58)		0	
Stomatitis	0	0	1 (0.58)	1 (0.58)
Vomiting	3 (1.74)	2 (1.16)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	23 (13.37)	2 (1.16)	10 (5.85)	4 (2.34)
Chest pain	0		2 (1.17)	
Death	2 (1.16)		0	
Disease progression	18 (10.47)		3 (1.75)	
Fatigue	1 (0.58)	1 (0.58)	1 (0.58)	1 (0.58)
General physical health deterioration	1 (0.58)		0	
Malaise	1 (0.58)	1 (0.58)	0	0
Mucosal inflammation	0	0	2 (1.17)	2 (1.17)
Product contamination microbial	0		1 (0.58)	
Pyrexia	1 (0.58)	1 (0.58)	1 (0.58)	1 (0.58)
Sudden death	1 (0.58)		0	
HEPATOBILIARY DISORDERS	2 (1.16)	2 (1.16)	0	0
Hepatic failure	1 (0.58)	1 (0.58)	0	0
Hepatitis	1 (0.58)	1 (0.58)	0	0
INFECTIONS AND INFESTATIONS	19 (11.05)	2 (1.16)	6 (3.51)	
Cellulitis	2 (1.16)		0	
Empyema	1 (0.58)		0	
Extradural abscess	1 (0.58)		0	
Gastroenteritis	1 (0.58)		0	
Lower respiratory tract infection	2 (1.16)		2 (1.17)	
Lung abscess	2 (1.16)		0	
Lung infection	2 (1.16)		1 (0.58)	

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	Crizotinib n (%)		Chemotherapy n (%)	
Pneumonia	8 (4.65)	2 (1.16)	3 (1.75)	1 (0.58)
Pneumonia bacterial	1 (0.58)		0	
Pneumonia influenzal	1 (0.58)		0	
Sepsis	1 (0.58)	0	1 (0.58)	1 (0.58)
Urinary tract infection	0	0	1 (0.58)	1 (0.58)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (1.16)		1 (0.58)	
Femur fracture	1 (0.58)		1 (0.58)	
Spinal fracture	1 (0.58)		0	
INVESTIGATIONS	5 (2.91)	4 (2.33)	0	3 (1.75)
Alanine aminotransferase increased	3 (1.74)	3 (1.74)	0	0
Aspartate aminotransferase increased	2 (1.16)	2 (1.16)	0	0
Blood glucose increased	1 (0.58)		0	
Electrocardiogram QT prolonged	1 (0.58)	1 (0.58)	0	0
Haemoglobin	0	0	1 (0.58)	1 (0.58)
Neutrophil count decreased	0	0	1 (0.58)	1 (0.58)
White blood cell count decreased	0	0	2 (1.17)	1 (0.58)
METABOLISM AND NUTRITION DISORDERS	5 (2.91)	2 (1.16)	2 (1.17)	1 (0.58)
Decreased appetite	2 (1.16)	2 (1.16)	1 (0.58)	1 (0.58)
Hyperglycaemia	1 (0.58)		0	
Hyperkalaemia	1 (0.58)	1 (0.58)	0	0
Hypoglycaemia	2 (1.16)		1 (0.58)	
Hypokalaemia	1 (0.58)		0	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4 (2.33)		3 (1.75)	
Back pain	2 (1.16)		2 (1.17)	
Muscular weakness	1 (0.58)		0	
Musculoskeletal pain	0		1 (0.58)	
Spinal column stenosis	1 (0.58)		0	

	Crizotinib n (%)		Chemotherapy n (%)	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0		2 (1.17)	
Colon cancer	0		1 (0.58)	
Colon cancer recurrent	0		1 (0.58)	
Tumour haemorrhage	0		1 (0.58)	
NERVOUS SYSTEM DISORDERS	10 (5.81)	0	3 (1.75)	1 (0.58)
Brain oedema	1 (0.58)		0	
Cerebral cyst	1 (0.58)		0	
Dizziness	1 (0.58)		0	
Headache	1 (0.58)	0	2 (1.17)	1 (0.58)
Intracranial pressure increased	2 (1.16)		0	
Lethargy	1 (0.58)		0	
Paraesthesia	1 (0.58)		0	
Presyncope	1 (0.58)		0	
Seizure	2 (1.16)		1 (0.58)	
PSYCHIATRIC DISORDERS	2 (1.16)		1 (0.58)	
Confusional state	0		1 (0.58)	
Delirium	1 (0.58)		0	
Mental status changes	1 (0.58)		0	
RENAL AND URINARY DISORDERS	2 (1.16)	1 (0.58)	0	0
Renal cyst	1 (0.58)	1 (0.58)	0	0
Ureteric stenosis	1 (0.58)		0	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	23 (13.37)	6 (3.49)	10 (5.85)	3 (1.75)
Acute respiratory distress syndrome	1 (0.58)		0	
Acute respiratory failure	1 (0.58)	1 (0.58)	0	0
Cough	1 (0.58)		0	
Dyspnoea	6 (3.49)		2 (1.17)	
Interstitial lung disease	3 (1.74)	3 (1.74)	0	0
Organising pneumonia	0	0	1 (0.58)	1 (0.58)
Pleural effusion	2 (1.16)		3 (1.75)	

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	Crizotinib n (%)		Chemotherapy n (%)	
Pneumonitis	1 (0.58)	1 (0.58)	0	0
Pulmonary artery thrombosis	1 (0.58)	1 (0.58)	0	0
Pulmonary embolism	7 (4.07)	0	3 (1.75)	1 (0.58)
Pulmonary oedema	0	0	1 (0.58)	1 (0.58)
Respiratory failure	1 (0.58)		0	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.58)	1 (0.58)	0	0
Drug eruption	1 (0.58)	1 (0.58)	0	0
SURGICAL AND MEDICAL PROCEDURES	1 (0.58)		0	
Cancer surgery	1 (0.58)		0	
VASCULAR DISORDERS	2 (1.16)	1 (0.58)	2 (1.17)	2 (1.17)
Deep vein thrombosis	1 (0.58)		2 (1.17)	
Pelvic venous thrombosis	1 (0.58)		0	

Subjects are only counted once per treatment for each row.
MedDRA (v18.1) coding dictionary applied.

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Permanent discontinuations due to adverse events:

A summary of permanent treatment discontinuations due to AEs by treatment arm is provided in Table 22.

Table 22   Treatment-emergent all-causality adverse events associated with permanent discontinuation from treatment by treatment group (all cycles) – safety analysis.

MedDRA Preferred Term or Clustered Term	Crizotinib (N=172) n (%)	Chemotherapy (N=171) n (%)
Any AEs	34 (19.8)	34 (19.9)
Disease progression	8 (4.7)	3 (1.8)
Interstitial lung disease (ILD)	5 (2.9)	1 (0.6)
Dyspnoea	4 (2.3)	1 (0.6)
Elevated transaminases	3 (1.7)	0
Death	2 (1.2)	0
Hepatotoxicity	2 (1.2)	0
Pulmonary embolism	2 (1.2)	0
Pneumonia	2 (1.2)	0
Arrhythmia	1 (0.6)	0
Decreased appetite	1 (0.6)	0
Extradural abscess	1 (0.6)	0
GI perforation	1 (0.6)	0
General physical health deterioration	1 (0.6)	2 (1.2)
Intracranial pressure increased	1 (0.6)	0
Sepsis	1 (0.6)	1 (0.6)
Sudden death	1 (0.6)	0
Pleural effusion	0	4 (2.3)
Neutropenia	0	3 (1.8)
Asthenia	0	2 (1.2)
Fatigue	0	2 (1.2)
Neuropathy	0	2 (1.2)
Pericardial effusion	0	2 (1.2)
Anaemia	0	1 (0.6)
Acne	0	1 (0.6)
Alopecia	0	1 (0.6)
Cardiac failure	0	1 (0.6)
Cardiomyopathy	0	1 (0.6)
Cataract	0	1 (0.6)
Dermatitis allergic	0	1 (0.6)
Drug hypersensitivity	0	1 (0.6)
Lymphangitis	0	1 (0.6)
Melaena	0	1 (0.6)
Tumour haemorrhage	0	1 (0.6)
MedDRA (v18.0) coding dictionary was applied. Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of subjects; v=version.		

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Deaths:

A summary of deaths reported during the study is provided in Table 23.

Table 23   Summary of Deaths by Treatment Group – (Safety Analysis)

	Crizotinib (N=172) n (%)	Chemotherapy (Without Crossover) (N=171) n (%)	Total (N=343) n (%)
All death causes	115 (66.9)	124 (72.5)	239 (69.7)
Within 28 days of last dose of study drug	27 (15.7)	6 (3.5)	33 (9.6)
More than 28 days after last dose of study drug	88 (51.2)	118 (69.0)	206 (60.1)
Death within 30 days of first dose of study drug	3 (1.7)	3 (1.8)	6 (1.8)
Death within 60 days of first dose of study drug	10 (5.8)	9 (5.3)	19 (5.5)
Data were based on the 'Notice of Death' CRF page. Abbreviations: CRF=case report form; N/n=number of subjects.			

The Grade 5 TEAE and treatment-related AEs are summarized in Table 24.

Table 24   Grade 5 Treatment-Emergent Adverse Events by Treatment Arm (All-Causality and Treatment Related) – Safety Analysis Population

	Crizotinib (N=172) n (%)		Chemotherapy (N=171) n (%)	
	All-Causality	Treatment-Related	All-Causality	Treatment-Related
Any AEs[a]	30 (17.4)	3 (1.7)	7 (4.1)	1 (0.6)
Disease progression	18 (10.5)	0	3 (1.8)	0
Interstitial lung disease	3 (1.7)	2 (1.2)	0	0
Dyspnoea	2 (1.2)	0	1 (0.6)	0
Death	2 (1.2)	0	0	0
Arrhythmia	1 (0.6)	1 (0.6)	0	0
Pulmonary embolism	1 (0.6)	0	0	0
Pneumonia	1 (0.6)	0	0	0
Respiratory failure	1 (0.6)	0	0	0
Sepsis	1 (0.6)	0	1 (0.6)	1 (0.6)
Sudden death	1 (0.6)	0	0	0
Pericardial effusion	0	0	1 (0.6)	0
Tumour haemorrhage	0	0	1 (0.6)	0
AE = adverse event; N = number of subjects in a treatment group; n = number of subjects with AEs associated with death; NSCLC = non-small cell lung cancer. [a] One crizotinib-treated subject had 2 Grade 5 AEs - Acute respiratory distress syndrome and sepsis.				

CONCLUSIONS:

- Crizotinib treatment resulted in a statistically significant, robust, and clinically meaningful improvement in PFS as compared to standard of care chemotherapy in the treatment of subjects with previously treated advanced ALK-positive NSCLC (7.7 months vs 3.0 months, HR: 0.487, 1 sided p-value <0.0001).

- Crizotinib treatment resulted in a clinically and statistically significant increase in ORR compared to chemotherapy (65% vs 20%, 2 sided p-value <0.0001), with objective responses that were rapid, with a median TTR of 6 weeks, and durable, with a median DR estimate of 32.1 weeks.

- There was no statistically significant improvement in the secondary outcome of OS for subjects randomized to receive crizotinib as compared to subjects randomized to receive chemotherapy. There was, however, a numerical improvement in OS in the crizotinib arm compared to the chemotherapy arm (HR: 0.854 [95% CI: 0.661, 1.104], 1 sided p-value 0.1145 [stratified log-rank test]). These OS analyses were not adjusted for the potentially confounding effects of crossover, as 154 (88.5%) subjects in the chemotherapy arm subsequently received crizotinib treatment as follow-up systemic therapy.

- Crizotinib had a distinct side effect profile that was generally tolerable and manageable by dosing interruption, dose reduction, and/or standard medical therapy.

- Patient-reported visual events were transient with minimal impact on daily activities.

- Crizotinib treatment resulted in significantly greater improvement from baseline in patient-reported key lung cancer symptoms and global QoL compared to the chemotherapy arm.