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GENERIC DRUG NAME / COMPOUND NUMBER: Crizotinib / PF-02341066

PROTOCOL NO.: A8081005

PROTOCOL TITLE:

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 Anaplastic Lymphoma Kinase (ALK) Gene Locus.

Study Centers:

A total of 143 centers in 22 countries enrolled subjects in this study; 47 in the United Sates (US), 10 each in Italy and Japan, 9 each in China, France, Germany and Spain, 6 in Brazil and the United Kingdom, 3 each in Australia, Canada, Hong Kong, South Korea and Taiwan, 2 each in Bulgaria, Greece, Hungary, Poland and Russian Federation and 1 each in Ireland, Netherlands and Sweden. An additional 34 centers received study drug, but did not enroll subjects.

Study Initiation Date and Study Completion Date:

Study Initiation Date: 07 January 2010.

Study Completion Date: 29 December 2015.

Phase of Development: Phase 2.

Study Objectives:

Primary Objectives

- To assess the antitumor efficacy of oral single-agent crizotinib administered to subjects with advanced NSCLC after failure of at least 1 line of chemotherapy and harbor a translocation or inversion event involving the ALK gene locus as measured by objective response rate (ORR).

- To assess the safety and tolerability of oral crizotinib.

Secondary Objectives

- To assess secondary measures of clinical efficacy including overall survival (OS), duration of response (DR), time to tumor response (TTR), disease control rate (DCR) at 6 and 12 weeks, and progression-free survival (PFS);

- To determine pharmacokinetics (PK) in this subject population using population pharmacokinetic (popPK) methods 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 changes from Baseline in expression of biomarkers in signaling pathways (including Janus kinase [JAK]/signal transducers and activators of transcription [STAT], mitogen-activated protein kinase [MEK]/extracellular signal-regulated kinase [ERK], and phosphatidyl inositol-3-kinase [PI3K]/protein kinase B [AKT] pathways) to PK and outcome measures;

- To assess patient-reported outcomes of health-related quality of life (QoL), disease/treatment-related symptoms of lung cancer, and general health status;

- To evaluate the effect of crizotinib on the QT interval (QTc);

- To identify and evaluate potential pharmacogenomic (PG) markers for possible association with selected observed toxicities, i.e., potential markers of adverse hepatic and renal drug reactions.

METHODS

Study Design:

This was a multicenter, multinational, open-label, single arm, Phase 2 study to assess the antitumor efficacy and safety of crizotinib administered to subjects with advanced NSCLC after failure of at least 1 line of chemotherapy and whose tumors harbored a translocation or inversion event involving the ALK gene locus.

Only ALK fusion-positive (ALK-positive) NSCLC subjects were enrolled in the study. Fluorescence in situ hybridization (FISH) was the primary assay used to detect ALK fusion events in tumor samples. An investigational-use only (IUO) population and a non-IUO population subjects are defined as FISH ALK-positive based on the central laboratory and local assay testing only, respectively.

Crizotinib (250 mg) was administered orally twice daily (BID) at approximately the same times each day using a continuous dosing schedule. To facilitate visits and assessments, treatment cycles were defined as 21-day periods. Radiographic tumor assessments including brain scans for objective tumor response and progression were performed at 6-week intervals, and after 10 cycles, assessments may have been performed at 12-week intervals. Bone scans were required at screening. Repeat bone and brain scans were performed in case of bone metastases at Baseline and if new bone metastases were suspected.

An electrocardiogram (ECG) substudy was conducted to further evaluate the effect of crizotinib on corrected QTc and to evaluate a potential crizotinib concentration-QTc relationship. A PK substudy was also performed to evaluate single-dose and multiple-dose

PK profiles of crizotinib and its metabolite (PF-06260182) in a fasted state in Chinese subjects for the PK substudy. The details of the PK assessments for this substudy were summarized in a separate report. A single dose of crizotinib (250 mg) was administered 7 days prior to the start of Cycle 1 (Day-7), after which subjects began receiving multiple, continuous crizotinib doses (i.e., 250 mg BID from Day 1 of Cycle 1). Table 1 and Table 2 provide an overview of the schedule of activities.

Table 1: Subject Evaluation Schedule/Schedule of Time and Events

Protocol Activities	Screening [a]	Study Treatment [b]				End of Treatment	
		Cycle 1		Cycles ≥2	Cycles >10		
	≤28 Days Prior to Dosing	Day 1 (±2) [c]	Day 15 (±2)	Day 1 (±2; except as noted below)	Visits on alternate cycles Day 1 (±4; except as noted below)	End of Rx/ Withdrawal [d]	Post Rx Follow-up
Baseline Documentation							
Informed Consent [e]	X						
Medical/Oncological History [f]	X						
Baseline Signs/Symptoms		X					
Mandatory Tumor Tissue for Molecular Profiling [g]	X						
Physical Examination [h]	X	(X)		X	X	X	
ECOG Performance Status	X	X		X	X	X	
Ophthalmologic Examination [i]	X			Cycle 5, then every 4 cycles (France only)	France only: every 4 cycles		
Laboratory Studies							
Hematology [j]	X	(X)	X	X	X [j]	X	
Blood Chemistry [j]	X	(X)	X	X	X [j]	X	
Urinalysis Dipstick and Reflex Microscopy [j]	X (Korea only)	X (Korea only)		Korea only: X All countries [u]	Korea only: X All countries [u]	Korea only: X All countries [u]	
Coagulation [j]	X						
12-lead ECG [k]	X	X		Cycle 2			
Female Subjects: Pregnancy Test (as Appropriate) [l]	X			X [l]	X [l]	X	
Disease Assessments							
Tumor Assessments (Including Scans) [m]	X			every 6 weeks (±1 week)	every 12 weeks (±1 week)	X	
Other Clinical Assessments							
Contraceptive Check (as Appropriate)	X			X	X	X	
Adverse Events[n]	X	X	X	X	X	X	X
Concomitant Medications/Treatments[o]	X	X	X	X	X	X	X
EORTC QLQ-C30, QLQ-LC13, EQ-5D and VSAQ-ALK[p]		X		X	X	X	X
MUGA Scan or Echocardiogram (France and Ireland only)	X			Cycle 3, then every 4 cycles	every 4 cycles		
Survival Follow-up[q]							X

Protocol Activities	Screening [a]	Study Treatment [b]				End of Treatment	
		Cycle 1		Cycles ≥2	Cycles >10		
	≤28 Days Prior to Dosing	Day 1 (±2) [c]	Day 15 (±2)	Day 1 (±2; except as noted below)	Visits on alternate cycles Day 1 (±4; except as noted below)	End of Rx/ Withdrawal [d]	Post Rx Follow-up
Study Treatment							
Crizotinib				Twice Daily			
Special Laboratory Studies							
Optional Tumor Tissue for Molecular Profiling[r]	X			Cycle 2		X	
Pharmacokinetics[s]		X		Cycles 2, 3, 5			
Optional Blood Sample for Pharmacogenomics[t]		X					

Source: Protocol.

( ) – if not performed within 7 days of the first dose of crizotinib.

Abbreviations: ALK=anaplastic lymphoma kinase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CT=computed tomography; DNA=deoxyribonucleic acid; EC=Ethics Committee; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 Questionnaire; EQ-5D=EuroQol-5D; FISH=fluorescence in situ hybridization; HLA-DQA1*02:01=Major histocompatibility complex, class 2, DQ alpha 1*02:01; IRB=Institutional Review Board; K_2EDTA=dipotassium ethylenediamine tetraacetic acid; MRI=magnetic resonance imaging; MUGA=multiple gate acquisition; PK=pharmacokinetic; PKD1=polycystic kidney disease 1; PKD2=polycystic kidney disease 2; QLQ-LC13=Quality of Life Questionnaire – Lung Cancer 13; QTc=corrected QT; Rx=treatment; VHL=von Hippel-Lindau; VSAQ-ALK=Visual Symptom Assessment Questionnaire – Anaplastic Lymphoma Kinase.

a. Screening: Subjects who were treated on Arm B of Study A8081007 did not need to be re-screened if they had required laboratory tests and physical examination within 3 weeks of scheduled Day 1 of Cycle 1 dosing.

b. Study Treatment: All assessments were performed prior to dosing with study drugs unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings. All cycles were 3 weeks in duration. Upon the IRB/EC approval of Amendment 11 and after Cycle 10, clinic visits could have been reduced to every other cycle. Sufficient study drug for 2 cycles of treatment was dispensed at each clinic visit. During the non-clinical visit cycles, the Investigator was responsible for ensuring the subject contacted the clinical site in order to provide an update of adverse events and concomitant medications.

c. Cycle 1/Day 1: Blood chemistry, hematology, urinalysis, and physical examination not required if acceptable screening assessment was performed within 7 days prior to the start of study treatment.

d. 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).

e. Informed Consent: Obtained prior to undergoing any trial specific procedure.

f. Medical/Oncological History: Included information on prior regimens.

g. Mandatory Tumor Tissue for Molecular Profiling: For subjects not previously screened in Study A8081007, paraffin block (s) of adequate size to allow if possible for at least 10 slides with cuts that were 5 microns thick were used. If no block was available, then the sites were to try to obtain, if possible, at least 10 slides with cuts that were 5 microns thick. Archived or fresh tumor samples were acceptable. These samples were used for the assessment of ALK gene fusion by FISH. Samples could have been tested at the site local laboratory but samples (blocks or slides enough if possible for 10 slides of 5 microns thick) were sent to the central laboratory for confirmation of ALK fusion by FISH. For those subjects enrolled based upon Amendment 10 and lacking sufficient or appropriate tissue for FISH testing by the central laboratory, other ALK testing results could have been acceptable but had to be discussed and approved on a case-by-case basis by the Sponsor. Tumor samples could also have been used for analysis of the presence of ALK protein and ALK fusion transcripts. The mandatory tumor tissue could have been completed outside the 28-day screening window.

h. Physical Examination: Included an examination of major body systems, height (at screening only), weight, blood pressure and pulse rate (at Baseline and on Day 1 of each cycle).

i. Ophthalmologic Examination: Included visual acuity, slit lamp, and fundoscopy, and was 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

Protocol Activities	Screening [a]	Study Treatment [b]				End of Treatment	
		Cycle 1		Cycles ≥2	Cycles >10		
	≤28 Days Prior to Dosing	Day 1 (±2) [c]	Day 15 (±2)	Day 1 (±2; except as noted below)	Visits on alternate cycles Day 1 (±4; except as noted below)	End of Rx/ Withdrawal [d]	Post Rx Follow-up

exams were performed after the completion of every 4 cycles.

j. Hematology, Blood Chemistry, Coagulation, and Urinalysis: If ALT or AST ≥ Grade 3 or ALT or AST ≥ Grade 2 and total bilirubin ≥ Grade 2, repeat ALT or AST and total bilirubin were obtained within 48 hours and then repeated every 48-72 hours until ALT/AST < Grade 1. A 4 mL serum sample obtained just prior to the first dose of study drug (Day -7) 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. Reflex Microscopy was required if urine dipstick was positive for blood or protein. Upon IRB/EC approval of Amendment 15 and after Cycle 10, laboratory tests (at least: ALT/AST/alkaline phosphatase/total bilirubin) were also performed on Day 1 of each cycle. Such tests could be done locally (preferably at the clinical site's local laboratory).

k. 12-lead ECG: Triplicate ECG measurements (approximately 2 minutes apart) were measured at all time points, except a single ECG measurement at screening. The ECG on Day 1 of Cycles 1 and 2 was obtained at 0 hour (predose) and 2-6 hours following morning crizotinib dosing. ECGs were performed immediately before PK blood draws at respective time points. If the QTc was prolonged (>500 msec), then the ECG was read by a cardiologist at the site for confirmation. At selected clinical sites, an ECG substudy was conducted.

l. Pregnancy Test: All female subjects of childbearing potential were required to have a negative pregnancy test at screening. The test was repeated whenever one menstrual cycle was missed during the active treatment period or a potential pregnancy was otherwise suspected, and could also have been repeated as per request of IRB/ECs or if required by local regulations.

m. Tumor Assessments: CT or MRI included chest, brain, abdomen and pelvis at screening. A bone scan was also required at screening. All subsequent scans were based on a calendar schedule beginning from the date of first dose of crizotinib. Scans performed 6 weeks after the first dose of crizotinib had a +1 week allowance; all subsequent scans were performed at 6 week intervals (±1 week), and after 10 cycles were performed at 12-week intervals (±1 week). Brain was included in subsequent tumor assessments if a subject had brain metastases, otherwise brain was only evaluated when clinically indicated. Repeat bone scans were required every 12 weeks only if bone metastases were present at Baseline otherwise a repeat bone scan was required only if new bone metastases were suspected. A bone scan was also required at the time of determination of response for subjects who had bone metastases. For subjects that crossed over from Arm B on Study A8081007, repeat brain and bone scans were required if the scans were not obtained within the appropriate screening window. CT or MRI scan was also performed whenever disease progression was suspected (eg, symptomatic deterioration). If renal cysts were observed, active surveillance with appropriate imaging was performed at the time of renal cyst diagnosis and thereafter following the same schedule as for tumor imaging. All images were reviewed by an independent radiology laboratory until written notification by the Sponsor.

n. Adverse Events: subjects were followed for adverse events from the time they signed the informed consent until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities resolved or were determined to be "chronic" or "stable", whichever was later. Serious adverse events were monitored and reported from the time that the subject provided informed consent as described in the protocol.

o. 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.

p. EORTC QLQ-C30, QLQ-LC13 EQ-5D, and VSAQ-ALK: Subjects completed 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 End of Treatment visit had also to complete the VSAQ-ALK at the 28-day Follow-up visit after last dose. All self-assessment questionnaires had to be 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.

q. Survival Follow-Up: After discontinuation of study treatment, post-study survival status was collected every 2 months until death or until 12 months after the last subject had discontinued study treatment. This included collection of information on subsequent anticancer therapies. Telephone contact was acceptable.

r. Optional Tumor Tissue for Molecular Profiling: Paraffin block (s) of adequate size to allow for at least 10 slides if possible with cuts that were 5 microns thick. If no block was available, then at least 10 slides, if possible, with cuts that were 5 microns were acceptable. Archived or fresh tumor samples were acceptable for screening. A tumor

Protocol Activities	Screening [a]	Study Treatment [b]				End of Treatment	
		Cycle 1					
	≤28 Days Prior to Dosing	Day 1 (±2) [c]	Day 15 (±2)	Cycles ≥2 Day 1 (±2; except as noted below)	Cycles >10 Visits on alternate cycles Day 1 (±4; except as noted below)	End of Rx/ Withdrawal [d]	Post Rx Follow-up

specimen was only needed at the End of Treatment, if a subject discontinued due to disease progression.

s. Pharmacokinetics: Subjects enrolled in the ECG substudy only: refer to protocol for further details regarding concurrent PK sampling on Cycles 1, 2, 3, and 5, Day 1. For all other subjects, PK plasma samples were collected prior to and 2-6 hours following morning crizotinib dosing (effective from the original protocol to Amendment 10); PK plasma samples were no longer required after Amendment 11 was approved locally, except for the subjects enrolled in the ECG substudy. At each sampling time point, 2 mL of blood was drawn into K_2EDTA tubes. Unused plasma sample remaining after completion of PK assessments could also have been used to investigate biomarkers (eg, protein or circulating nucleic acid markers) of potential relevance to the mechanism of crizotinib, the development of resistance to crizotinib, or the identification of subjects who might benefit from treatment with crizotinib. Additionally, blood samples could have been requested from subjects experiencing unexpected or serious adverse events.

t. Optional Blood Sample for Pharmacogenomics: A single 4 mL blood sample was collected for the analysis of DNA sequence variation in genes that could affect the PK of crizotinib, or that could be associated with adverse drug reactions. Examples of genes that may affect PK include, but may not be limited to, genes encoding drug metabolizing enzymes and transporters. Genes that may be associated with specific adverse events include, but may not be limited to, HLA-DQA1*02:01 for liver toxicities and PKD1, PKD2 and VHL for renal toxicities.

u. As clinically indicated.

Table 2: Reduced Schedule of Activities

Protocol Activities	Study Treatment[1]	End of Treatment	
	Visits on Day 1 of Alternate Cycles (±4; except as noted below)	End of Txt/ Withdrawal[2]	Post Txt Follow-up
Physical Examination[3]	X	X	
Blood Pressure and Pulse Rate	X	X	
Ophthalmologic Examination[4]	**France only**: every 4 cycles **All countries:** X[4]		
Laboratory Studies			
Hematology and Blood Chemistry, excluding Liver Functions Tests (LFTs)[5]	**X**	X	
LFTs: ALT/AST/alkaline phosphatase/total bilirubin[5]	**Day 1 of each cycle (±4)**	X	
Urinalysis dipstick and Reflex Microscopy[6]	**Korea only: X** **(all other countries:** as clinically indicated)	**Korea only: X (all other countries:** as clinically indicated)	
Female subjects: Pregnancy Test (as appropriate)[7]	X[7]	X[7]	
Contraceptive Check (as appropriate)	X	X	
Disease Assessments			
Tumor Assessments [8]	As per local clinical practice		

Protocol Activities	Study Treatment[1] Visits on Day 1 of Alternate Cycles (±4; except as noted below)	End of Treatment End of Txt/ Withdrawal[2]	End of Treatment Post Txt Follow-up
Other Clinical Assessments			
Adverse Events[9]	X	X	X
Concomitant Medications/Treatments[10]	X	X	X
Multiple Gate Acquisition (MUGA) Scan or Echocardiogram (France only)	**France only**: every 4 cycles		
Study Treatment			
PF-02341066	Twice daily		
Survival Follow-up [11]			

Source: Protocol. Abbreviations: Txt=treatment.

Footnotes for Schedule of Activities

1. All assessments should be performed prior to dosing with study medications unless otherwise indicated. All cycles are 3 weeks in duration. Sufficient study medication for 2 cycles of treatment will be dispensed at each clinic visit. During the non-clinical visit cycles, the Investigator is responsible for ensuring the subject contacts the clinical site in order to provide an update of adverse events and concomitant medications.
2. End of Treatment/Withdrawal: Obtain blood pressure, pulse rate, laboratory tests (including LFTs), and physical examination if not completed during the previous 4 weeks on study.
3. Physical Examination: Includes an examination of major body systems and weight.
4. Ophthalmologic Examination: Includes visual acuity, slit lamp, and fundoscopy, and should be performed by an ophthalmologist. The ophthalmologic examination should be repeated during the study when visual disturbances have been observed and when there is an increase in the grade for visual disturbances. For all subjects enrolled in France, ophthalmology exams will be performed after the completion of every 4 cycles.
5. Hematology, Blood Chemistry, and Urinalysis: Required tests are listed in Appendix 1 of the protocol. Where possible, laboratory tests should be performed at the clinical site's local laboratory. Where that is not possible, subjects will provide the laboratory test results carried out at a non-clinical site laboratory, eg, by telephone, and bring a copy of the laboratory test results at the next cycle visit; process depends on local medical practice. The copy of the laboratory test results must be retained in the subject's file at the clinical site for documentation purposes. If ALT or AST ≥ grade 3 **or** ALT or AST ≥ grade 2 and total bilirubin ≥ grade 2, obtain repeat ALT or AST and total bilirubin within 48 hours and then repeat every 48-72 hours until ALT/AST < Grade 1.
6. Reflex Microscopy required if urine dipstick is positive for blood or protein.
7. Pregnancy Test: All female subjects of childbearing potential are required to repeat the test whenever one menstrual cycle is missed during the active treatment period or a potential pregnancy is otherwise suspected, and the test may also be repeated as per request of IRB/ECs or if required by local regulations.
8. Tumor Assessments: Will be repeated at the frequency as per local clinical practice, and will no longer be recorded on the CRF. However, tumor assessment information should be retained in the subject's file for documentation purposes
9. Adverse Events: subjects must be followed for adverse events with the frequency as per local clinical practice until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later. Serious adverse events should be monitored and reported from the time that the subject provides informed consent as described in the protocol.
10. Concomitant Medications/Treatments: Concomitant medications and treatments will be recorded up to 28 days post the last dose of study treatment.
11. NOTE: Post-study survival status is no longer required.

Number of Subjects (Planned and Analyzed):

Approximately 1100 subjects were projected to be enrolled into this trial. A total of 1069 subjects were enrolled and 1066 subjects received at least1 dose of crizotinib and were included in the safety analysis (SA) population. Three subjects who were enrolled but not treated were withdrawn from the study before receiving treatment because they were not eligible and were mistakenly entered into the interactive voice response system. A total of 144 (13.5%) subjects of Study A8081007, including 143 subjects from the chemotherapy arm and 1 subject initially erroneously randomized in the crizotinib arm but not treated, were enrolled in A8081005 study to receive treatment with crizotinib.

Main Inclusion Criteria:

- Eligible female or male subjects ≥18 years of age (for subjects enrolled in Japan: consent from a legally acceptable representative was required for all subjects who were under 20 years old).

- Have histologically or cytologically proven diagnosis of NSCLC that was locally advanced or metastatic; at least 1 prior treatment for locally advanced or metastatic disease.

- Positive for translocation or inversion events involving the ALK gene locus as determined by the ALK break apart FISH assay. Upon local approval of Protocol Amendment 10, positive ALK test results from other methods such as immunohistochemistry (IHC) or reverse transcriptase polymerase chain reaction (RT-PCR) testing may have also been acceptable after discussion and approval by the Sponsor.

- Randomized to Arm B (pemetrexed or docetaxel) of Study A8081007 and was discontinued from treatment due to response evaluation criteria in solid tumors (RECIST) version 1.1-defined progression of disease as determined by independent radiology review or ineligible for Study A8081007 due to not meeting the requirement for prior treatment for advanced disease, or ECOG performance status 3 or the laboratory or RECIST eligibility criteria (but must meet all eligibility criteria of this protocol).

- Have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 to 3 and an adequate organ function as defined in the protocol.

- Subjects with brain metastases were eligible if asymptomatic or, if treated, were neurologically stable for at least 2 weeks.

Study Treatment:

Crizotinib 250 mg (two 100 mg tablets and one 50 mg tablet) was administered orally BID on a continuous dosing schedule at the same time each day. 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 was adjusted for toxicity. Intra-subject dose reduction by 1 and, if needed, 2 dose levels was allowed depending on the type and severity of toxicity encountered (Dose Level 1 was 200 mg BID, and Dose Level 2 was 250 mg once daily [QD]). Subjects were instructed that if they vomited any time after taking a dose, then they should not "make it up" with an extra dose, but instead, they should resume subsequent doses as prescribed. Any missed dose was taken up to 6 hours prior to the next scheduled dose, otherwise it was skipped, and dosing was resumed with subsequent doses as prescribed.

Efficacy, Outcomes Research, Pharmacokinetic and Pharmacodynamic Endpoints:

Efficacy Endpoints:

Primary Endpoints:

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

Secondary Endpoints:

- OS, DR, TTR, DCR at 6 and 12 weeks, and PFS.
- Plasma concentrations of PF-02341066.
- Types of echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion variants and ALK protein expression.
- Protein expression of identified biomarkers in serial tumor samples from surgery or biopsy, when available.
- Health-related QoL, lung cancer disease/treatment-related specific symptoms, and general health status.
- QTc.
- Genotype of alleles possibly associated with adverse hepatic or renal drug reactions, eg, major histocompatibility complex, class 2, DQ alpha 1*02:01 (HLA-DQAI*2:01), polycystic kidney disease 1 (PKD1), polycystic kidney disease 2 (PKD2), and von Hippel-Lindau (VHL).

Safety Evaluations:

Safety evaluations included reporting of AEs, serious adverse events, periodic physical examinations (major body systems, weight and height [at screening only]), clinical laboratory parameters (hematology, blood chemistry, coagulation [screening only], urinalysis [introduced in Protocol Amendment 11: 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]), vital signs (blood pressure [BP], and pulse rate), pregnancy testing, electrocardiogram (12-lead electrocardiogram [ECG]), multiple gated acquisition (MUGA) scan or echocardiogram analysis (France and Ireland only), ECOG PS, concomitant medications, follow-up systemic therapies, and ophthalmologic examination (visual acuity, slit lamp and fundoscopy).

Statistical Methods:

The main purpose of this study was to characterize antitumor efficacy and safety of PF-02341066 in this study population. Hence, no specific hypothesis tests were planned. No specific statistical decision rule was applied.

Determination of Sample Size

The goal of the primary analysis of objective response was to estimate ORR including a 95% confidence interval (CI). No specific hypothesis tests were planned. The sample size was set at 250 subjects, which was considered adequate to estimate ORR and its 95% CI, in case the true ORR ranged from 30% to 50%. Subsequently final sample size was projected as 1100 subjects in order to understand the possible genetic mechanisms for specific AEs, to account for subjects crossing over to this study, and to meet country-specific regulatory requirements.

Electrocardiogram Substudy

Based upon the standard deviation (std. dev) of change from Baseline of QT interval using Fridericia's correction (QTcF) of 16 msec (Study 1001), a total sample size of 40 subjects from either Study 1007 (crizotinib arm) or Study 1005 had been deemed sufficient for greater than 90% probability that all 5 boundaries of upper one-sided 95% CIs for the change from Baseline of QTc at all 5 QTc sampling time points on Cycle 2 Day 1 were under 20 msec, assuming the true change from Baseline in QTc was 10 msec.

Analysis Populations

A SA population was defined as all subjects who were enrolled and received ≥1 dose of study drug (excluding Day -7 PK dosing for subjects enrolled into the China PK substudy).

The following specific population data sets were analyzed:

- SA (ALK-positive by IUO) population, defined as all subjects in the SA population who were FISH ALK-positive by the central laboratory.
- SA (ALK-positive by non-IUO) population, defined as all subjects in the SA population who were ALK-positive by local assay testing only (i.e., other than by the central laboratory).
- Response-Evaluable (RE) (ALK-positive by IUO) population, defined as all subjects in the SA ALK-positive by IUO population who had adequate Baseline tumor assessments.
- RE (ALK-positive by non-IUO) population, defined as all subjects in the SA ALK-positive by non-IUO population who had adequate Baseline tumor assessments.
- PRO-Evaluable population, defined as the subjects from the SA population who completed a Baseline PRO assessment and ≥1 post-Baseline PRO assessment.
- PK concentration population, defined as all subjects in the SA population who had ≥1 concentration measurement following treatment.

- All Genotyped population, defined as all subjects in the SA population who had ≥1 genotype result.

- PG Evaluable population, defined as subjects in the All Genotyped population who had an HLA genotype result and who were designated as an alanine aminotransferase (ALT) Case or Control. ALT Cases were defined as those subjects with a Baseline ALT of ≤1x Upper Limit Of Normal (ULN) and at least one on treatment ALT assessment of >3x ULN; ALT Controls represented those subjects with Baseline and on-treatment assessments of ALT of ≤1x ULN.

- Ophthalmologic Examination Evaluable population, defined as subjects from the SA population who reported visual disturbances and who had the required postdose ophthalmologic examination. These subjects had at least one of the following: 1) Baseline (performed during the screening period) and ≥1 post-Baseline visual acuity exam, or 2) Baseline and ≥1 post-Baseline slit lamp examination, or 3) Baseline and ≥1 post-Baseline fundoscopy.

- ECG-Evaluable population (non-ECG substudy), defined as subjects from the SA population who had a Baseline (last ECG prior to Cycle 1 Day 1 dose) and ≥1 post-Baseline ECG measurement and were not included in the ECG substudy.

- ECG-Evaluable population (ECG substudy), defined as subjects from the SA population and had at least 1 required Cycle 2 Day 1 ECG measurement performed by the core ECG laboratory.

Analysis of Efficacy Parameters

Primary analyses of endpoints dependent on tumor assessments (ORR, DCR, DR, TTR and PFS) were based on investigator assessment of tumor data.

Primary Endpoint

Derived Tumor Assessment:

The derived tumor assessment (i.e., Best Overall Response) was based on the target lesion measurements, non-target lesion assessments, and new lesion records provided by the investigator, independent of the overall response category provided by the investigator.

The ORR was defined as the percent of subjects with a confirmed complete response (CR) or partial response (PR) according to RECIST v 1.1, relative to the RE population.

The ORR was estimated and 95% exact CI for the true ORR was provided. Waterfall plots displaying the best percentage change in tumor size by BOR were presented.

Stable disease (SD) was categorized according to duration in several time intervals, specifically, 0 to <3 months, 3 to <6 months, 6 to <9 months, 9 to <12 months, and ≥12 months.

ORR was also analyzed by age group (<65 years, ≥65 years), gender, race (white, black, Japanese, Korean, Chinese, other Asians, and other races), race group (Asian and non-Asian), Baseline ECOG PS (0, 1, 2, and 3), and number of prior systemic regimens (1, 2, 3, and >3).

Secondary Endpoints

PFS and OS were analyzed in the SA (ALK-positive by IUO) and the SA (ALK positive by non-IUO) populations.

Estimates of PFS and OS curves obtained from the Kaplan-Meier method were presented graphically. The median event time (and other quartiles) and corresponding 2-sided 95% CI were provided. For OS, the 6-month and 1-year survival probabilities were estimated using the Kaplan-Meier method.

TTR and DR were summarized by descriptive statistics in the RE populations of subjects with a confirmed CR or PR. The Kaplan-Meier method was also used for DR. The DCRs were provided at 6 and 12 weeks.

Endpoint definitions:

PFS was defined as the time from the date of the Cycle 1 Day 1 dose to the date of the first documentation of objective tumor progression or death on study due to any cause, whichever occurred first. PFS (in months) was calculated as (first event date −Cycle 1 Day 1 dose date+1)/30.4.

OS was defined as the time from the Cycle 1 Day 1 dose to the date of death due to any cause. OS (in months) was calculated as (date of death − date of Cycle 1 Day 1 dose+1)/30.4. For subjects who were alive/lost to follow-up, the OS was censored on the last date that subjects were known to be alive. Subjects lacking data beyond the date of the Cycle 1 Day 1 dose had their OS censored at the date of the Cycle 1 Day 1 dose.

Six-month and 1-year survival probabilities were defined as the probabilities of survival at 6 months and 1 year, respectively, after the date of the Cycle 1 Day 1 dose based on the Kaplan-Meier estimate.

DR was defined as the time from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed, to the first documentation of objective tumor progression or to death on study due to any cause, whichever occurred first. DR (in weeks) was calculated as (first date of PD or death −first date of CR or PR that was subsequently confirmed+1)/7.02. DR was only calculated for the subgroup of subjects from the RE population with a confirmed objective tumor response. Censoring for DR was identical to the censoring rules for PFS.

TTR was defined as the time (in weeks) from the date of Cycle 1 Day 1 dose to first documentation of objective tumor response (CR or PR) that was subsequently confirmed. For subjects proceeding from PR to CR, the onset of PR was taken as the onset of response. TTR (weeks) was calculated as (first event date − Cycle 1 Day 1 dose date+1)/7.02. TTR was calculated for the RE population in the subgroup of subjects with a confirmed objective tumor response.

DCR at 6 and 12 weeks was defined as the percentage of subjects in the RE population with a confirmed CR, confirmed PR, or SD (according to RECIST v 1.1) at 6 weeks and 12 weeks, respectively.

Covariates and Subpopulations:

The primary and secondary endpoints were analyzed in certain subpopulations, such as, age group, gender, race groups, and ECOG PS.

Analysis of Pharmacokinetic and Pharmacodynamic Parameters

Pharmacokinetic Analysis

All subjects who have ≥ 1 measurement of PF-02341066 or PF-06260182 at the time of reporting were included in PK analysis.

Predose concentrations for crizotinib, its metabolite PF-06260182, and ratio of PF-06260182 to crizotinib were summarized before the reporting data cut-off. All crizotinib and its metabolite PF-06260182 plasma concentration data were listed by subject, by actual collection time and day in clinical study report.

Population Pharmacokinetic Analysis (PopPK)

The plasma concentration data from this study were pooled with data from other crizotinib studies, as appropriate, for popPK analyses and reported separately.

Pharmacodynamic Analysis

Concentration-QTc modeling

Concentration-QTc modeling analysis was conducted using the ECG data from this study and/or combined data with other clinical studies of crizotinib and reported separately.

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.

Biomarker Analysis

Analyses of change from Baseline in the expression of biomarkers relevant to signaling pathways were not performed because paired Baseline and on-treatment (Cycle 2) tumor tissue required for the analysis, which were to be collected on an optional basis, were not available.

Pharmacokinetic/Pharmacodynamic Modeling

PopPK/pharmacodynamic analyses were performed based on emerging clinical response data from this study, and safety data from this study and other crizotinib studies. The analyses were reported separately.

Analysis of Pharmacogenomic Parameters

PG markers included genotypes of alleles possibly associated with hepatic toxicity, including HLA-DQA1*02:01, HLA-DQB1*02:02, HLA-DRB1*07:01 and human tenascin XB (TNXB)/rs12153855. Complete genotyping of polymorphic alleles involving the HLA gene locus, including, MHC class I HLA-A, B, C, and MHC class II HLA-DP, DQ, DR loci, was performed.

Summary of Type of ALK Testing

ALK marker status by central laboratory was tabulated vs ALK marker status from a laboratory developed test, when both were available.

Descriptive statistics were also presented for the percentage of ALK-positive cells in the SA – ALK Positive by IUO population and in the RE - ALK Positive by IUO population.

In addition, a subject listing of ALK percentage positivity and BOR based on derived tumor assessment was presented for the RE - ALK Positive by IUO population. Bar graphs/box plots of ALK percentage positivity by BOR were also provided for this group of subjects.

AEs

Subjects were followed-up for AEs from the time they signed the informed consent until at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities resolved or were determined “chronic” or “stable”, whichever was later.

Analyses of Other Parameters

The subscales of the EORTC QLQ-C30 and QLQ-LC13 were scored based on the EORTC scoring manual. The transformed scores range from 0-100. Higher scores indicate higher (“worse”) symptom severity, higher (“better”) functioning, and better global QoL. Negative change from Baseline scores indicate an improvement in symptoms, decreased functioning, or decreased QoL, while positive change scores indicate an increase in functioning or increased QoL and deterioration in symptoms.

RESULTS

Subject Disposition and Demography:

In this study, 1066 subjects received at least 1 dose of crizotinib and all subjects (100%) discontinued study treatment. The most common reason for study discontinuations was death reported in 726 (68.1%) subjects (Table 3).

Table 3: Subject Disposition (SA Population)

	Crizotinib 250 mg BID
Number (%) of Subjects	1066
Treated	1066
Completed	0
Discontinued	1066 (100.0)
Discontinuations from study	
Subjects died	726 (68.1)
Completed[a]	244 (22.9)
Lost to follow-up	22 (2.1)
Other	5 (0.5)
Subjects refused further follow-up	69 (6.5)

Abbreviations: BID=twice daily; N/n=number of subjects; SA=safety analysis.
[a] "Completed" were those subjects who were on treatment or on survival follow-up upon achievement of the Primary Completion Date, when the Sponsor sent written notification to the clinical sites that survival follow up was no longer required.

Demographic Characteristics

A summary of demographic characteristics by treatment arm in the FA population is provided in Table 4.

Table 4: Demographic Characteristics (SA Population)

Parameter	Crizotinib 250 mg BID N=1066
Sex, n (%)	
Male	465 (43.6)
Female	601 (56.4)
Age (years)	
Mean (std. dev)	52.2 (12.33)
Median	52.0
Range	19 – 84
<65, n (%)	894 (83.9)
≥65, n (%)	172 (16.1)
Race, n (%)	
White	532 (49.9)
Black	20 (1.9)
Asian	495 (46.4)
Racial designation for Asian	
Japanese	81 (7.6)
Korean	144 (13.5)
Chinese	252 (23.6)
Other	18 (1.7)
Other	19 (1.8)
Smoking classification, n (%)	
Never smoked	702 (65.9)
Ex-smoker	321 (30.1)
Smoker	43 (4.0)

Abbreviations: BID=twice daily; CSR=clinical study report; N/n=number of subjects; SA=safety analysis; std dev=standard deviation.

Efficacy, Outcomes Research, Pharmacokinetic and Pharmacodynamic Results:

Efficacy Results

Primary Endpoint:

ORR

A summary of best overall response in the [RE (ALK-positive by IUO) and RE (ALK-positive by non-IUO)] study populations is provided in Table 5. Based on the derived tumor assessment in both populations, [RE (ALK-positive by IUO) and RE (ALK-positive by non-IUO)], ORR was 54.1% (95% CI: 50.8, 57.4) and 40.5% (95% CI: 32.8, 48.6), respectively.

Table 5: Best Overall Response (RE [ALK-positive by IUO] and [ALK-positive by non-IUO] Populations)

	RE [ALK-positive by IUO]	RE [ALK-positive by non-IUO]
	Crizotinib 250 mg BID N=908 n (%)	Crizotinib 250 mg BID N=158 n (%)
Best Overall Response		
Complete Response	11 (1.2)	1 (<1.0)
Partial Response	480 (52.9)	63 (39.9)

	RE [ALK-positive by IUO]	RE [ALK-positive by non-IUO]
	Crizotinib 250 mg BID N=908 n (%)	**Crizotinib 250 mg BID N=158 n (%)**
Stable Disease	251 (27.6)	46 (29.1)
Objective progression	90 (9.9)	28 (17.7)
Early death	37 (4.1)	10 (6.3)
Indeterminate	39 (4.3)	10 (6.3)
Objective response rate (CR + PR)	491 (54.1)	64 (40.5)
95% exact CI [%] [a]	[50.8, 57.4]	[32.8, 48.6]
SD duration (months) [b]		
0 to <3 months	65 (25.9)	5 (10.9)
3 to <6 months	79 (31.5)	14 (30.4)
6 to <9 months	33 (13.1)	8 (17.4)
9 to <12 months	16 (6.4)	8 (17.4)
≥12 months	58 (23.1)	11 (23.9)

Abbreviations: ALK=anaplastic lymphoma kinase; BID=twice daily; CI=confidence interval; IUO=investigational-use only; N/n=number of subjects; CR=complete response; PR=partial response; RE=response-evaluable; SD=stable disease.
Best Overall Response was based on the derived tumor assessment. Early death was death within 42 days (6 weeks) from first dose. The RE population was defined as all subjects in the safety analysis set who had an adequate Baseline disease assessment.

a. Used exact method based on F-distribution.
b. Percentage was based on the number of SD subjects.

Secondary Endpoints:

DR

DR in the [RE (ALK-positive by IUO) and RE (ALK-positive by non-IUO)] study populations is summarized in Table 6. The median DR of the [RE (ALK-positive by IUO)] subjects was 11.8 months (95% CI: 10.4, 12.8). The median DR of the [RE (ALK-positive by non-IUO)] was 9.5 months (95% CI: 6.9, 15.2).

Table 6: Duration of Response, Objective Responders Only (RE [ALK-positive by IUO] and [ALK-positive by non-IUO] Populations)

	RE [ALK-positive by IUO]	RE [ALK-positive by non-IUO]
	Crizotinib 250 mg BID N=908 n (%)	**Crizotinib 250 mg BID N=158 n (%)**
Subjects with a response (CR or PR)	491 (54.1)	64 (40.5)
Status after response[a]		
Subsequent progression or death	373 (76.0)	43 (67.2)
Without subsequent progression or death	118 (24.0)	21 (32.8)
Kaplan-Meier Estimates of Duration of Response (Months)		
25th percentile (95%CI)[b]	5.5 [4.9, 5.7]	4.4 [4.2, 8]

	RE [ALK-positive by IUO]	RE [ALK-positive by non-IUO]
	Crizotinib 250 mg BID N=908 n (%)	Crizotinib 250 mg BID N=158 n (%)
50th percentile (95%CI)[b]	11.8 [10.4, 12.8]	9.5 [6.9, 15.2]
75th percentile (95%CI)[b]	25 [20, 27.4]	20.8 [12.5, NR]

Abbreviations: ALK=anaplastic lymphoma kinase; BID=twice daily; CI=confidence interval; CR=complete response; IUO=investigational-use only; N/n=number of subjects; NR=not reported, not reached; PR=partial response; RE=response evaluable.
Tumor assessment was based on the derived tumor assessment.
Duration of response was the time from the date of first documentation of CR or PR to the date of first documentation of objective progression or death due to any cause.
a. Percent was based on the number of subjects with confirmed objective response (CR or PR).
b. Based on the Brookmeyer and Crowley Method.

TTR

TTR in the [RE (ALK-positive by IUO) and RE (ALK-positive by non-IUO)] study populations are summarized in Table 7.

Table 7: TTR, Objective Responders Only (RE [ALK-positive by IUO] and [ALK-positive by non-IUO] Populations)

	RE [ALK-positive by IUO]	RE [ALK-positive by non-IUO]
	Crizotinib 250 mg BID N=908 n (%)	Crizotinib 250 mg BID N=158 n (%)
Time to tumor response (weeks)[a]		
N	491	64
Mean (std. dev)	10.3 (13.2)	9.5 (9.9)
Median	6.1	6.3
Range	2.7-164	4.7-65.9
Category (weeks)[b]		
0 - <6	90 (18.3)	19 (29.7)
6 - <12	304 (61.9)	35 (54.7)
12 - <14	28 (5.7)	5 (7.8)
14 - <24	40 (8.2)	3 (4.7)
≥24	29 (5.9)	2 (3.1)

Abbreviations: ALK=anaplastic lymphoma kinase; BID=twice daily; IUO=investigational-use only; N/n=number of subjects; RE=response evaluable; std. dev=standard deviation.
Time to response was the time from the date of first dose to the first documentation of objective tumor response (CR or PR) that was subsequently confirmed. Best overall response was based on the derived tumor assessment.
a. Descriptive statistics are presented for subjects with an event.
b. Category is presented for subjects with an event.

DCR

The DCRs at Week 6 and Week 12 are presented in Table 8.

Table 8: Disease Control Rates at Week 6 and Week 12 (RE [ALK-positive by IUO] and [ALK-positive by non-IUO] Populations)

	RE [ALK-positive by IUO]	RE [ALK-positive by non-IUO]
	Crizotinib 250 mg BID N=908 n (%) [95% CI] [a]	Crizotinib 250 mg BID N=158 n (%) [95% CI] [a]
Disease Control Rate at Week 6	742 (81.7) [79.0, 84.2]	110 (69.6) [61.8, 76.7]
Disease Control Rate at Week 12	643 (70.8) [67.7, 73.8]	97 (61.4) [53.3, 69.0]

Abbreviations: ALK=anaplastic lymphoma kinase; BID=twice daily; CI=confidence interval; IUO=investigational-use only; N/n=number of subjects; RE=response evaluable.
Tumor assessment was based on the derived tumor assessment.
[a] Used exact method based on F-distribution.

PFS

A summary of PFS is provided in Table 9. The median PFS was 8.4 months in the SA (ALK-positive by IUO) population, and it was 6.9 months in the SA (ALK-positive by non-IUO) population, respectively.

Table 9: Progression-Free Survival (SA [ALK-positive by IUO] and [ALK-positive by non-IUO] Populations)

	SA [ALK-positive by IUO]	SA [ALK-positive by non-IUO]
	Crizotinib 250 mg BID N=908 n (%)	Crizotinib 250 mg BID N=158 n (%)
Number with Event	702 (77.3)	119 (75.3)
Type of Event		
Objective progression	614 (67.6)	100 (63.3)
Death without objective progression	88 (9.7)	19 (12.0)
Number Censored	206 (22.7)	39 (24.7)
Reason for Censorship		
No adequate Baseline assessments	0	0
No on-study disease assessments	7 (<1.0)	1 (<1.0)
Given new anticancer treatment prior to tumor progression	85 (9.4)	17 (10.8)
Off treatment prior to progression	41 (4.5)	9 (5.7)
Withdrew consent for follow-up	0	0
Lost to follow-up	2 (<1.0)	0
Unacceptable gap (>14 weeks) between PD or Death to the most recent prior adequate assessment	16 (1.8)	3 (1.9)
In follow-up for progression	55 (6.1)	9 (5.7)
Probability of Being Event Free at Month 6 [a] [95% CI] [b]	61.1 [57.7, 64.3]	55.2 [46.6, 62.9]
Kaplan-Meier Estimates of Time to Event (month)		
25th percentile (95%CI)[c]	4.1 [3.7, 4.2]	2.6 [1.4, 4.0]
50th percentile (95%CI)[c]	8.4 [7.1, 9.7]	6.9 [5.6, 9.4]

	SA [ALK-positive by IUO]	SA [ALK-positive by non-IUO]
	Crizotinib 250 mg BID N=908 n (%)	**Crizotinib 250 mg BID N=158 n (%)**
75th percentile (95%CI)[c]	20.6 [17.7, 22.7]	15.2 [10.9, 20.2]

Abbreviations: ALK=anaplastic lymphoma kinase; BID=twice daily; CI=confidence interval; IUO=investigational-use only; N/n=number of subjects; PD=progressive disease; SA=safety analysis.
Tumor assessment was based on the derived tumor assessment.
a. Estimated from the Kaplan-Meier curve.
b. Calculated using the normal approximation to the log-transformed cumulative hazard function.
c. Based on the Brookmeyer and Crowley method.

OS and Probability of Survival

An overview of OS and survival probabilities at 6 months and 12 months is provided in Table 10. The median OS was 21.8 months (95% CI: 19.4, 24.0) and the probabilities of survival at 6 months and 1 year were 81.7% (95% CI: 79.0, 84.0) and 66.5% (95% CI: 63.3, 69.5), respectively, in the SA (ALK positive by IUO) population.

The median OS was 16.9 months (95% CI: 13.4, 21.5) and the probabilities of survival at 6 months and 1 year were 77.5% (95% CI: 70.1, 83.3) and 62.4% (95% CI: 54.3, 69.6), respectively, in the SA (ALK positive by non-IUO) population.

Table 10: OS (SA [ALK-positive by IUO] and [ALK-positive by non-IUO] Populations)

	SA [ALK-positive by IUO]	SA [ALK-positive by non-IUO]
	Crizotinib 250 mg BID N=908 n (%)	**Crizotinib 250 mg BID N=158 n (%)**
Number of Deaths	594 (65.4)	115 (72.8)
Number Censored	314 (34.6)	43 (27.2)
Reason for Censorship		
Subject remains in follow-up	237 (26.1)	35 (22.2)
Subject no longer being followed for survival	0	0
Withdrew consent for follow-up	58 (6.4)	8 (5.1)
Lost to follow-up	19 (2.1)	0
Probability of Survival at 6 Months [a] (95% CI) [b]	81.7 [79.0, 84.0]	77.5 [70.1, 83.3]
Probability of Survival at 12 Months [a] (95% CI) [b]	66.5 [63.3, 69.5]	62.4 [54.3, 69.6]
Kaplan-Meier Estimates of Time to Event (month)		
Quartiles (95% CI)[c]		
25th percentile (95% CI)[c]	8.5 [7.6, 9.7]	7.7 [4.2, 10.3]
50th percentile (95% CI)[c]	21.8 [19.4, 24.0]	16.9 [13.4, 21.5]
75th percentile (95% CI)[c]	58.1 [49.3, NR]	40.0 [32.7, NR]

	SA [ALK-positive by IUO]	SA [ALK-positive by non-IUO]
	Crizotinib 250 mg BID N=908 n (%)	**Crizotinib 250 mg BID N=158 n (%)**

Abbreviations: ALK=anaplastic lymphoma kinase; BID=twice daily; CI=confidence interval; IUO=investigational-use only; N/n=number of subjects; NR=not reported, not reached; SA=safety analysis.
Subjects in follow-up include subjects still on treatment.
In follow-up as of data cut-off.
a. Estimated from the Kaplan-Meier curve.
b. Derived from the CI for the log-transformed cumulative hazard function.
c. Based on the Brookmeyer and Crowley method.

Patient-Reported Outcomes:

European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-LC13 Scale Scores

EORTC QLQ-C30 Global Quality of Life

A statistically significant (95% CI excluded 0) and clinically meaningful (≥10-point) improvement from Baseline was observed for global QoL (Cycles 3 to 14).

A majority of the subjects had either an improved (42.5% of subjects) or stable (38.5% of subjects) score in global QoL over the course of therapy (including all Cycles).

EORTC QLQ-C30 Functioning Domains

A majority of the subjects had improved or stable scores in the functioning domains over the course of therapy (included all Cycles).

Symptoms (EORTC QLQ-C30)

A statistically significant and clinically meaningful improvement (ie, decrease) from Baseline (up to and including Cycle 30) was observed early and maintained at several cycles in patient-reported symptoms of appetite loss, dyspnoea, fatigue, insomnia and pain. Clinically significant worsening of symptoms (i.e., increases) were reported in constipation and diarrhoea scales.

The symptoms that had the highest percentage (≥40%) of subjects 'improved' from Baseline were pain (48.2%), fatigue (46.2%), insomnia (43.0%), and dyspnoea (42.1%). The symptoms that had the highest percentage (≥40%) of subjects 'worsening' from Baseline were constipation (43.9%) and diarrhoea (43.8%) (Table 11).

Symptoms (EORTC QLQ-LC13)

A statistically significant and clinically meaningful improvement (i.e., decrease) from Baseline (up to and including Cycle 30) was observed early and maintained at several cycles in patient-reported symptoms of alopecia, coughing, dyspnoea, pain in arm or shoulder, pain in chest, and pain in other parts.

The symptoms that had the highest percentage (≥40%) of subjects 'improved' from Baseline were coughing (51.0%), dyspnoea (41.3%), and pain in other parts (40.8%).

Table 11: Change in EORTC (QLQ-C30 and QLQ-LC13) Scales (PRO-Evaluable Population)

		Crizotinib 250 mg BID N=976		
		Improved [a] n (%)	Stable [b] n (%)	Worsening [c] n (%)
EORTC QLQ-C30	**Global QoL**	415 (42.5)	376 (38.5)	179 (18.3)
Functional Scales QLQ-C30	Physical functioning	333 (34.1)	506 (51.8)	136 (13.9)
	Role functioning	342 (35.0)	415 (42.5)	217 (22.2)
	Emotional functioning	338 (34.6)	509 (52.2)	122 (12.5)
	Cognitive functioning	234 (24.0)	525 (53.8)	212 (21.7)
	Social functioning	403 (41.3)	375 (38.4)	191 (19.6)
Symptom Scales/Items QLQ-C30	Fatigue	451 (46.2)	364 (37.3)	160 (16.4)
	Nausea and vomiting	213 (21.8)	507 (51.9)	255 (26.1)
	Pain	470 (48.2)	392 (40.2)	113 (11.6)
	Dyspnoea	411 (42.1)	408 (41.8)	154 (15.8)
	Insomnia	420 (43.0)	396 (40.6)	159 (16.3)
	Appetite loss	355 (36.4)	420 (43.0)	200 (20.5)
	Constipation	185 (19.0)	356 (36.5)	428 (43.9)
	Diarrhoea	104 (10.7)	438 (44.9)	427 (43.8)
	Financial difficulties	249 (25.5)	553 (56.7)	167 (17.1)
Symptom Scales/Items QLQ-LC13	Dyspnoea	403 (41.3)	430 (44.1)	139 (14.2)
	Coughing	498 (51.0)	343 (35.1)	132 (13.5)
	Haemoptysis	89 (9.1)	863 (88.4)	21 (2.2)
	Sore mouth	119 (12.2)	744 (76.2)	111 (11.4)
	Dysphagia	149 (15.3)	701 (71.8)	123 (12.6)
	Peripheral neuropathy	216 (22.1)	518 (53.1)	238 (24.4)
	Alopecia	274 (28.1)	565 (57.9)	132 (13.5)
	Pain in chest	359 (36.8)	524 (53.7)	90 (9.2)
	Pain in arm or shoulder	352 (36.1)	498 (51.0)	120 (12.3)
	Pain in other parts	398 (40.8)	396 (40.6)	159 (16.3)

Abbreviations: BID=twice daily; EORTC QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 Questionnaire; n/N=number of subjects; PRO=patient-reported outcome; QoL=quality of life; QLQ-C30=Quality of Life Questionnaire – Core 30 Questionnaire; QLQ-LC13=Quality of Life Questionnaire – Lung Cancer 13.
%=(n/N)*100.
a. A subject with at least a 10-point improvement in the average of mean changes was improved.
b. A subject who was neither improved nor worsened was stable.
c. A subject with at least a 10-point deterioration in the average of mean changes was worsened.

EuroQol five dimensions questionnaire (EQ-5D)

EQ-5D visual analog score (VAS)

A statistically significant (95% CI excluded 0) improvement in health status as measured by the EQ-5D VAS scores was observed as early as Cycle 2, and this improvement was maintained through Cycle 30.(Table 12).

Table 12: Summary of mean Change from Baseline of EQ-5D VAS (Cycles 1 to 30 and EOT; PRO-Evaluable Population)

			Crizotinib 250 mg BID (N=974)		
Time Point	n	Median	Mean	SD	95% CI
Cycle 2/Day 1	926	5.00	5.72	17.51	(4.59, 6.85)
Cycle 3/Day 1	875	5.00	8.57	18.82	(7.32, 9.82)
Cycle 4/Day 1	826	8.00	10.01	19.73	(8.66, 11.36)
Cycle 5/Day 1	804	9.00	10.38	19.85	(9, 11.75)
Cycle 6/Day 1	771	8.50	10.17	20.38	(8.73, 11.61)
Cycle 7/Day 1	728	7.00	9.91	19.76	(8.47, 11.35)
Cycle 8/Day 1	693	9.00	10.35	19.22	(8.92, 11.78)
Cycle 9/Day 1	667	9.00	10.69	19.82	(9.18, 12.19)
Cycle 10/Day 1	633	7.00	10.34	19.15	(8.85, 11.84)
Cycle 11/Day 1	573	7.00	10.09	19.72	(8.48, 11.71)
Cycle 12/Day 1	409	8.00	9.69	18.81	(7.86, 11.52)
Cycle 13/Day 1	512	8.00	9.74	19.64	(8.04, 11.45)
Cycle 14/Day 1	351	10.00	10.93	18.67	(8.97, 12.89)
Cycle 15/Day 1	461	5.00	8.71	20.53	(6.83, 10.59)
Cycle 16/Day 1	289	5.00	8.47	20.66	(6.08, 10.87)
Cycle 17/Day 1	417	5.00	7.99	20.8	(5.99, 9.99)
Cycle 18/Day 1	244	5.00	7.62	19.86	(5.11, 10.12)
Cycle 19/Day 1	372	6.00	8.17	18.92	(6.24, 10.1)
Cycle 20/Day 1	219	6.00	8.03	18.45	(5.57, 10.48)
Cycle 21/Day 1	339	5.00	6.96	18.71	(4.96, 8.95)
Cycle 22/Day 1	179	5.00	6.59	18.97	(3.79, 9.39)
Cycle 23/Day 1	310	4.50	5.53	19.5	(3.35, 7.71)
Cycle 24/Day 1	154	5.00	7.61	19.58	(4.49, 10.73)
Cycle 25/Day 1	299	4.00	4.97	17.98	(2.92, 7.01)
Cycle 26/Day 1	128	6.50	8.54	18.97	(5.22, 11.86)
Cycle 27/Day 1	272	2.50	5.24	17.61	(3.13, 7.34)
Cycle 28/Day 1	120	5.00	7.93	19.53	(4.4, 11.46)
Cycle 29/Day 1	249	2.00	5.05	17.07	(2.92, 7.18)
Cycle 30/Day 1	108	6.00	8.07	19.95	(4.27, 11.88)
EOT	450	0.00	0.09	23.92	(-2.13, 2.31)

Abbreviations: Med=median, SD=standard deviation. EOT=End of Treatment. EOT is based on the actual CRF visit label. Visit windows were applied for the EQ-5D data with the expected Day 1 of each cycle as the midpoint.

Visual Symptom Assessment Questionnaire (VSAQ-ALK) Results Summary

The results of the first question on the VSAQ-ALK, "Have You Experienced any Visual Disturbances?" in the SA population up to and including Cycle 30 are presented in Table 13.

At Baseline, 16.0% of subjects reported experiencing a visual disturbance. During the first 30 cycles, 27.4% to 64.5% of subjects reported experiencing a visual disturbance, with the highest proportion at Cycle 2 and the lowest at Cycle 30 (Table 13).

Subjects were instructed to complete the remaining questions on the VSAQ-ALK only if they had a visual disturbance.

Table 13: Visual Symptom Assessment Question 1: Have You Experienced any Visual Disturbances? (Cycles 1 to 30 and EOT; SA Population)

Time Point	Total N+	Crizotinib 250 mg BID N=1066	
		Yes n (%)	No n (%)
Baseline	821	131 (16.0)	690 (84.0)
Cycle 2 / Day 1	798	515 (64.5)	283 (35.5)
Cycle 3 / Day 1	768	434 (56.5)	334 (43.5)
Cycle 4 / Day 1	754	394 (52.3)	360 (47.7)
Cycle 5 / Day 1	743	365 (49.1)	378 (50.9)
Cycle 6 / Day 1	731	357 (48.8)	374 (51.2)
Cycle 7 / Day 1	699	320 (45.8)	379 (54.2)
Cycle 8 / Day 1	670	293 (43.7)	377 (56.3)
Cycle 9 / Day 1	653	284 (43.5)	369 (56.5)
Cycle 10 / Day 1	621	265 (42.7)	356 (57.3)
Cycle 11 / Day 1	565	227 (40.2)	338 (59.8)
Cycle 12 / Day 1	403	173 (42.9)	230 (57.1)
Cycle 13 / Day 1	507	209 (41.2)	298 (58.8)
Cycle 14 / Day 1	354	147 (41.5)	207 (58.5)
Cycle 15 / Day 1	468	183 (39.1)	285 (60.9)
Cycle 16 / Day 1	296	129 (43.6)	167 (56.4)
Cycle 17 / Day 1	418	156 (37.3)	262 (62.7)
Cycle 18 / Day 1	249	100 (40.2)	149 (59.8)
Cycle 19 / Day 1	378	139 (36.8)	239 (63.2)
Cycle 20 / Day 1	221	86 (38.9)	135 (61.1)
Cycle 21 / Day 1	344	134 (39.0)	210 (61.0)
Cycle 22 / Day 1	181	71 (39.2)	110 (60.8)
Cycle 23 / Day 1	312	109 (34.9)	203 (65.1)
Cycle 24 / Day 1	155	54 (34.8)	101 (65.2)
Cycle 25 / Day 1	302	108 (35.8)	194 (64.2)
Cycle 26 / Day 1	130	40 (30.8)	90 (69.2)
Cycle 27 / Day 1	276	90 (32.6)	186 (67.4)
Cycle 28 / Day 1	118	37 (31.4)	81 (68.6)
Cycle 29 / Day 1	249	76 (30.5)	173 (69.5)
Cycle 30 / Day 1	106	29 (27.4)	77 (72.6)
EOT	428	168 (39.3)	260 (60.7)

Abbreviations: BID=twice daily; CRF=case report form; EOT=End of Treatment; N/N+n=number of subjects; SA=safety analysis; VSAQ=visual symptom assessment questionnaire.
Baseline was Cycle 1 Day 1.
%=(n/N+)*100, N+ was the number of subjects who had completed the first question.
EOT was based on the actual CRF visit label.
Visit windows were applied for the VSAQ data with the expected Day 1 of each cycle as the midpoint.

Pharmacokinetic Results:

Secondary endpoints

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

Summary of predose concentrations 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 14.

Table 14: Plasma concentrations of crizotinib (PF-02341066) and its metabolite PF-06260182, and PF-06260182 to crizotinib ratio, following 250 mg BID oral dosing of crizotinib

	Predose Plasma Concentrations[a] ng/mL (%)		
	Crizotinib (PF-02341066) N=906	PF-06260182 N=904	PF-06260182 to crizotinib ratio
Cycle 1 Day 1 (N=13, 13, 13)	1.95 (55)	0.00601 (167)	0.00416 (157)
Cycle 2 Day 1 (N=447, 431, 430)	279 (46)	76.2 (79)	0.263 (55)
Cycle 3 Day 1 (N=398, 385, 385)	297 (44)	80.8 (58)	0.264 (31)
Cycle 5 Day 1 (N=297, 290, 290)	294 (48)	81.4 (61)	0.266 (31)

N is the number of observations for crizotinib above limit of quantification.
Abbreviations: BID=twice daily; CV=coefficient of variation; PK=pharmacokinetic.
[a] Geometric mean (%CV).
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)])

Pharmacodynamic Results:

Secondary endpoints

Molecular Profiling (ALK Status)

ALK-positivity was determined by the IUO test in 908 subjects. The mean percentage of ALK-positive cells was 59.49% (Table 15).

Table 15: Descriptive Statistics for ALK Percentage of Positive Cells by Central Laboratory Test (SA [ALK-positive by IUO] Population)

Number of Subjects	Crizotinib 250 mg BID N=908
Percent of ALK-Positive Tumor Cells (%)	
n	908
Mean (standard deviation)	59.49 (21.18)
Median	60.00
Range	(15.00-100.00)

Abbreviations: ALK=anaplastic lymphoma kinase; BID=twice daily; IUO=investigational-use only; N/n=number of subjects; SA=safety analysis.
ALK-positive by IUO included all enrolled subjects with IUO results indicating ALK-positivity.

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

Analyses of change from Baseline in the expression of biomarkers relevant to signaling pathways were not performed because paired Baseline and on-treatment (Cycle 2) tumor tissue required for the analysis, which were collected on an optional basis, were not available.

Pharmacogenomic Results:

Assessment of Candidate Gene Alleles

The frequencies of the 4 candidate gene alleles, HLA-DQA1*02:01, HLA-DQB1*02:02, HLA-DRB1*07:01 and TNXB/rs12153855, among ALT Cases and ALT Controls were similar (Table 16), with no statistically significant differences observed that would support or suggest any predictive (i.e., diagnostic) value of these markers in identifying subjects who may be at increased risk for hepatic toxicity.

Table 16: ALT Case-Control Analysis of Pre-Defined Candidate Genetic Variants (PG Evaluable Population)

	Crizotinib 250 mg BID - ALT Cases	Crizotinib 250 mg BID - ALT Controls
Number of Participants Analyzed	74	115
Genetic Variants	(%)	(%)
HLA-DQA1*02:01	20.3	20.0
HLA-DQB1*02:02	17.6	16.5
HLA-DRB1*07:01	20.3	20.0
TNXB/rs12153855	10.8	16.5

Abbreviations: ALT=alanine aminotransferase; CI=confidence interval; HLA=major histocompatibility complex; N/n=number of subjects; PG=pharmacogenomic; TNXB=human tenascin XB gene; ULN=upper limit of normal.
%=(n/N)*100. N=total (N=74 for ALT Cases; N=115 for ALT Controls).
ALT Cases are defined as those subjects with a Baseline ALT of ≤1x ULN and at least one on-treatment ALT assessment of >3x ULN, and ALT controls represent those subjects with Baseline and on-treatment assessments of ALT of ≤1x ULN.

Exploratory Assessment of Additional Gene Alleles

The frequency of 2 additional HLA gene alleles, HLA-B*57:01 and HLA-DRB1*15:01, were also similar between ALT Cases and ALT Controls (Table 17), with no statistically significant associations observed that would support or suggest any predictive (i.e., diagnostic) value of these markers in identifying subjects who may be at increased risk for hepatic toxicity.

Table 17: ALT Case-Control Analysis of Additional HLA Genetic Variants (PG Evaluable Population)

	Crizotinib 250 mg BID - ALT Cases	Crizotinib 250 mg BID - ALT Controls
Number of Participants Analyzed	74	115
Genetic Variants	(%)	(%)
HLA-B*57:01	2.7	4.3
HLA-DRB1*15:01	17.6	20.9

Abbreviations: ALT=alanine aminotransferase; CI=confidence interval; HLA=major histocompatibility complex; N/n=number of subjects; PG=pharmacogenomic; TNXB=human tenascin XB gene; ULN=upper limit of normal.
%=(n/N)*100. N=total (N=74 for ALT Cases; N=115 for ALT Controls).
ALT Cases are defined as those subjects with a Baseline ALT of ≤1x ULN and at least one on-treatment ALT assessment of >3x ULN, and ALT controls represent those subjects with Baseline and on-treatment assessments of ALT of ≤1x ULN.

Safety Results:

Primary Endpoint

Percentage of subjects with adverse Events

Treatment-emergent adverse events due to all causality and treatment-related are summarized in Table 18. Almost all subjects experienced treatment-related AEs (96%) and 11.5% of all subjects experienced treatment-related SAEs. A total of 5.7% of subjects permanently discontinued due to treatment related AEs.

Table 18: Treatment-Emergent (All Causality and Treatment-Related) Adverse Events – SA Population

	Crizotinib 250 mg BID N=1066 n (%)	
	All causality	Treatment related
No. of AEs	16367	8644
Subjects with AEs	1061 (99.5)	1023 (96.0)
Subjects with serious AEs	539 (50.6)	123 (11.5)
Subjects with Grade 3 or 4 AEs	699 (65.6)	428 (40.2)
Subjects with Grade 5 AEs	242 (22.7)	17 (1.6)
Subjects with permanent discontinuation due to AEs	215 (20.2)	61 (5.7)
Subjects s with dose reduction due to AEs	209 (19.6)	196 (18.4)
Subjects with temporary discontinuation due to AEs	509 (47.7)	331 (31.1)

Abbreviations: AE=adverse event; BID=twice daily; CSR=clinical study report; N/n=number of subjects; SA=safety analysis.

Secondary endpoints

Electrocardiograms (ECGs)

ECGs were obtained from all subjects during the study. Most subjects had a maximum QTcF interval <480 msec (97.5%) (Table 19).

Table 19: Percentage of subjects with maximum Postdose QTcF Intervals (Except ECG Substudy Group) – SA Population

	Crizotinib 250 mg BID N=999 n (%)
Maximum QTcF Interval (msec)	
<450	897 (89.8)
450 - <480	77 (7.7)
480 - <500	10 (1.0)
≥500	15 (1.5)

Abbreviations: BID=twice daily; N/n=number of subjects; QTcF=corrected QT interval for heart rate using Fridericia's correction formula SA=safety analysis.
%=(n/N)•100.
N=number of subjects having a post-Baseline assessment.
n=number of subjects within category.

Serious Adverse Events

Serious adverse events are summarized in Table 20.

Table 20: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All causalities and treatment related)

	Crizotinib 250 mg BID	
	All causalities (%)	**Treatment related (%)**
Number (%) of Subjects:		
Evaluable for adverse events	1066	1066
With adverse events	539 (50.56)	123 (11.54)
Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v 18.1) Preferred Term		
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**13 (1.22)**	**5 (0.47)**
Anaemia	4 (0.38)	
Basophilia	1 (0.09)	1 (0.09)
Eosinophilia	1 (0.09)	1 (0.09)
Febrile neutropenia	6 (0.56)	4 (0.38)
Leukocytosis	1 (0.09)	
Monocytosis	1 (0.09)	1 (0.09)
Thrombocytopenia	1 (0.09)	
Thrombocytosis	1 (0.09)	1 (0.09)
CARDIAC DISORDERS	**36 (3.38)**	**6 (0.56)**
Acute myocardial infarction	2 (0.19)	
Angina pectoris	2 (0.19)	
Angina unstable	1 (0.09)	
Atrial fibrillation	3 (0.28)	1 (0.09)

	Crizotinib 250 mg BID	
	All causalities (%)	**Treatment related (%)**
Bradycardia	1 (0.09)	
Cardiac arrest	2 (0.19)	1 (0.09)
Cardiac failure	2 (0.19)	1 (0.09)
Cardiac failure congestive	1 (0.09)	
Cardiac tamponade	1 (0.09)	
Coronary artery stenosis	1 (0.09)	
Cyanosis	1 (0.09)	
Left ventricular failure	1 (0.09)	
Myocardial infarction	2 (0.19)	
Myocarditis	1 (0.09)	1 (0.09)
Palpitations	1 (0.09)	
Pericardial effusion	7 (0.66)	
Pericarditis	1 (0.09)	
Supraventricular tachycardia	1 (0.09)	1 (0.09)
Syncope	6 (0.56)	
Tachycardia	2 (0.19)	1 (0.09)
EYE DISORDERS	**7 (0.66)**	**2 (0.19)**
Cataract	2 (0.19)	1 (0.09)
Glaucoma	1 (0.09)	
Optic atrophy	1 (0.09)	1 (0.09)
Retinal detachment	1 (0.09)	
Vision blurred	1 (0.09)	
Vitreous haemorrhage	1 (0.09)	
GASTROINTESTINAL DISORDERS	**52 (4.88)**	**12 (1.13)**
Abdominal pain	6 (0.56)	
Abdominal wall haematoma	1 (0.09)	
Ascites	1 (0.09)	
Colitis	1 (0.09)	1 (0.09)
Constipation	3 (0.28)	1 (0.09)
Diarrhoea	4 (0.38)	2 (0.19)
Diarrhoea haemorrhagic	1 (0.09)	1 (0.09)
Dysphagia	7 (0.66)	
Gastric ulcer	1 (0.09)	1 (0.09)
Gastritis	1 (0.09)	
Gastrointestinal haemorrhage	3 (0.28)	2 (0.19)
Ileus	3 (0.28)	1 (0.09)
Intestinal obstruction	1 (0.09)	
Intestinal perforation	1 (0.09)	
Nausea	9 (0.84)	4 (0.38)
Oesophageal stenosis	1 (0.09)	
Oesophagitis	2 (0.19)	1 (0.09)
Pancreatic atrophy	1 (0.09)	
Pancreatitis	3 (0.28)	
Pancreatitis acute	1 (0.09)	
Peptic ulcer haemorrhage	1 (0.09)	
Peritoneal disorder	1 (0.09)	1 (0.09)
Rectal haemorrhage	1 (0.09)	
Retroperitoneal haemorrhage	1 (0.09)	
Small intestinal obstruction	1 (0.09)	
Subileus	1 (0.09)	
Upper gastrointestinal haemorrhage	1 (0.09)	
Vomiting	6 (0.56)	

	Crizotinib 250 mg BID	
	All causalities (%)	**Treatment related (%)**
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**192 (18.01)**	**14 (1.31)**
Asthenia	7 (0.66)	
Chest discomfort	2 (0.19)	
Chest pain	5 (0.47)	1 (0.09)
Chills	1 (0.09)	
Condition aggravated	2 (0.19)	
Death	8 (0.75)	3 (0.28)
Device dislocation	1 (0.09)	
Disease progression	135 (12.66)	
Fatigue	4 (0.38)	1 (0.09)
Gait disturbance	1 (0.09)	
General physical health deterioration	9 (0.84)	1 (0.09)
Generalised oedema	3 (0.28)	2 (0.19)
Mass	1 (0.09)	1 (0.09)
Multi-organ failure	1 (0.09)	
Oedema peripheral	7 (0.66)	5 (0.47)
Pain	1 (0.09)	
Pyrexia	18 (1.69)	
Vascular stent thrombosis	1 (0.09)	
HEPATOBILIARY DISORDERS	**11 (1.03)**	**9 (0.84)**
Cholecystitis	1 (0.09)	
Drug-induced liver injury	3 (0.28)	3 (0.28)
Hepatic failure	2 (0.19)	1 (0.09)
Hepatitis	1 (0.09)	1 (0.09)
Hepatocellular injury	1 (0.09)	1 (0.09)
Hepatotoxicity	3 (0.28)	3 (0.28)
IMMUNE SYSTEM DISORDERS	**1 (0.09)**	
Contrast media allergy	1 (0.09)	
INFECTIONS AND INFESTATIONS	**162 (15.20)**	**15 (1.41)**
Abdominal abscess	1 (0.09)	1 (0.09)
Abscess limb	1 (0.09)	
Appendicitis	8 (0.75)	
Bacteraemia	2 (0.19)	
Bone abscess	1 (0.09)	
Bronchitis	2 (0.19)	
Candiduria	1 (0.09)	
Cellulitis	13 (1.22)	2 (0.19)
Chest wall abscess	1 (0.09)	
Clostridium difficile infection	1 (0.09)	
Cystitis	1 (0.09)	
Diverticulitis	1 (0.09)	
Empyema	1 (0.09)	
Gastroenteritis	6 (0.56)	
Herpes zoster	3 (0.28)	
Infection	1 (0.09)	
Infectious pleural effusion	2 (0.19)	
Infective spondylitis	1 (0.09)	
Lower respiratory tract infection	3 (0.28)	
Lung abscess	1 (0.09)	
Lung infection	14 (1.31)	3 (0.28)
Lymphangitis	1 (0.09)	

	Crizotinib 250 mg BID	
	All causalities (%)	**Treatment related (%)**
Meningitis	1 (0.09)	
Metapneumovirus infection	1 (0.09)	
Oesophageal candidiasis	2 (0.19)	
Osteomyelitis chronic	1 (0.09)	
Peritonitis	1 (0.09)	
Pneumonia	74 (6.94)	6 (0.56)
Pneumonia bacterial	1 (0.09)	
Pneumonia fungal	1 (0.09)	
Pneumonia staphylococcal	1 (0.09)	
Pyelonephritis	1 (0.1)	
Renal abscess	2 (0.19)	1 (0.09)
Renal cyst infection	2 (0.19)	2 (0.19)
Respiratory tract infection	5 (0.47)	
Sepsis	8 (0.75)	
Septic shock	4 (0.38)	
Skin infection	4 (0.38)	
Soft tissue infection	1 (0.09)	
Staphylococcal sepsis	1 (0.09)	
Upper respiratory tract infection	7 (0.66)	
Urinary tract infection	7 (0.66)	
Urinary tract infection bacterial	1 (0.09)	
Viral infection	1 (0.09)	
Viral upper respiratory tract infection	1 (0.09)	
Wound infection	2 (0.19)	
INJURY, POISONING AND PROCEDURAL COMPLICATION	**31 (2.91)**	**1 (0.09)**
Ankle fracture	2 (0.19)	
Bone fissure	1 (0.09)	
Craniocerebral injury	1 (0.09)	
Dislocation of vertebra	1 (0.09)	
Fall	6 (0.56)	
Femoral neck fracture	4 (0.38)	
Femur fracture	4 (0.38)	
Hip fracture	1 (0.09)	
Humerus fracture	1 (0.09)	
Joint dislocation	1 (0.09)	
Lower limb fracture	1 (0.09)	
Overdose	1 (0.09)	
Pelvic fracture	1 (0.09)	
Postoperative wound complication	1 (0.09)	
Radiation necrosis	1 (0.09)	
Radiation pneumonitis	1 (0.09)	
Radius fracture	2 (0.19)	
Road traffic accident	2 (0.19)	
Spinal compression fracture	2 (0.19)	1 (0.09)
Subdural haemorrhage	1 (0.09)	
Traumatic haematoma	1 (0.09)	
Upper limb fracture	1 (0.09)	
Wound dehiscence	1 (0.09)	

	Crizotinib 250 mg BID	
	All causalities (%)	**Treatment related (%)**
INVESTIGATIONS	**13 (1.22)**	**10 (0.94)**
Alanine aminotransferase increased	5 (0.47)	5 (0.47)
Blood albumin decreased	1 (0.09)	1 (0.09)
Blood bilirubin increased	1 (0.09)	
Blood creatinine increased	1 (0.09)	1 (0.09)
Blood lactate dehydrogenase increased	1 (0.09)	1 (0.09)
C-reactive protein increased	1 (0.09)	
Electrocardiogram QT prolonged	1 (0.09)	1 (0.09)
Hepatic enzyme increased	1 (0.09)	1 (0.09)
Troponin I increased	1 (0.09)	
METABOLISM AND NUTRITION DISORDERS	**24 (2.25)**	**8 (0.75)**
Decreased appetite	3 (0.28)	1 (0.09)
Dehydration	4 (0.38)	2 (0.19)
Failure to thrive	2 (0.19)	
Fluid retention	1 (0.09)	
Hypercalcaemia	1 (0.09)	1 (0.09)
Hyperglycaemia	2 (0.19)	
Hyperkalaemia	1 (0.09)	
Hypoalbuminaemia	1 (0.09)	
Hypocalcaemia	1 (0.09)	
Hypoglycaemia	1 (0.09)	
Hypokalaemia	5 (0.47)	1 (0.09)
Hypomagnesaemia	1 (0.09)	
Hyponatraemia	4 (0.38)	2 (0.19)
Hypophosphataemia	1 (0.09)	1 (0.09)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**27 (2.53)**	**3 (0.28)**
Arthralgia	2 (0.19)	
Back pain	5 (0.47)	
Bursitis	1 (0.09)	
Chest wall mass	1 (0.09)	1 (0.09)
Joint swelling	1 (0.09)	
Lumbar spinal stenosis	1 (0.09)	
Muscular weakness	2 (0.19)	
Musculoskeletal pain	3 (0.28)	1 (0.09)
Myalgia	1 (0.09)	
Myopathy	1 (0.09)	
Neck pain	2 (0.19)	
Osteoarthritis	1 (0.09)	
Pain in extremity	2 (0.19)	
Pathological fracture	5 (0.47)	
Spinal column stenosis	1 (0.09)	
Spondylolisthesis	1 (0.09)	
Systemic lupus erythematosus	1 (0.09)	1 (0.09)

	Crizotinib 250 mg BID	
	All causalities (%)	**Treatment related (%)**
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS)	**12 (1.13)**	**4 (0.38)**
Basal cell carcinoma	1 (0.09)	1 (0.09)
Breast cancer	1 (0.09)	
Gallbladder cancer	1 (0.09)	
Malignant melanoma	2 (0.19)	1 (0.09)
Metastases to meninges	1 (0.09)	
Neoplasm malignant	1 (0.09)	
Neuroendocrine tumour	1 (0.09)	
Plasma cell myeloma	1 (0.09)	
Prostate cancer	1 (0.09)	
Small cell lung cancer	1 (0.09)	1 (0.09)
Squamous cell carcinoma of skin	2 (0.19)	2 (0.19)
NERVOUS SYSTEM DISORDERS	**49 (4.60)**	**3 (0.28)**
Aphasia	2 (0.19)	
Ataxia	1 (0.09)	
Brain oedema	3 (0.28)	
Cerebellar infarction	1 (0.09)	
Cerebral haemorrhage	4 (0.38)	
Cerebral infarction	1 (0.09)	
Cerebrovascular accident	1 (0.09)	
Chorea	1 (0.09)	
Coma	1 (0.09)	
Depressed level of consciousness	1 (0.09)	
Dizziness	2 (0.19)	1 (0.09)
Dysarthria	2 (0.19)	
Generalised tonic-clonic seizure	1 (0.09)	
Haemorrhage intracranial	1 (0.09)	
Headache	4 (0.38)	
Intracranial pressure increased	1 (0.09)	
Ischaemic stroke	1 (0.09)	
Nervous system disorder	2 (0.19)	
Neurological decompensation	1 (0.09)	
Paraplegia	1 (0.09)	
Peripheral motor neuropathy	1 (0.09)	
Peripheral sensorimotor neuropathy	1 (0.09)	
Peripheral sensory neuropathy	1 (0.09)	
Pyramidal tract syndrome	1 (0.09)	1 (0.09)
Seizure	9 (0.84)	1 (0.09)
Spinal cord compression	2 (0.19)	
Transient ischaemic attack	3 (0.28)	
Tremor	1 (0.09)	
Vocal cord paralysis	2 (0.19)	
PSYCHIATRIC DISORDERS	**14 (1.31)**	**1 (0.09)**
Completed suicide	1 (0.09)	
Confusional state	7 (0.66)	1 (0.09)
Depression	3 (0.28)	
Disorientation	1 (0.09)	
Mania	1 (0.09)	
Mental status changes	2 (0.19)	
Suicide attempt	1 (0.09)	

	Crizotinib 250 mg BID	
	All causalities (%)	**Treatment related (%)**
RENAL AND URINARY DISORDERS	**29 (2.72)**	**17 (1.59)**
Acute kidney injury	5 (0.47)	3 (0.28)
Dysuria	2(0.19)	
Haematuria	1 (0.09)	
Hydronephrosis	2 (0.19)	
Nephrolithiasis	2 (0.19)	1 (0.09)
Renal cyst	13 (1.22)	13 (1.22)
Renal cyst haemorrhage	1 (0.09)	
Renal failure	1 (0.09)	
Ureteral polyp	1 (0.09)	
Urinary retention	2 (0.19)	
Urinary tract obstruction	1 (0.09)	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**2 (0.19)**	
Benign prostatic hyperplasia	1 (0.09)	
Pelvic pain	1 (0.09)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**143 (13.41)**	**30 (2.81)**
Acute respiratory distress syndrome	1 (0.09)	
Acute respiratory failure	3 (0.28)	
Alveolitis	1 (0.09)	1 (0.09)
Asphyxia	1 (0.09)	
Atelectasis	1 (0.09)	
Bronchial hyperreactivity	1 (0.09)	
Chronic obstructive pulmonary disease	1 (0.09)	
Cough	3 (0.28)	
Dyspnoea	39 (3.66)	6 (0.56)
Epistaxis	1 (0.09)	
Haemoptysis	3 (0.28)	1 (0.09)
Haemothorax	1 (0.09)	
Hypoxia	4 (0.38)	
Interstitial lung disease	5 (0.47)	2 (0.19)
Lung infiltration	1 (0.09)	
Oropharyngeal pain	1 (0.09)	
Pleural effusion	14 (1.31)	1 (0.09)
Pleuritic pain	1 (0.09)	
Pneumonia aspiration	4 (0.38)	
Pneumonitis	17 (1.59)	14 (1.31)
Pneumothorax	8 (0.75)	
Pulmonary arterial hypertension	1 (0.09)	
Pulmonary artery thrombosis	2 (0.19)	
Pulmonary embolism	26 (2.44)	4 (0.38)
Pulmonary haemorrhage	1 (0.09)	
Pulmonary oedema	1 (0.09)	
Pulmonary thrombosis	1 (0.09)	
Rales	2 (0.19)	
Respiratory failure	17 (1.59)	1 (0.09)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**2 (0.19)**	**1 (0.09)**
Paraneoplastic pemphigus	1 (0.09)	
Rash	1 (0.09)	1 (0.09)
SURGICAL AND MEDICAL PROCEDURES	**1 (0.09)**	
Pleural decortication	1 (0.09)	

	Crizotinib 250 mg BID	
	All causalities (%)	**Treatment related (%)**
VASCULAR DISORDERS	**41 (3.85)**	**8 (0.75)**
Deep vein thrombosis	14 (1.31)	4 (0.38)
Embolism	1 (0.09)	
Haematoma	3 (0.28)	1 (0.09)
Hypotension	1 (0.09)	1 (0.09)
Hypovolaemic shock	1 (0.09)	
Orthostatic hypotension	1 (0.09)	1 (0.09)
Peripheral arterial occlusive disease	1 (0.09)	
Peripheral embolism	2 (0.19)	
Phlebitis	1 (0.09)	
Superior vena cava syndrome	4 (0.38)	
Thrombophlebitis	1 (0.09)	1 (0.09)
Thrombosis	5 (0.47)	
Vasculitis	1 (0.09)	1 (0.09)
Vena cava thrombosis	2 (0.19)	
Venous thrombosis	4 (0.38)	

Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA (v 18.1) coding dictionary applied.

Non-Serious Adverse events:

Non-serious adverse events are summarized in Table 21. Vision disorder, nausea, vomiting, and diarrhoea were the most common treatment related AEs.

Table 21: Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and treatment related) in > 5% of Subjects

	Crizotinib 250 mg BID	
	All causalities (%)	**Treatment related (%)**
Number (%) of Subjects:		
Evaluable for adverse events	1066	1066
With adverse events	1038 (97.37)	991 (92.96)
Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v18.1) Preferred Term		
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**332 (31.14)**	**242 (22.70)**
Anaemia	138 (12.95)	74 (6.94)
Leukopenia	101 (9.47)	92 (8.63)
Lymphopenia	71 (6.66)	
Neutropenia	180 (16.89)	169 (15.85)
CARDIAC DISORDERS	**93 (8.72)**	**74 (6.94)**
Bradycardia	93 (8.72)	74 (6.94)
EYE DISORDERS	**587 (55.07)**	**557 (52.25)**
Photopsia	96 (9.01)	92 (8.63)
Vision blurred	80 (7.50)	64 (6.00)
Visual impairment	460 (43.15)	443 (41.56)

	Crizotinib 250 mg BID	
	All causalities (%)	**Treatment related (%)**
GASTROINTESTINAL DISORDERS	**933 (87.52)**	**872 (81.80)**
Abdominal pain	118 (11.07)	57 (5.35)
Abdominal pain upper	106 (9.94)	68 (6.38)
Constipation	475 (44.56)	368 (34.52)
Diarrhoea	548 (51.41)	498 (46.72)
Dyspepsia	81 (7.60)	
Dysphagia	56 (5.25)	
Nausea	603 (56.57)	546 (51.22)
Vomiting	565 (53.00)	496 (46.53)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**754 (70.73)**	**562 (52.72)**
Asthenia	156 (14.63)	93 (8.72)
Chest pain	105 (9.85)	226 (21.20)
Fatigue	326 (30.58)	
Oedema	96 (9.01)	68 (6.38)
Oedema peripheral	450 (42.21)	356 (33.40)
Pyrexia	181 (16.98)	
INFECTIONS AND INFESTATIONS	**278 (26.08)**	
Nasopharyngitis	113 (10.60)	
Upper respiratory tract infection	145 (13.60)	
Urinary tract infection	62 (5.82)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**59 (5.53)**	
Fall	59 (5.53)	
INVESTIGATIONS	**551 (51.69)**	**387 (36.30)**
Alanine aminotransferase increased	302 (28.33)	287 (26.92)
Aspartate aminotransferase increased	233 (21.86)	224 (21.01)
Blood alkaline phosphatase increased	76 (7.13)	
Blood creatinine increased	105 (9.85)	68 (6.38)
Blood lactate dehydrogenase increased	60 (5.63)	
Neutrophil count decreased	84 (7.88)	80 (7.50)
Weight decreased	109 (10.23)	
Weight increased	98 (9.19)	
White blood cell count decreased	98 (9.19)	94 (8.82)
METABOLISM AND NUTRITION DISORDERS	**488 (45.78)**	**226 (21.20)**
Decreased appetite	326 (30.58)	226 (21.20)
Hyperglycaemia	55 (5.16)	
Hypoalbuminaemia	98 (9.19)	
Hypocalcaemia	99 (9.29)	
Hypokalaemia	77 (7.22)	
Hyponatraemia	54 (5.07)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**418 (39.21)**	
Arthralgia	131 (12.29)	
Back pain	184 (17.26)	
Muscle spasms	79 (7.41)	
Muscular weakness	57 (5.35)	
Musculoskeletal pain	74 (6.94)	
Pain in extremity	137 (12.85)	

	Crizotinib 250 mg BID	
	All causalities (%)	**Treatment related (%)**
NERVOUS SYSTEM DISORDERS	**541 (50.75)**	**340 (31.89)**
Dizziness	265 (24.86)	150 (14.07)
Dysgeusia	213 (19.98)	206 (19.32)
Headache	214 (20.08)	74 (6.94)
Hypoaesthesia	65 (6.10)	
Paraesthesia	83 (7.79)	
PSYCHIATRIC DISORDERS	**190 (17.82)**	
Anxiety	76 (7.13)	
Insomnia	136 (12.76)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**470 (44.09)**	
Cough	260 (24.39)	
Dyspnoea	224 (21.01)	
Haemoptysis	55 (5.16)	
Oropharyngeal pain	75 (7.04)	
Productive cough	71 (6.66)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**244 (22.89)**	**95 (8.91)**
Alopecia	67 (6.29)	
Pruritus	84 (7.88)	
Rash	134 (12.57)	95 (8.91)

Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA (v 18.1) coding dictionary applied.

Deaths:

A total of 727 deaths reported due to all causes during the study and the most common cause of deaths was disease under study in 653 subjects (61.3%). Overall, 236 (22.1%) subjects died during treatment (ie, ⩽28 days after the last dose of study drug), and 491 (46.1%) subjects died >28 days after the last dose of study drug (Table 22).

Table 22: Deaths - SA population

	Crizotinib 250 mg BID N=1066 n (%)
Deaths from all causes	727 (68.2)
Within 28 days of last dose of study drug	236 (22.1)
More than 28 days after last dose of study drug	491 (46.1)
Deaths within 30 days of first dose of study drug	44 (4.1)
Deaths within 60 days of first dose of study drug	76 (7.1)
Cause of death [a]	
Disease under study	653 (61.3)
Study drug toxicity	12 (1.1)
Unknown [b]	31 (2.9)
Other	34 (3.2)

Summary of death data was based on the NOD CRF page.
Abbreviations: BID=twice daily; CRF=case report form; N/n=number of subjects; NOD=Notice of Death; SA=safety analysis.
[a] More than 1 cause of death may have been reported.
[b] Unknown cause of death included "Not Reported".

Grade 5 treatment-related AEs:

In total, 17 (1.6%) subjects experienced Grade 5 treatment related AEs with the most common being interstitial lung disease (Table 23: Overview of Grade 5 Treatment-Related Adverse Events – SA PopulationTable 23).

Table 23: Overview of Grade 5 Treatment-Related Adverse Events – SA Population

MedDRA Preferred Term or Clustered Term	Crizotinib 250 mg BID N=1066 n (%)
Any AE	17 (1.6)
Interstitial lung disease	4 (0.4)
Pneumonia	3 (0.3)
Death	3 (0.3)
Hepatotoxicity	2 (0.2)
Lung infection	2 (0.2)
Dyspnoea	1 (0.1)
Pulmonary embolism	1 (0.1)
Cardiac arrest	1 (0.1)

MedDRA v18.1 coding dictionary was applied.
Abbreviations: AE=adverse event; BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of subjects; SA=safety analysis; v=version.

Permanent Discontinuations Associated With AEs

All-causality and treatment-related AEs associated with permanent discontinuation of treatment, which occurred at a frequency ≥1% (ie, ≥11 subjects), are presented in Table 24.

Table 24: Treatment-Emergent Adverse Events in ≥1% of Subjects Associated with Permanent Discontinuation from Treatment (All Causality and Treatment-Related) – SA Population

MedDRA Preferred Term or Clustered Term	Crizotinib 250 mg BID N=1066 n (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Any all causality AEs[a]	10 (0.9)	8 (0.8)	40 (3.8)	23 (2.2)	134 (12.6)	215 (20.2)
Disease progression	0	0	0	0	52 (4.9)	52 (4.9)
Pneumonia	0	0	3 (0.3)	1 (0.1)	14 (1.3)	18 (1.7)
Interstitial lung disease	3 (0.3)	2 (0.2)	3 (0.3)	3 (0.3)	5 (0.5)	16 (1.5)
Dyspnoea	0	2 (0.2)	3 (0.3)	2 (0.2)	4 (0.4)	11 (1.0)
Any treatment related AEs[a]	10 (0.9)	3 (0.3)	23 (2.2)	11 (1.0)	14 (1.3)	61 (5.7)
Interstitial lung disease	3 (0.3)	2 (0.2)	3 (0.3)	3 (0.3)	3 (0.3)	14 (1.3)

AEs ordered by descending frequency of occurrence in total number of subjects.
Data were based on AE CRF page.
MedDRA (v18.1) coding dictionary was applied.
Abbreviations: AE=adverse event; BID=twice daily; CRF=case report form; MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of subjects; SA=safety analysis; v=version.
[a] Any AE columns also include AEs that occurred in <1% of subjects.

CONCLUSIONS:

- Crizotinib 250 mg orally BID had clinically meaningful antitumor activity as a single-agent in subjects with ALK-positive advanced NSCLC after failure of at least 1 line of chemotherapy, with a derived tumor assessment ORR of 54.1% (95% CI: 50.8, 57.4) in the ALK-positive by IUO population and responses that were rapid, with a median TTR of 6.1 weeks, and durable with a median DR of 11.8 months.

- Crizotinib had a clinically meaningful median PFS of 8.4 months (95% CI: 7.1, 9.7), a median OS of 21.8 months (95% CI: 19.4, 24.0), and probabilities of survival at 6 months and 12 months of 81.7% and 66.5%, respectively.

- Crizotinib had a side effect profile with AEs that were generally tolerable and manageable by dosing interruption, dose reduction, and/or standard medical therapy, as the most common treatment-related AEs were visual and gastrointestinal in nature, which have been mostly mild to moderate in severity. Patient-reported visual events were transient with minimal impact on daily activities.

- Crizotinib treatment resulted in statistically significant and clinically meaningful improvements from Baseline in key patient-reported lung cancer symptoms and patient-reported global QoL.

- There were no statistically significant associations observed that would support or suggest any predictive (ie, diagnostic) value of the 4 candidate gene alleles (HLA-DQA1*02:01, HLA-DQB1*02:02, HLA-DRB1*07:01, and TNXB/rs12153855) and of the 2 additional exploratory gene alleles (HLA-B*57:01 and HLA-DRB1*15:01) in identifying subjects who may be at increased risk for hepatic toxicity.