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

PROTOCOL NO.: A8081014

PROTOCOL TITLE: Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of Crizotinib Versus Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated Subjects With Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus.

Study Centers: This was a multicenter study conducted at 169 centers in 31 countries. Twenty-eight in United States, 16 in Italy, 15 in Japan, 9 each in Spain, and France, 8 each in Australia, Belgium, and China, 7 in Germany, 5 each in Brazil, Canada, and United Kingdom, 4 each in Portugal, Russia, Taiwan, and Singapore, 3 each in Chile, Finland, Korea, Netherlands, Ukraine and Switzerland, 2 each in Hong Kong, India, and South Africa, and 1 each in Austria, Ireland, Luxembourg, Mexico, Peru, and Norway.

Study Initiation Date and Primary Completion or Final Completion Dates:

Study Initiation Date = 13 January 2011
Final Completion Date = Ongoing at data cutoff 30 November 2013

Phase of Development: Phase 3

Study Objectives:

Primary Objective

- To demonstrate that crizotinib (Arm A) is superior to first-line chemotherapy, pemetrexed/cisplatin or pemetrexed/carboplatin (Arm B), in prolonging PFS in subjects with advanced non-squamous Non-Small Cell Lung Cancer (NSCLC) whose tumors harbor a translocation or inversion event involving the Anaplastic Lymphoma Kinase (ALK) gene locus.

Secondary Objectives

- To compare secondary measures of clinical efficacy including Objective Response Rate (ORR), Overall Survival (OS), disease control rate (DCR) at 12 weeks, and times to overall, intracranial and extracranial progression (Time to Overall Progression [TTP], Time to Intracranial Progression [IC-TTP], Time to Extracranial Progression [EC-TTP]) between the 2 treatment arms and to evaluate OS at 1 year and 18 months, duration of response (DR), and time to tumor response (TTR).

- To evaluate the safety and tolerability of crizotinib compared to chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin).
- To evaluate PK of crizotinib (including its active moieties, if appropriate) in this subject population using population PK (POPPK) methods and explore correlations between PK, response and/or safety findings, Arm A only.
- To correlate ALK gene fusion variants to outcome measures.
- To compare patient-reported outcomes (PRO) of health-related quality of life, functioning, disease/treatment-related symptoms of lung cancer, and general health status in both treatment arms.
- To assess health care resource utilization (HCRU) with respect to hospitalization (ie, length of stay, frequency) and concomitant medication use for select adverse events (AEs) (eg, hematologic events).

METHODS

Study Design:

This is an open label, multicenter, randomized, Phase 3, efficacy and safety study of crizotinib versus [vs] first line chemotherapy, ie, pemetrexed/cisplatin or pemetrexed/carboplatin, in subjects with ALK positive, non-squamous NSCLC.

A total of 334 subjects were planned to be randomized in a 1:1 ratio to receive crizotinib or chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin). The choice of platinum doublet chemotherapy in the chemotherapy arm was made by the investigator. Each treatment cycle was defined as 3 weeks (21 days). Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0-1 or 2), race (Asian or non-Asian), and brain metastases (presence or absence).

Subjects were to continue in the assigned treatment arm until Response Evaluation Criteria in Solid Tumors (RECIST; Version 1.1) defined progressive disease (PD), as determined by independent radiology review (IRR), unacceptable toxicity, death, or consent withdrawal. In the crizotinib arm, subjects could continue crizotinib treatment beyond the time of RECIST defined PD, as determined by IRR, at the discretion of the investigator if the subject was perceived to be experiencing clinical benefit. In the chemotherapy arm, subjects could be dosed for up to 6 cycles of chemotherapy as long as they met the chemotherapy retreatment criteria. If a subject completed the 6 cycles of chemotherapy, he/she was to remain in the study with no additional treatment (ie, maintenance therapy was not permitted) and with ongoing tumor assessments until RECIST defined PD, as determined by IRR. Once subjects in the chemotherapy arm had RECIST defined PD, as determined by IRR, they were allowed to cross over to receive crizotinib treatment providing they met the safety screening inclusion/exclusion criteria for crizotinib.

The schedule of activities is shown in Table 1.

Table 1: Schedule of Activities

Protocol Activities	Screening[a]	Study Treatment[b]				End of Treatment	
		Cycle 1			Cycles ≥2		
	≤28 Days Prior to Dosing	Day 1 (±2)[c]	Day 7 (±1)	Day 15 (±2)	Day 1 (±2; ±7 for Imaging)	End of Treatment/ Withdrawal[d]	Post Treatment 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						
Optional tumor tissue for molecular profiling (Arm A and crossover)[h]						X	
Physical examination[i]	X	(X)			X	X	
ECOG performance status	X	X			X	X	
Ophthalmologic examination[j]	X				Cycle 5 and every 4 cycles thereafter - France only; End of every cycle – India only; All subjects – anytime there was a change in CTCAE grade		
Laboratory studies							
Urinalysis -– protein/blood by dipstick (all subjects); reflex microscopy if dipstick positive (all subjects)[k]	X	X (Korea only); all subjects as clinically indicated			X (Korea only); all subjects as clinically indicated	X (Korea only)	
Hematology[l]	X	(X)		X	X	X	
Blood chemistry[l]	X	(X)		X	X	X	
Coagulation[l]	X	(X)					
12-lead ECG[m]	X single	X in triplicate			X (Cycles 2, 3) in triplicate		
Pregnancy test (as appropriate)[n]	X					X	
Disease Assessments							
Tumor assessments (including scans)[o]	X				X (every 6 ± 1 week; every 12 ± 1 week for crossover or crizotinib past progression subjects)	X	X
Other clinical assessments							
Adverse events and hospitalizations[p]	X	X		X	X	X	X
Concomitant medications/treatments[q]	X	X		X	X	X	X
EORTC QLQ-C30 and QLQ-LC13[r]		X	X	X	X	X	
VSAQ-ALK and EQ-5D[s]		X			X	X	

Protocol Activities	Screening[a]	Study Treatment[b]				End of Treatment	
		Cycle 1			Cycles ≥2		
	≤28 Days Prior to Dosing	Day 1 (±2)[c]	Day 7 (±1)	Day 15 (±2)	Day 1 (±2; ±7 for Imaging)	End of Treatment/ Withdrawal[d]	Post Treatment Follow-Up
MUGA scan or echocardiogram[t]	X				Cycle 3, then every 4 cycles		
Survival follow-up[u]							X
Study treatment							
Study randomization	X (Day -7 to Day 0)						
Vitamin premedication	X (commencing Day -7 until end of Cycle 6)						
Crizotinib (Arm A and crossover)		Once or Twice Daily					
Cisplatin and pemetrexed (Arm B option)		X			X (6 cycle maximum)		
Carboplatin and pemetrexed (Arm B option)		X			X (6 cycle maximum)		
Special laboratory studies							
Pharmacokinetics (Arm A only)[v]		X			X (Cycles 2, 3, 5)		
Optional blood sample for pharmacogenomics (crizotinib-treated subjects only)[w]		X					
Hypogonadism laboratory tests[x] (males on crizotinib [Arm A and those crossing over from Arm B])	X			X	X (Cycle 2 Day 1, Cycle 5 Day 1, Cycle 7 Day 1, and every 4 cycles thereafter)	X	
Hypogonadism laboratory tests[x] (males on chemotherapy [Arm B])	X			X	X (Cycle 2 Day 1, Cycle 5 Day 1)	X	
DXA scan[y] (males on crizotinib [Arm A and those crossing over from Arm B])	X				X (Cycle 7 Day 1)[y]	X see footnote [y] for details	
DXA scan[y] (males on chemotherapy [Arm B])	X					X[y]	

Abbreviations: AE=adverse event; ALK=anaplastic lymphoma kinase; ALT=alanine transaminase; Arm A=crizotinib arm; Arm B=chemotherapy arm; AST=aspartate transaminase; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; DNA=deoxyribonucleic acid; DXA=dual energy X-ray absorptiometry; EORTC=European Organization for the Research and Treatment of Cancer; EQ-5D=EuroQol-5D; FISH=fluorescence in-situ hybridization; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; IEC=Independent Ethics Committee; IRB=Institutional Review Board; K_2EDTA=dipotassium ethylenediamine tetraacetic acid; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition; NCI=National Cancer Institute; PD=progressive disease; PK=pharmacokinetic; QLQ-C30=Quality of Life Questionnaire-Core 30; QLQ-LC13=Quality of Life Questionnaire-Supplement Module for Lung Cancer (LC13); QTc=corrected QT interval; RECIST=Response Evaluation Criteria in Solid Tumors; ULN=upper limit of normal; VSAQ-ALK=Visual Symptom Assessment Questionnaire-ALK.

[a] **Screening:** For Arm B subjects who crossed over to receive crizotinib treatment, screening laboratory tests were ideally to be performed within the previous 5 days, whereas the physical examination, ECOG performance status, and pregnancy test did not need to be repeated if these were performed within 21 days of the previous evaluation. Screening ECG was to be repeated. The results of these tests had to meet eligibility criteria in order for the subject to receive crossover crizotinib treatment. Screening

ophthalmology examination and mandatory tumor tissue for molecular profiling did not need to be repeated.

[b] **Study Treatment**: All assessments were to be performed prior to dosing with study treatment unless otherwise indicated. Every effort was to be made to start study treatment within 2 days of randomization to ensure comparability of the 2 treatment arms and the time of treatment start after randomization. Acceptable time windows for performing each assessment are described in the column headings. All cycles were 21 days in duration.
Once the primary endpoint (progression-free survival) for the study has been summarized and reported in this clinical study report, ongoing subjects in Arm A or those subjects who crossed over to receive crizotinib treatment will only need to visit the study site every other cycle for study assessments instead of every cycle. Hematology and blood chemistry tests will still be required in the non-visit cycle ie, approximately 3 weeks after previous laboratory testing, but can be done locally. Enough study treatment for 2 cycles of treatment will be dispensed at each site visit. During the non-visit cycle, subjects are to telephone the study site to provide an update of adverse events and concomitant medications and to provide results of the local laboratory tests.

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

[d] **End of Treatment/Withdrawal:** These assessments were to be obtained, if not completed, during the previous 4 weeks on study (during the last 6 weeks for disease assessments). The end of treatment visit was usually scheduled for 28 days post last dose of study treatment or when the decision was taken to provide alternative anticancer therapy, whichever was sooner. For male subjects only: all attempts were to be made to obtain the blood sample for hypogonadism assessment and DXA scan for bone mineral density and muscle mass assessment at least 4 weeks after the last dose of study treatment if possible and prior to the commencement of new anticancer therapy.

[e] **Informed Consent:** Had to be obtained prior to undergoing any study-specific procedure.

[f] **Medical/Oncological History:** To include information on smoking history, prior regimens, and tumor marker status.

[g] **Mandatory Tumor Tissue for Molecular Profiling:** Paraffin block(s) were to be of adequate size to allow, if possible, at least 10 slides with cuts that were 5 microns thick. If no block was available, then the sites were to try to obtain at least 10 slides with cuts that were 5 microns thick. Archived or fresh tumor samples obtained according to the institutional practice for biopsy were acceptable. These samples were used for the assessment of ALK gene fusion by FISH by the central laboratory. Tumor samples that were sent directly to the central laboratory for testing could also be tested by FISH by a secondary laboratory for concordance. Tumor samples could also be used for analysis of the presence of ALK protein and ALK fusion transcripts. The mandatory tumor tissue sample could be completed outside the 28-day screening window.

[h] **Optional Tumor Tissue for Molecular Profiling (Arm A and crossover):** An optional fresh tumor sample was to be collected at the end of treatment if a subject discontinued due to PD. This included subjects who crossed over from Arm B to crizotinib.

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

[j] **Ophthalmologic Examination:** Included visual acuity, fundoscopy, and slit lamp, and was to be performed by an ophthalmologist. The ophthalmologic examination was to be repeated during the study when visual disturbances had been observed, when there had been a reported change in CTCAE grade, or as clinically indicated. For all subjects enrolled in France, ophthalmology examinations were to be performed after the completion of every 4 cycles. For all subjects enrolled in India, ophthalmology examinations were to be performed after the completion of every cycle.

[k] **Dipstick Urinalysis and Reflex Microscopy:** In Korea (after Protocol Amendment 4), repeat examinations were to be completed at Day 1 of every cycle and at the end of treatment; all other countries were to perform examinations as clinically indicated, eg, upon diagnosis of renal cysts. Reflex microscopy was required if urine dipstick was positive for blood or protein.

[l] **Hematology, Blood Chemistry, and Coagulation:** For subjects on crizotinib treatment: liver function tests were to be repeated within 48 hours if the following was observed and repeated weekly until recovery to baseline levels:
- if a subject entered the study with AST or ALT and total bilirubin baseline values within the normal range who subsequently presented with AST or ALT ≥3 x ULN concurrent with total bilirubin ≥2 x ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 ULN or not available,
- OR if a subject entered the study with pre-existing AST or ALT baseline values above the normal range who subsequently presented with AST or ALT ≥2 times the baseline values and ≥3 x ULN, or ≥8 x ULN (whichever was smaller) concurrent, in subjects with pre-existing values of total bilirubin above the normal range, with a total bilirubin increased by 1 x ULN, or >3 x ULN (whichever was smaller).

During this time, crizotinib treatment was to be withheld and recommenced if appropriate after consulting dose-modification. A 4 mL serum sample obtained just prior to the first dose of study treatment was to be stored frozen on-site through completion of the study for possible use as a baseline reference should additional laboratory tests be indicated, eg, additional testing to exclude other causes for liver injury.

[m] **12-lead ECG:** All subjects were required to have a single ECG measurement at screening. Triplicate ECG measurements (approximately 2 minutes apart) were to be measured at all later time points with all 3 measurements obtained within a 10-minute time window for each time point. ECGs were to be performed immediately before PK blood draws at respective time points. After Protocol Amendment 6, additional triplicate ECG measurements were required in all subjects randomized to Arm A. ECGs were to be obtained at 0 hour (predose) on Day 1 of Cycles 1, 2, and 3. Subsequent ECGs were to be taken at 3 and 5 hours after morning crizotinib dosing on Day 1 of Cycles 1, 2, and 3. After Protocol Amendment 6, all ECG tracings were to be sent electronically to a core ECG laboratory for blinded manual interval measurements. For Arm B subjects and subjects crossing over to crizotinib from Arm B (triplicate ECG assessments), ECGs were to be obtained at 0 hour (prior to the start of dosing) on Day 1 of Cycles 1, 2, and 3. For all subjects, if the QTc was prolonged (>500 msec), then the ECG was to be read by a cardiologist at the site for confirmation (to look for spurious QT effects). Additional ECGs were to be performed as clinically indicated.

[n] **Pregnancy Test:** All female subjects of child-bearing potential were required to have a negative pregnancy test at screening. The test was to be repeated whenever 1 menstrual cycle was missed during treatment or a potential pregnancy was otherwise suspected, and again at end of treatment. Pregnancy tests could also be repeated at the request of IRB/IECs or if required by local regulations.

[o] **Tumor Assessments:** CT or MRI was to include chest, abdomen and pelvis (CAP) at all time points. Bone scintigraphy/bone scans and brain scans/head CT/MRI were also required at screening. All subsequent scans were based on a calendar schedule beginning from the date of randomization. The first post-randomization scan was to be performed at 6 weeks (+1 week); all subsequent scans could be performed at 6 weeks (±1 week). The brain was to be included in subsequent tumor assessments if a subject had brain metastases; otherwise, the brain was to be evaluated every 12 weeks. Bone metastases, if present at baseline, were to be followed on study by separate CT/MRI/scan or X-ray every 6 weeks if the metastases were outside the CAP field of imaging. In all subjects, repeat bone scintigraphy/bone scans were required every 12 weeks to monitor for new lesions. A CT or MRI scan was also to be performed whenever PD was suspected (eg, symptomatic deterioration). All scans were to be sent to an independent radiology laboratory for a blinded RECIST review. Tumor assessments were to continue until PD had been determined by the independent radiologist, which included those subjects who had stopped treatment for reasons other than PD but remained on study. Crossover subjects and subjects continuing crizotinib therapy after independent radiology review had declared PD were to continue to have tumor assessments; however, these no longer required central independent radiology review. The tumor assessments after central review progression had been declared were to be performed every 12 weeks ± 1 week.

[p] **Adverse Events and Hospitalizations:** Subjects were to be followed for adverse events and hospitalizations 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 treatment-related toxicities had resolved or were determined to be "chronic" or "stable", whichever was later. Serious adverse events were to be monitored and reported from the time that the subject provided informed consent. Hospitalizations were to be recorded from 28 days prior to the start of study treatment and up to 28 days post the last dose of study treatment. Adverse events were graded using NCI CTCAE Version 4.

[q] **Concomitant Medications/Treatments:** Concomitant medications and treatments were to be recorded from 28 days prior to the start of study treatment and up to 28 days post the last dose of study treatment.

[r] **EORTC QLQ-C30 and QLQ-LC13:** Subjects were to complete all EORTC QLQ-C30 and QLQ-LC13 self-assessment questionnaires in the study site at the specified time points with the exception of the Day 7 assessment. The Day 7 assessment could be completed at home and was to be given to subjects along with completion guidelines/on-site training at the Cycle 1/Day 1 visit (baseline). At Cycle 1/Day 1, site staff (eg, site coordinators) were to instruct subjects that the Day 7 assessment was to be completed without help from friends or family members and also recommend that this assessment be completed in the morning. On Day 7 (or the day prior), a member of the site staff was to call to remind subjects to complete the assessment that day and to return completed questionnaires at their next visit (Day 15). All other scheduled assessments of the EORTC QLQ-C30 and QLQ-LC13 could not be taken home and were to be completed in the site prior to any other study or medical procedures. Questionnaires were also to be completed in crossover subjects at the same specified time points.

[s] **VSAQ-ALK and EQ-5D:** Subjects were to complete the VSAQ-ALK and the EQ-5D questionnaires at the study site prior to any study or medical procedure. All self-assessment questionnaires were to be completed by the subjects while at the site and could not be taken home. Translation of the VSAQ-ALK into different languages was undertaken and many language versions were available. However, if the VSAQ-ALK was not available in the subject's preferred language, the subject did not need to complete this assessment. Questionnaires were also to be completed by crossover subjects at the same specified time points.

[t] **MUGA Scan or Echocardiogram:** MUGA scans or echocardiograms were to be obtained from all subjects until sufficient data were available to discontinue collecting from newly enrolled subjects. The rationale for discontinuing this procedure will be provided to the IRB/IEC along with the amended protocol.

[u] **Survival Follow Up:** After discontinuation of study treatment and/or confirmed PD, post-study survival status was to be collected every 2 months until death or until 18 months after the randomization of the last subject (End of Study definition). This included collection of information on subsequent anticancer therapies. Telephone contact was acceptable.

[v] **Pharmacokinetics (Arm A only; not crossover subjects):** At 2-6 hours (3 and 5 hours after amendment 6) post AM crizotinib dose on Cycle 1 Day 1, 0 (predose) and 2-6 (3 and 5 hours after amendment 6) post AM crizotinib dose on Day 1 in Cycles 2, 3 and 5, 3 mL of blood was to be drawn into a K_2EDTA tube. Additional PK samples could be collected if the subject experienced a serious and/or unexpected adverse event.

[w] **Optional Blood sample for Pharmacogenomics:** A 2-mL blood sample was to be collected for the analysis of DNA sequence variation in genes that may affect the PK of crizotinib, or that may be associated with specific adverse events or toxicities related to crizotinib.

[x] **Hypogonadism Laboratory Tests (male subjects only, both treatment arms):** All male subjects enrolled after Protocol Amendment 6 were to undergo hypogonadism laboratory tests. In subjects' crossing over to crizotinib from Arm B, the schedule of laboratory tests used in Arm A was to be repeated. Male subjects enrolled in Arm B after Protocol Amendment 6 could optionally also undergo hypogonadism laboratory tests after appropriate informed consent at the time of crossover to crizotinib therapy. Blood draws had to be done between 08:00 and 11:00. If a decrease of ≥25% from baseline was observed in total testosterone or free testosterone, a repeat laboratory analysis of both these parameters had to be performed at the next study site visit to confirm hypogonadism.

[y] **Dual-energy X-ray Absorptiometry (DXA) Scans for Bone Mineral Density and Muscle Mass Measurements:** All male subjects enrolled after Protocol Amendment 6 were to undergo a baseline DXA scan. Subsequent DXA scans were to be performed based upon the following schedule:

Arm A/and subjects crossing over to crizotinib from Arm B: DXA scans were to be performed at Cycle 7/Day 1 and again at end of treatment unless a previous DXA scan was performed within the last 2 months.

Arm B: A DXA scan was to be performed at the end of treatment visit and a repeat (re-baseline) DXA scan was needed if there was a gap of more than 2 months between the end of chemotherapy treatment in Arm B and crossover to crizotinib. Male subjects enrolled in Arm B after Protocol Amendment 6 could optionally also undergo DXA scans after appropriate informed consent at the time of crossover to crizotinib therapy

Number of Subjects (Planned and Analyzed):

A total of 334 subjects were planned to be enrolled in the study.

Analyzed in randomized phase: A total of 343 subjects were randomized and included in the Full Analysis (FA) population (172 in the crizotinib arm and 171 in the chemotherapy arm). Of these, 340 treated subjects had at least 1 dose of study medication and were included in the Safety Analysis (SA) population (171 in the crizotinib arm and 169 in the chemotherapy arm).

Diagnosis and Main Criteria for Inclusion:

Male or female subjects were to be 18 years of age or older; have histologically or cytologically proven diagnosis of locally advanced, not suitable for local treatment, recurrent, or metastatic non-squamous NSCLC; positive for translocation or inversion events involving the ALK gene locus as determined by an ALK break-apart FISH test; have had no prior systemic treatment for locally advanced or metastatic disease (except prior adjuvant chemotherapy for Stage I-III or combined modality chemotherapy radiation for locally advanced disease if completed >12 months prior to documented PD); tumors must have had measurable disease as per RECIST, version 1.1; and ECOG PS 0-2.

Study Treatment:

Subjects were randomized in a 1:1 ratio to receive either crizotinib or first-line chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin).

Test Product

Crizotinib capsules, 250 mg twice daily (BID), were to be administered orally at approximately the same time each day on a continuous daily dosing schedule. Cycles were defined in 21 day periods to facilitate scheduling of visits and assessments. In order to keep the treatment conditions similar between treatment arms, subjects in the crizotinib arm were also required to take folic acid, 350-1000 µg, orally daily beginning approximately 7 days before the first dose of crizotinib and continuing daily for up to 3 weeks after the first dose of crizotinib. Similarly, Vitamin B_{12}, 1000 µg, was to be injected intramuscularly approximately 7 days before the first dose of crizotinib only.

Reference Therapy

Standard doses of chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) were to be administered by intravenous (IV) infusion according to standard of care:

- Pemetrexed (500 mg/m^2) was to be administered by intravenous (IV) infusion over 10 minutes or according to institutional administration timing.
- Cisplatin (75 mg/m^2) was to be administered by infusion after adequate hydration, according to institutional practices, beginning approximately 30 minutes after the end of the pemetrexed infusion.

- Carboplatin (at a dose calculated to produce an area under the concentration time curve [AUC] of 5 or 6 mg•min/mL) was to be administered by infusion, according to institutional practices, beginning approximately 30 minutes after the end of the pemetrexed infusion.

In order to reduce treatment-related hematologic and gastrointestinal toxicities, subjects were required to take folic acid, 350-1000 μg, orally daily beginning approximately 7 days before the first dose of pemetrexed and continuing daily until 3 weeks after the last dose of pemetrexed. In addition, Vitamin B_{12}, 1000 μg, was to be injected intramuscularly (or according to local standard of care or local regulations) approximately 7 days before the first dose of pemetrexed and repeated approximately every 9 weeks until discontinuation of chemotherapy.

In order to reduce cutaneous reactions, subjects were also required to take a corticosteroid equivalent to 4 mg dexamethasone given orally BID on the day before, the day of, and the day after pemetrexed dosing. Intramuscular, intraperitoneal, or IV administration of a corticosteroid with the same total dose as oral dexamethasone was allowed per country regulations and according to institutional practices.

Efficacy, Pharmacodynamics, Pharmacokinetic Outcomes Research Endpoints:

Primary Endpoint

- PFS based on RECIST Version 1.1 (determined by IRR).

Secondary Endpoints

- ORR (determined by IRR), OS, Disease Control Rate (DCR) at 12 weeks, TTP, IC-TTP, EC-TTP, OS at 1 year and 18 months, DR and TTR.

- Type, incidence, severity, seriousness, and relationship to study treatments of AEs and any laboratory abnormalities.

- Plasma concentrations of crizotinib (including its active moieties, if appropriate).

- Proportions of subjects with each of the 8 ALK fusion variants of the EML4-ALK fusion.

- Time to Deterioration (TTD) in pain in chest, dyspnea, or cough subject-reported disease symptoms.

- Subject-reported global quality of life, disease/treatment-related symptoms, and general health status.

- HCRU with respect to hospitalizations and concomitant medication use for select AEs (eg, hematologic events).

The observation period for the efficacy endpoints was from randomization until progressive disease (PD; as determined by IRR) or initiation of subsequent antitumor therapy in the

absence of PD or death, whichever came first. For OS, the observation period was from randomization to death or the last date the subject was known to be alive in the absence of death.

Safety Evaluations:

Safety evaluations included AEs, laboratory parameters (hematology, coagulation, urinalysis, and clinical chemistry), physical examinations including vital signs, measurement of body weight, ECOG PS, 12-lead electrocardiograms (ECGs), multiple gated acquisition (MUGA) scans or echocardiograms (ECHO), and ophthalmologic examinations. Hypogonadism evaluation (for male subjects) including total and free testosterone levels and dual energy X-ray absorptiometry (DXA) scan was included in Protocol Amendment 6.

Patient Reported Outcomes:

Global quality of life, functioning, lung cancer specific disease/treatment-related symptoms, and general health status were assessed using the European Organization for the Research and Treatment of Cancer (EORTC) quality of life questionnaire Core 30 (QLQ C30), its corresponding quality of life questionnaire supplement module for lung cancer LC13 (QLQ LC13), and the EuroQol 5D (EQ 5D) questionnaire. Subjects were to be asked to complete the self-administered EORTC QLQ C30 and QLQ LC13 at baseline, Cycle 1 Day 7 and Day 15, and then Day 1 of each subsequent cycle until end of treatment/withdrawal.

Statistical Methods:

The following population sets were used:

Full Analysis (FA) Population:

The FA population included all subjects who were randomized with study treatment assignment designated according to the initial randomization. The FA population was the primary population for evaluating efficacy endpoints, subject characteristics, and subject disposition.

Safety Analysis (SA) Population:

The SA population included all randomized subjects who received at least 1 dose of study treatment, with treatment assignments designated according to actual study treatment received during the first cycle. The SA population was the primary population for safety and treatment evaluations; in addition, this population was used when summarizing efficacy data by treatment group (ie, by chemotherapy regimen: pemetrexed/cisplatin or pemetrexed/carboplatin).

Pharmacokinetic (PK) Analysis Population:

The PK concentration population (also referred to as the PK evaluable population) included any subject in the SA population who had at least 1 plasma concentration of crizotinib or its metabolite, PF-06260182, determined following crizotinib treatment as of the data cutoff

date. The plasma predose (0 hours) concentration population included any subject in the PK concentration population who had at least 1 predose (0 hours) concentration (trough concentration [C_{trough}]) of crizotinib or PF-06260182, with actual sample collection times between -1.2 to 0 hours prior to morning dosing.

PRO Evaluable Population:

The PRO evaluable population included all subjects from the FA population who completed a baseline (last PRO assessment prior to randomization day) and at least 1 postbaseline PRO assessment prior to crossover or end of randomized study treatment. The PRO evaluable population was the primary population for the analysis of change from baseline scores and TTD in subject reported pain in chest, dyspnea, or cough.

ALK Gene Fusion Variant Evaluable Population:

The ALK gene fusion variant evaluable population was defined as subjects from the FA population who had a result from EML4-ALK gene fusion variant testing of either no rearrangement, or 1 of 9 results reflecting 8 specific rearrangements (V1, V2, V3a, V3b, V3a/b, V4, V5a, V6, and V7). Testing for ALK gene fusion variants was performed using the Response Genetics, Inc. EML4 ALK RT PCR gene fusion test (the polymerase chain reaction [PCR] test).

Pharmacogenomics Evaluable Population:

The pharmacogenomics evaluable population was defined as subjects from the SA population in the crizotinib group who provided a blood sample for pharmacogenomics analysis at baseline (Day 1 of Cycle 1).

Subjects in the chemotherapy arm who had RECIST-defined PD, as determined by IRR, were allowed to cross over to receive crizotinib treatment, providing they met safety screening inclusion/exclusion criteria for crizotinib therapy. The following analysis subgroups were included: subjects randomized crizotinib (subgroup 1), subjects randomized to chemotherapy (subgroup 2), and subjects randomized to chemotherapy who crossed over to receive crizotinib (subgroup 3). However, analyses based on subgroup 3 have not been presented in the disclosure document as these are not the primary or secondary endpoints of the study.

Primary Efficacy Analysis

PFS based on RECIST Version 1.1 (determined by IRR)

PFS was defined as the time from the date of randomization to the date of the first documentation of objective tumor progression (by IRR) or death on study due to any cause, whichever occurred first. The study was to be considered positive if the 1-sided log-rank test for PFS, stratified for baseline stratification factors (ECOG PS, race, brain metastases), was significant at the 0.0247 level. Estimates of the PFS curves obtained from the Kaplan-Meier method were presented. The median event time (and other quartiles) and corresponding 2-sided 95% confidence intervals (CIs) were provided for each treatment arm and treatment

group, where appropriate. The Cox regression model, stratified for baseline stratification factors, was fitted. The estimated hazard ratio (HR) and 2-sided 95% CIs were provided.

Secondary Efficacy Analyses

ORR (determined by IRR), OS, DCR at 12 weeks, TTP, IC-TTP, EC-TTP, OS at 1 year and 18 months, Duration of Response (DR) and TTR

ORR was defined as the percentage of subjects with complete response (CR) or partial response (PR) according to RECIST Version 1.1, as determined by IRR. 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 (ECOG PS, race, brain metastases) and a 2-sided unstratified test (eg, Pearson). Treatment difference of ORR and its 95% CI based on the normal distribution were provided.

OS was defined as the time from randomization to the date of death due to any cause. One-year and 18-month survival probabilities were defined as the probabilities of survival at 1 year and 18 months, respectively, after the date of randomization based on the Kaplan-Meier estimate. Differences in OS between treatment arms were analyzed by a 1-sided log-rank test stratified for baseline stratification factors (ECOG PS, race, brain metastases). Estimates of the OS curves obtained from the Kaplan-Meier method were presented. The Cox regression model, stratified for baseline stratification factors, was fitted. The estimated hazard ratio (HR) and 2-sided 95% CIs were provided.

DCR at 12 weeks was defined as the percentage of subjects with CR, PR, or stable disease at 12 weeks according to RECIST Version 1.1, as determined by IRR. A 2-sided unstratified test (eg Pearson) was used to compare DCR between the two treatment arms.

TTP was defined as the time from randomization to first documentation of objective tumor progression (by IRR). Differences between treatment arms were analyzed by the unstratified log rank test. IC-TTP was defined as the time from randomization to first documentation of objective intracranial disease progression, based on either new brain metastases or progression of existing brain metastases. EC-TTP was defined as the time from randomization to first documentation of objective extracranial disease progression, based on either new extracranial lesions or progression of existing extracranial lesions.

DR was defined as the time from the first documentation of objective tumor response (CR or PR), as determined by IRR, to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. DR was summarized for the subgroup of responders (CR and PR) using the Kaplan-Meier method.

TTR was defined as the time from randomization to first documentation of objective tumor response (CR or PR), as determined by IRR. TTR was summarized in the subgroup of responders (CR and PR) using descriptive statistics.

Patient-Reported Outcomes (TTD in pain in chest, dyspnea, or cough subject reported disease symptoms and subject reported global quality of life, disease/treatment-related symptoms, and general health status)

Time to deterioration (TTD) in pain in chest, dyspnea, or cough symptoms (from QLQ-LC13) was a composite endpoint, defined as the time from randomization to the earliest date the subject's scale scores showed a 10-point or greater increase after baseline in any of these 3 symptoms. TTD analyses for the composite endpoint and each of the 3 pre-specified symptoms were summarized using Kaplan-Meier methods. The estimated Kaplan-Meier plots were provided for the composite and each symptom within it, and the unstratified 2-sided log-rank test was the primary method to compare the time to first deterioration between the 2 treatment arms. The median time and 2-sided 95% CI for the median was also provided based on the Brookmeyer Crowley method. To compare actual scores and change from baseline scores between treatment arms, repeated measures mixed-effects modelling was carried out for the EORTC QLQ-C30, QLQ-LC13 domain and single-item scores, and the EQ-5D visual analogue scale. In the chemotherapy arm, data until crossover to crizotinib or end of treatment (maximum 6 cycles) were included in the analyses and 2-sided p-values were reported that were not adjusted for multiple testing.

Pharmacokinetic analysis

Plasma concentrations of crizotinib and its metabolite PF-06260182

Predose (0 Hour) plasma concentrations of crizotinib, its metabolite PF-06260182, and the PF-06260182-to-crizotinib ratio were summarized using descriptive statistics.

Pharmacodynamic analysis

Proportions of subjects with each of the 8 ALK fusion variants of the EML4 ALK fusion

ALK gene fusion variant analysis data were summarized using descriptive statistics. For each ALK variant separately and for subjects with no identified ALK rearrangement, best objective response and ORR were summarized for each treatment arm with the corresponding exact 2-sided 95% CI using a method based on the F distribution.

Health care resource utilization analysis

HCRU with respect to hospitalizations and concomitant medication use for select AEs (eg, hematologic events)

Data regarding hospitalizations, the causality of AEs associated with the hospitalization, and concomitant medication use were summarized.

Safety

Type, incidence, severity, seriousness, and relationship to study treatments of AEs and any laboratory abnormalities

Safety data were analyzed in the SA population. All AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1. The severity of all AEs was graded by the investigator using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. Safety data (AEs, laboratory parameters, vital signs, ECOG PS, ECGs, MUGA scans or ECHO, and ophthalmologic examinations) were summarized using descriptive statistics.

RESULTS

Subject Disposition and Demography:

Subject disposition data is summarized in Table 2. A total of 172 subjects were randomized to the crizotinib arm and 171 were randomized to the chemotherapy arm. Fifty-two (30.2%) subjects in the crizotinib arm and 54 (31.6%) subjects in the chemotherapy arm (including the crossover phase) were discontinued from the study. The most common reason for discontinuation from the study in both treatment arms was death (44 subjects in the crizotinib arm and 46 subjects in the chemotherapy arm.

Table 2: Subject Disposition and Subjects Analyzed by Treatment Arm

	Crizotinib n (%)	Chemotherapy n (%)	Total n (%)
Randomized to study treatment	172	171	343
Treated	171	169	340
Completed	0	0	0
Discontinued from study	52 (30.2)	54 (31.6)[a]	106 (30.9)
Subject Died	44	46	90
Lost to Follow-Up	0	2	2
Subject Refused Further Follow-up	7	5	12
Other	1	1	2
Ongoing in study at date of cutoff	119 (69.2)	115 (67.3)[a]	234 (68.2)
Randomized not treated	1 (0.6)	2 (1.2)	3 (0.9)
Full analysis population	172 (100)	171 (100)	343 (100)
Safety analysis population	171 (99.4)	169 (98.8)	340 (99.1)
PRO evaluable population			
EORTC QLQ-C30 and QLQ-LC13	166 (96.5)	163 (95.3)	329 (95.9)
EQ-5D	160 (93.0)	160 (93.6)	320 (93.3)
PK concentration population	169 (98.3)	NA	169 (49.3)
ALK variant evaluable population	70 (40.7)	78 (45.6)	148 (43.1)

Abbreviations: n=number of subjects; ALK=anaplastic lymphoma kinase; EORTC=European Organization for the Research and Treatment of Cancer; EQ-5D=EuroQol-5D; n=number of subjects; NA=not applicable; PK=pharmacokinetic; PRO=patient-reported outcome; QLQ-C30=Quality of Life Questionnaire-Core 30; QLQ-LC13=Quality of Life Questionnaire-Supplement Module for Lung Cancer (LC13).

[a] Includes data before and after crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment.

Subject demographic data is presented in Table 3. Demographic characteristics were comparable between the 2 treatment arms in the FA population.

Table 3: Demographic Characteristics by Treatment Arm - Full Analysis Population

	Crizotinib (N=172)	Chemotherapy (N=171)	Total (N=343)
Sex, n (%)			
Male	68 (39.5)	63 (36.8)	131 (38.2)
Female	104 (60.5)	108 (63.2)	212 (61.8)
Age, years			
Mean (SD)	50.9 (11.9)	52.9 (13.1)	51.9 (12.6)
Age category, n (%)			
<45 years	56 (32.6)	44 (25.7)	100 (29.2)
45-<55 years	52 (30.2)	46 (26.9)	98 (28.6)
55-<65 years	41 (23.8)	49 (28.7)	90 (26.2)
≥65 years	23 (13.4)	32 (18.7)	55 (16.0)
Smoking classification, n (%)			
Never smoked	106 (61.6)	112 (65.5)	218 (63.6)
Ex-smoker	56 (32.6)	54 (31.6)	110 (32.1)
Smoker	10 (5.8)	5 (2.9)	15 (4.4)

Abbreviations: n/N=number of subjects; SD=standard deviation

Efficacy, Pharmacokinetic, Pharmacodynamic, or Outcomes Research Results:

Primary Efficacy Endpoint

PFS based on RECIST Version 1.1 (determined by IRR)

PFS based on IRR review is presented in Table 4. The required number of PFS events for the final analysis was achieved and a data cutoff of 30 November 2013 was used. The study met its primary objective of demonstrating that crizotinib significantly prolongs PFS compared to first-line platinum-based chemotherapy, as assessed by IRR. The median PFS was 10.9 months for 172 subjects randomized to crizotinib and 7.0 months for 171 subjects randomized to chemotherapy. The Hazard ratio comparing crizotinib with chemotherapy was 0.454 (95% CI: 0.346, 0.596), with a p-value of <0.0001 (1-sided stratified log-rank test).

Table 4: Progression-Free Survival Based on Independent Radiology Review by Treatment Arm (Stratified) - Full Analysis Population

	Crizotinib (N=172)	Chemotherapy (N=171)[a]
Number with event, n (%)	100 (58.1)	137 (80.1)
Objective progression	89 (51.7)	132 (77.2)
Death without objective progression	11 (6.4)	5 (2.9)
Number censored, n (%)	72 (41.9)	34 (19.9)
No on-study disease assessments	0	2 (1.2)
Given new anticancer treatment prior to tumor progression	12 (7.0)	6 (3.5)
Withdrew consent for follow-up	3 (1.7)	6 (3.5)
Unacceptable gap (>14 weeks) between PD or death to the most recent prior adequate assessment	0	2 (1.2)
In follow-up for progression	56 (32.6)	18 (10.5)
No scans/data available	1 (<1.0)	0
Kaplan-Meier estimates of time to event, months		
25% quartile (95% CI)[b]	5.4 (4.0, 6.8)	4.0 (2.8, 5.3)
50% quartile (95% CI)[b]	10.9 (8.3, 13.9)	7.0 (6.8, 8.2)
75% quartile (95% CI)[b]	NR (15.7, NR)	10.8 (9.5, 11.2)
Versus chemotherapy		
Hazard ratio[c]	0.454	
95% CI of hazard ratio	(0.346, 0.596)	
p-value[d]	<0.0001	

Abbreviations: CI=confidence interval; N=number of subjects; NR=not reached; PD=progressive disease.
a Only includes data before crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment.
b.Based on the Brookmeyer and Crowley method.
c Based on the Cox Proportional hazards model stratified by ECOG PS, race group, and brain metastases. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of crizotinib.
d One-sided p-value from log-rank test stratified by ECOG PS, race group, and brain metastases.

Secondary Efficacy Endpoints

Overall Survival and Survival Probabilities at 1 Year and 18 Months

Analyses of the secondary efficacy endpoints supported the primary PFS outcome. At the time of the PFS analysis, a total of 44 (25.6%) subjects in the crizotinib arm and 46 (26.9%) subjects in the chemotherapy arm were known to have died. With only 26% of OS events at the time of the final PFS analysis and 120 subjects randomized to chemotherapy receiving subsequent crizotinib treatment, the median OS was not reached in either treatment arm. There was, however, a numerical improvement in OS in the crizotinib arm (HR: 0.821; 95% CI: 0.536, 1.255; p value=0.1804). The 1 year and 18 month survival probabilities were

similar between the treatment arms: 84% and 69%, respectively, for crizotinib and 79% and 67%, respectively, for chemotherapy (Table 5).

Table 5: Summary of Overall Survival by Treatment Arm (Stratified) - Full Analysis Population

	Crizotinib (N=172)	Chemotherapy (N=171)[a]
Number of deaths, n (%)	44 (25.6)	46 (26.9)
Number censored, n (%)	128 (74.4)	125 (73.1)
Reason for censorship, n (%):		
Subject remains in follow-up	119 (69.2)	115 (67.3)
Subject no longer being followed for survival	2 (1.2)	3 (1.8)
Withdrew consent for follow-up	7 (4.1)	5 (2.9)
Lost to follow-up	0	2 (1.2)
Survival probability:[b]		
at Month 12 (95% CI)[c]	83.5 (76.7, 88.5)	78.6 (71.3, 84.2)
at Month 18 (95% CI)[c]	68.6 (59.5, 76.1)	67.3 (58.1, 74.9)
Kaplan-Meier estimates of time to event, months		
25% quartile (95% CI)[d]	15.5 (12.5, 26.5)	14.9 (8.8, 23.0)
50% quartile (95% CI)[d]	NR	NR
75% quartile (95% CI)[d]	NR	NR
Versus chemotherapy		
Hazard ratio[e]	0.821	
95% CI of hazard ratio	(0.536, 1.255)	
p-value[f]	0.1804	

Abbreviations: CI=confidence interval; N=number of subjects; NR=not reached.

[a] Includes events before and after crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment.

[b] Estimated from the Kaplan-Meier curve.

[c] Calculated using the normal approximation to the log transformed cumulative hazard rate.

[d] Based on the Brookmeyer and Crowley method.

[e] Based on the Cox Proportional hazards model stratified by ECOG PS, race group, and brain metastases. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of crizotinib.

[f] One-sided p-value from the log-rank test stratified by ECOG PS, race group, and brain metastases.

Objective Response Rate

The study demonstrated a statistically significant (2-sided p value <0.0001) improvement in IRR-assessed ORR for crizotinib compared with chemotherapy, with ORRs of 74% (95% CI: 67%, 81%) in the crizotinib arm and 45% (95% CI: 37%, 53%) in the chemotherapy arm (Table 6).

Table 6: Best Overall Response Based on Independent Radiology Review by Treatment Arm - Full Analysis Population

	Crizotinib (N=172)	Chemotherapy (N=171)[a]
Objective response rate (CR + PR), n (%)	128 (74.4)	77 (45.0)
95% exact CI[b]	(67.2, 80.8)	(37.4, 52.8)
Treatment comparison versus chemotherapy		
Treatment difference in ORR	29.4	
95% CI of difference[c]	(19.5, 39.3)	
p-value[d]	<0.0001	

Early death is within 6 weeks (42 days) from randomization.
Abbreviations: CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; N=number of subjects; ORR=objective response rate; PS=performance status.
[a] Only includes data before crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment.
[b] Using exact method based on F distribution.
[c] Calculated based on a normal distribution.
[d] P-value is from a 2-sided Pearson chi-square test.

Time to Tumor Response

The responses on crizotinib treatment were rapid and durable with a median TTR of 6.1 weeks. In the chemotherapy arm, the median TTR was 12.1 weeks (Table 7).

Table 7: Time to Tumor Response Based on Independent Radiology Review by Treatment Arm (Objective Responders Only) - Full Analysis Population

	Crizotinib (N=172)	Chemotherapy (N=171)[a]
Time to response, weeks		
n	128	77
Mean (SD)	8.2 (5.2)	13.2 (7.7)
Median	6.1	12.1
Range	2.7-41.4	5.1-36.7

Abbreviations: n/N=number of subjects; SD=standard deviation.
[a] Only includes data before crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment.

Duration of Response

The median DR estimate, using the Kaplan-Meier method, was 49.0 weeks (95% CI: 35.1, 60.0 weeks) for crizotinib and 22.9 weeks (95% CI: 18.0, 25.1 weeks) for chemotherapy (Table 8).

Table 8: Duration of Response Based on Independent Radiology Review by Treatment Arm (Objective Responders Only) - Full Analysis Population

	Crizotinib (N=172)	Chemotherapy (N=171)[a]
Subjects with objective response (CR or PR), n (%)	128 (74.4)	77 (45.0)
Kaplan-Meier estimates of duration of response, weeks		
25% quartile (95% CI)[b]	23.1 (18.1, 26.9)	11.7 (11.3, 17.1)
50% quartile (95% CI)[b]	49.0 (35.1, 60.0)	22.9 (18.0, 25.1)
75% quartile (95% CI)[b]	NR (69.6, NR)	36.4 (25.4, 47.9)

Abbreviations: CI=confidence interval; N=number of subjects; NR=not reached.
[a] Only includes data before crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment
[b] Based on the Brookmeyer and Crowley method.

Disease Control Rate

At Week 12, crizotinib had a greater DCR compared to chemotherapy: 79% (95% CI: 72%, 84%) for crizotinib and 68% (95% CI: 61%, 75%) for chemotherapy, p-value=0.0381 (2-sided Pearson test) (Table 9).

Table 9: Summary of Disease Control Rate at Week 12 Based on Independent Radiology Review Assessment by Treatment Arm - Full Analysis Population

	Crizotinib (N=172)	Chemotherapy (N=171)[a]
Disease Control Rate at Week 12, n (%)	135 (78.5)	117 (68.4)
95% exact CI[b]	(71.6, 84.4)	(60.9, 75.3)
Treatment Comparison (vs Chemotherapy)		
Treatment Difference in DCR	10.067	
95% CI of Difference[c]	(0.8, 19.4)	
P-value[d]	0.0381	

Abbreviations: CI=confidence interval; DCR=disease control rate; N=number of subjects;
[a] Only includes data before crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment
[b] Using exact method based on F distribution
[c] Calculated based on a normal distribution
[d] P-value is from a 2-sided Pearson chi-square test.

Time to Progression

Median TTP was 13.6 months in the crizotinib arm and 7.0 months in the chemotherapy arm. The HR comparing crizotinib with chemotherapy was 0.441 (95% CI: 0.335, 0.582), with a p-value <0.0001 (1-sided unstratified log-rank test) (Table 10).

Table 10: Summary of Time to Progression Based on Independent Radiology Review Assessment by Treatment Arm (Unstratified) - Full Analysis Population

	Crizotinib (N=172)	Chemotherapy (N=171)[a]
Kaplan-Meier estimates of Time to Progression, months		
25% quartile (95% CI)[b]	5.6 (5.0, 7.0)	4.2 (3.1, 5.4)
50% quartile (95% CI)[b]	13.6 (8.5, 15.0)	7.0 (6.8, 8.3)
75% quartile (95% CI)[b]	NR (17.7, NR)	11.0 (9.6, 11.4)
Versus Chemotherapy		
Hazard Ratio[c]	0.441	
95% CI of Hazard Ratio	(0.335, 0.582)	
P-value[d]	<0.0001	

Abbreviations: CI=confidence interval; HR=hazard ratio; N=number of subjects; NR=not reached.
[a] Only includes data before crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment.
[b] Based on the Brookmeyer and Crowley method.
[c] Based on the Cox proportional hazards model. Assuming proportional hazards, a HR less than 1 indicates a reduction in hazard rate in favor of crizotinib.
[d] One-sided p-value from the unstratified log-rank test.

Time to Intracranial and Extracranial Progression

Time to IC-TTP and EC-TTP are shown in Table 11and Table 12 respectively. The improvement in TTP was observed when only extracranial lesions were evaluated; median EC-TTP was 15.2 months in the crizotinib arm and 7.2 months in the chemotherapy arm (HR: 0.387; 95% CI: 0.286, 0.524; p-value <0.0001). Median IC-TTP was not reached in the crizotinib arm and was 17.8 months in the chemotherapy arm. There was a numerical improvement in IC-TTP in the crizotinib arm (HR: 0.595; 95% CI: 0.338, 1.048; 1-sided p-value=0.0347).

Table 11: Summary of Time to Intracranial Progression Based on Independent Radiology Review Assessment by Treatment Arm (Unstratified) - Full Analysis Population

	Crizotinib (N=172)	Chemotherapy (N=171)[a]
Kaplan-Meier estimates of Time to Intracranial Progression, months		
25% quartile (95% CI)[b]	15.0 (13.6, NR)	11.2 (8.5, 17.8)
50% quartile (95% CI)[b]	NR	17.8 (13.9, NR)
75% quartile (95% CI)[b]	NR	NR (17.8, NR)
Versus Chemotherapy		
Hazard Ratio[c]	0.595	
95% CI of Hazard Ratio	(0.338, 1.048)	
P-value[d]	0.0347	

Abbreviations: CI=confidence interval; HR=hazard ratio; N=number of subjects; NR=not reached.
[a] Only includes data before crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment.
[b]Based on the Brookmeyer and Crowley method.
[c]Based on the Cox proportional hazards model. Assuming proportional hazards, a HR less than 1 indicates a reduction in hazard rate in favor of Crizotinib. A hazard ratio greater than 1 indicates a reduction in hazard rate in favor of chemotherapy.
[d]One-sided p-value from the unstratified log-rank test.

Table 12: Summary of Time to Extracranial Progression Based on Independent Radiology Review Assessment by Treatment Arm (Unstratified) - Full Analysis Population

	Crizotinib (N=172)	Chemotherapy (N=171)[a]
Kaplan-Meier estimates of Time to Extracranial Progression, months		
25% quartile (95% CI)[b]	6.8 (5.4, 8.3)	4.5 (4.0, 5.7)
50% quartile (95% CI)[b]	15.2 (12.6, 21.9)	7.2 (6.9, 8.5)
75% quartile (95% CI)[b]	NR	11.1 (9.8, 12.4)
Versus Chemotherapy		
Hazard Ratio[c]	0.387	
95% CI of Hazard Ratio	(0.286, 0.524)	
P-value[d]	<0.0001	

Abbreviations: CI=confidence interval; HR=hazard ratio; N=number of subjects; NR=not reached.
[a] Only includes data before crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment
[b] Based on the Brookmeyer and Crowley method.
[c]Based on the Cox proportional hazards model. Assuming proportional hazards, a HR less than 1 indicates a reduction in hazard rate in favor of Crizotinib. A hazard ratio greater than 1 indicates a reduction in hazard rate in favor of chemotherapy.
[d]One-sided p-value from the unstratified log-rank test

Patient Reported Outcomes

Time to Deterioration

A statistically significantly longer TTD was observed in the crizotinib arm than in the chemotherapy arm (2.1 months vs 0.5 months; HR: 0.615; Hochberg adjusted log-rank 2-sided p-value=0.0017) in the composite endpoint that included pain in chest, dyspnea, or cough symptoms (Table 13).

Table 13: Time to Deterioration in Pain (in Chest), Dyspnea, or Cough by Treatment Arm - PRO Evaluable Population

	Crizotinib (N=166)	Chemotherapy (N=163)[a]
Kaplan-Meier estimates of time to event, months		
25% quartile (95% CI)[b]	0.3 (0.3, 0.5)	0.3 (0.3, 0.3)
50% quartile (95% CI)[b]	2.1 (1.4, 4.3)	0.5 (0.4, 0.7)
75% quartile (95% CI)[b]	NR (11.1, NR)	3.4 (2.0, NR)
Versus chemotherapy		
Hazard ratio[c]	0.615	
95% CI of hazard ratio	(0.472, 0.802)	
p-value[d]	0.0004	

Abbreviations: CI=confidence interval; NR=not reached; N=number of subjects;
[a] Only includes data before crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment.
[b] Based on the Brookmeyer and Crowley method.
[c] 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.
[d] Two-sided p-value from the unstratified log-rank test.

EORTC QLQ C30

Overall, a statistically significantly (all 2-sided p-values <0.001) greater improvement from baseline was observed in the crizotinib arm compared with the chemotherapy arm in global quality of life, emotional functioning, physical functioning, role functioning, and social functioning (Table 14).

A statistically significantly greater improvement (p-values <0.001) was observed in the crizotinib arm compared to the chemotherapy arm in appetite loss, dyspnea, fatigue, insomnia, and pain. Statistically significantly greater deterioration was observed in the crizotinib arm for diarrhea (p-value <0.001). A statistically significantly greater deterioration was observed in the chemotherapy arm compared to the crizotinib arm for nausea and vomiting (p-value <0.05) (Table 15).

Table 14: Crizotinib versus Chemotherapy Overall Difference in Change From Baseline[a] Scores in QLQ-C30 Domain by Treatment Arm (Mixed Model Analysis) - PRO Evaluable Population

	Value	95% CI[b]	p-value[b]
Crizotinib vs Chemotherapy Overall			
QLQ-C30 Global QoL	13.8303	(10.74,16.92)	<.0001
QLQ-C30 Cognitive Functioning	3.3532	(0.60,6.11)	0.0170
QLQ-C30 Emotional Functioning	7.5165	(4.57,10.46)	<.0001
QLQ-C30 Physical Functioning	10.4035	(7.48,13.32)	<.0001
QLQ-C30 Role Functioning	15.5513	(11.29,19.81)	<.0001
QLQ-C30 Social Functioning	8.7641	(4.69,12.84)	<.0001

Abbreviations: CI=confidence interval; QLQ-C30= Quality of Life Questionnaire-Core 30.

[a] From a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

[b] P-values and confidence intervals are not adjusted for multiplicity.

Table 15: Crizotinib versus Chemotherapy Overall Difference in Change From Baseline[a] Scores in QLQ-C30 Symptoms by Treatment Arm (Mixed Model Analysis) - PRO Evaluable Population

	Value	95% CI[b]	p-value[b]
Crizotinib vs Chemotherapy Overall			
QLQ-C30 Appetite loss	-13.4976	(-18.03,-8.97)	<.0001
QLQ-C30 Constipation	-4.4336	(-9.00,0.13)	0.0570
QLQ-C30 Diarrhea	12.4906	(8.98,16.00)	<.0001
QLQ-C30 Dysponea	-13.4622	(-17.20,-9.73)	<.0001
QLQ-C30 Fatigue	-14.9987	(-18.52,-11.48)	<.0001
QLQ-C30 Financial Difficulties	-0.8186	(-4.56,2.92)	0.6681
QLQ-C30 Insomnia	-10.0430	(-14.22,-5.87)	<.0001
QLQ-C30 Nausea and Vomiting	-3.4446	(-6.84,-0.05)	0.0468
QLQ-C30 Pain	-9.9277	(-13.23,-6.62)	<.0001

Abbreviations: CI=confidence interval; QLQ-C30= Quality of Life Questionnaire-Core 30.

[a] From a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score (intercept and time from first dose are included as random effects).

[b] P-values and confidence intervals are not adjusted for multiplicity.

EORTC QLQ-LC13

A statistically significantly greater improvement observed in the crizotinib arm compared to the chemotherapy arm for alopecia (p-value <0.05), coughing (p-value <0.001), dyspnea (p-value <0.001), pain in arm or shoulder (p-value <0.001), pain in chest (p-value <0.001), and pain in other parts (p-value <0.001). Statistically significantly greater deterioration observed for peripheral neuropathy (p-value <0.05) (Table 16).

Table 16: Crizotinib versus Chemotherapy Overall Difference in Change From Baseline[a] Scores in QLQ-LC30 Symptoms by Treatment Arm (Mixed Model Analysis) - PRO Evaluable Population

	Value	95% CI[b]	p-value[b]
Crizotinib vs Chemotherapy Overall			
QLQ-LC13 Alopecia	-4.8149	(-8.52,-1.11)	0.0108
QLQ-LC13 Coughing	-8.3926	(-12.06,-4.72)	<.0001
QLQ-LC13 Dysphagia	0.6651	(-1.78,3.11)	0.5938
QLQ-LC13 Dyspnoea	-9.0080	(-11.96,-6.06)	<.0001
QLQ-LC13 Haemoptysis	-0.8828	(-1.82,0.06)	0.0656
QLQ-LC13 Pain in Arm or Shoulder	-6.0475	(-9.22,-2.88)	0.0002
QLQ-LC13 Pain in Chest	-8.0959	(-11.35,-4.84)	<.0001
QLQ-LC13 Pain in Other Parts	-6.7717	(-10.24,-3.31)	0.0001
QLQ-LC13 Peripheral Neuropathy	3.3521	(0.11,6.59)	0.0427
QLQ-LC13 Sore Mouth	-2.1521	(-5.00,0.69)	0.1382

Abbreviations: CI=confidence interval; QLQ-LC30=Quality of Life Questionnaire-Supplement Module for Lung Cancer (LC13).

[a] From a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-LC30 subscale baseline score (intercept and time from first dose are included as random effects).

[b] P-values and confidence intervals are not adjusted for multiplicity.

Pharmacokinetic Endpoint

Plasma concentrations of crizotinib (including its metabolite, PF-06260182)

Plasma concentration of crizotinib and its metabolite PF-06260182 are presented in Table 17. The plasma concentrations of crizotinib and PF-06260182 appeared to reach the steady state within the first cycle after repeated oral administration of crizotinib 250 mg BID. The geometric mean predose concentrations (C_{trough}) of crizotinib and its metabolites were similar across Day 1 of Cycles 2, 3, and 5.

Table 17: Predose Concentrations (C_{trough}) of Crizotinib and its Metabolite, PF-06260182, and PF-06260182 to Crizotinib Ratios Following 250 mg BID Oral Dosing of Crizotinib

	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 5 Day 1
N/n	91/100	85/94	82/86
Crizotinib C_{trough}, ng/mL[a]	324.2 (39)	320.9 (40)	308.2 (39)
PF-06260182 C_{trough}, ng/mL[a]	98.4 (46)	99.0 (49)	92.9 (55)
PF-06260182 to Crizotinib ratio	0.302 (25)	0.300 (25)	0.290 (25)

Abbreviations: BID=twice daily; C_{trough}=trough concentration; CV=coefficient of variation; n=number of observations for PF-06260182; N=number of observations for crizotinib and PF-06260182 to crizotinib ratio.
[a] Geometric mean (%CV).

Pharmacodynamic Endpoint

ALK Gene Fusion Variant Analysis

The proportion of subjects with each of the EML4-ALK fusion variants is presented in Table 18. Overall 88 subjects (59.5% of the evaluable population) were with no rearrangement, 39 (26.4%) with a V1 rearrangement, 11 (7.4%) with a V2 rearrangement, 2 (1.4%) with a V3a rearrangement and 8 (5.4%) with a V3a/b rearrangement. No V3b, V4, V5a, V6, or V7 rearrangements were observed. Among the 60 subjects with an ALK gene rearrangement, V1, V2, and V3 rearrangements represented 65.0%, 18.3%, and 16.7% of cases, respectively.

ORR, based on IRR, within treatment arm, was comparable between the ALK variant groups. However, the analysis is limited by the small sample size and large 95% CI.

Table 18: Best Overall Response Based on Independent Radiology Review by Treatment Arm and EML4-ALK Gene Fusion Variant - ALK Variant Evaluable Population

EML4-ALK gene fusion variant[b]	Crizotinib (N=70)		Chemotherapy (N=78)[a]	
	Subjects with variant, n (%)	ORR (CR + PR) n (%) (95% CI)[c]	Subjects with variant, n (%)	ORR (CR + PR) n (%) (95% CI)[c]
V1	19 (27.1)	16 (84.2) (60.4, 96.6)	20 (25.6)	9 (45.0) (23.1, 68.5)
V2	5 (7.1)	5 (100) (47.8, 100)	6 (7.7)	2 (33.3) (4.3, 77.7)
V3a	1 (1.4)	0 NA	1 (1.3)	1 (100) (2.5, 100)
V3a/b	3 (4.3)	3 (100) (29.2, 100)	5 (6.4)	3 (60.0) (14.7, 94.7)
No rearrangement	42 (60.0)	30 (71.4) (55.4, 84.3)	46 (59.0)	20 (43.5)(28.9, 58.9)

Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; CR=complete response; EML4=echinoderm microtubule-associated protein-like 4; n/N=number of subjects; NA=not applicable; ORR=objective response rate; PR=partial response.

[a] Only includes data before crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment.

[b] Variants V4, V5a, V6, and V7 were not detected.

[c] Using exact method based on F distribution.

Health care resource utilization analysis

Approximately 33% of subjects had a hospital admission while on treatment in the crizotinib arm. In the chemotherapy arm, during the period of chemotherapy treatment (maximum of 6 cycles) and prior to actual crossover to receive crizotinib treatment, approximately 34% of subjects were hospitalized. The median length of stay was 8 days in the crizotinib arm and 9 days in the chemotherapy arm (Table 19)

Table 19: Hospitalizations by Treatment Arm - Full Analysis Population

	Crizotinib (N=172)	Chemotherapy (N=171)[a]
Hospital admissions[b]		
Number (%) of subjects who had hospital admissions	57 (33.1)	58 (33.9)
Number of hospitalization events[c]	94	105
Length of stay per event, days:		
Mean (SD)	11.8 (11.3)	16.4 (40.9)
Median	8	9
Range	1-64	1-410

Data are based on the 'Hospitalization Status' from the Adverse Event case report form page.
Subjects can have multiple hospitalization events.
Abbreviations: N=number of subjects; SD=standard deviation.

[a] The chemotherapy arm only includes data prior to crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment. For subjects who completed 6 cycles of chemotherapy without progression and later crossed over to receive crizotinib treatment, the chemotherapy arm includes the hospitalization events that occurred between end of chemotherapy treatment and actual crossover to crizotinib.

[b] The follow-up period for hospitalization events could vary between the treatment arms and the events are not adjusted for duration of study treatment.

[c] More than 1 hospitalization event could be associated with a single subject.

Safety Results:

This section presents treatment-emergent adverse events (all-causality AEs and treatment-related AEs). The duration of study treatment was longer in the crizotinib arm (median 47 weeks) than in the chemotherapy arm (median 18 weeks). The AE analyses presented below were not adjusted for the longer duration of study treatment for the crizotinib arm compared with the chemotherapy arm.

Adverse events (AEs)

The treatment-emergent non-serious AEs reported in >=5% of subjects in any of the treatment arm by preferred term and by system organ class (all causality and treatment-related) are summarized in Table 20.

Overall, 168 (98.2%) subjects in the crizotinib group and 165 subjects (97.6%) subjects in the chemotherapy group experienced all causality treatment-emergent, non-serious AEs. Meaningfully different incidences of all-causality non-serious AEs were considered to be those that were reported with an incidence of ≥10% of subjects in either treatment arm and had a ≥5% absolute difference between treatment arms. All causality non-serious AEs of visual impairment, abdominal pain, abdominal pain upper, constipation, diarrhoea, dyspepsia, vomiting, oedema peripheral, pyrexia, nasopharyngitis, upper respiratory tract infection, aspartate aminotransferase increased, alanine aminotransferase increased, pain in extremity, dizziness, dysgeusia, headache, paraesthesia, insomnia, and cough, were reported with a meaningfully higher frequency in the crizotinib arm than in the chemotherapy arm. All

causality non-serious AEs of anaemia, asthenia, fatigue, neutrophil, platelet count decreased, were reported with a meaningfully higher frequency in the chemotherapy arm than in the crizotinib arm.

Overall, 166 (97.1%) subjects in the crizotinib group and 153 subjects (90.5%) subjects in the chemotherapy group experienced treatment-emergent, treatment-related, treatment-emergent, non-serious AEs. Treatment-related AEs reported by ≥30% of subjects included visual impairment, constipation, diarrhoea, vomiting, oedema peripheral, and alanine aminotransferase increased in the crizotinib arm, and decreased appetite and fatigue in the chemotherapy arm. Nausea reported in ≥30% of subjects in both the crizotinib and chemotherapy arms.

Table 20: Treatment-Emergent Non-Serious Adverse Events Reported in ≥5% Subjects in Any of the Treatment Arm by System Organ Class and Preferred Term (All Causalities and Treatment-Related) - Safety Analysis Set

System Organ Class Preferred Term	**Crizotinib (N=171) n (%)**		**Chemotherapy (N=169) n (%)**	
	All Causalities	**Treatment related**	**All Causalities**	**Treatment related**
Any AEs	**168 (98.2)**	**166 (97.1)**	**165 (97.6)**	**153 (90.5)**
Blood and lymphatic system disorders	**42 (24.6)**	**32 (18.7)**	**71 (42.0)**	**66 (39.1)**
Anaemia	14 (8.2)	4 (2.3)	51 (30.2)	43 (25.4)
Leukopenia	5 (2.9)	3 (1.8)	16 (9.5)	16 (9.5)
Neutropenia	28 (16.4)	28 (16.4)	36 (21.3)	35 (20.7)
Thrombocytopenia	1 (0.6)	0	14 (8.3)	13 (7.7)
Cardiac disorders	**16 (9.4)**	**13 (7.6)**	**0**	**0**
Bradycardia	16 (9.4)	13 (7.6)	0	0
Ear and labyrinth disorders	**4 (2.3)**	**2 (1.2)**	**10 (5.9)**	9 (5.3)
Tinnitus	4 (2.3)	2 (1.2)	10 (5.9)	9 (5.3)
Eye disorders	**122 (71.3)**	**118 (69.0)**	**22 (13.0)**	**6 (3.6)**
Conjunctivitis	3 (1.8)	0	10 (5.9)	0
Photopsia	17 (9.9)	17 (9.9)	5 (3.0)	2 (1.2)
Vision blurred	13 (7.6)	12 (7.0)	5 (3.0)	2 (1.2)
Visual impairment	97 (56.7)	96 (56.1)	5 (3.0)	3 (1.8)
Vitreous floaters	11 (6.4)	11 (6.4)	1 (0.6)	0
Gastrointestinal disorders	**160 (93.6)**	**151 (88.3)**	**129 (76.3)**	**117 (69.2)**
Abdominal pain	21 (12.3)	18 (10.5)	8 (4.7)	5 (3.0)
Abdominal pain upper	25 (14.6)	17 (9.9)	10 (5.9)	5 (3.0)
Constipation	74 (43.3)	55 (32.2)	50 (29.6)	33 (19.5)
Diarrhoea	104 (60.8)	97 (56.7)	21 (12.4)	14 (8.3)
Dyspepsia	23 (13.5)	15 (8.8)	4 (2.4)	2 (1.2)

System Organ Class Preferred Term	Crizotinib (N=171) n (%)		Chemotherapy (N=169) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Any AEs	**168 (98.2)**	**166 (97.1)**	**165 (97.6)**	**153 (90.5)**
Dysphagia	17 (9.9)	0	2 (1.2)	0
Gastrooesophageal reflux disease	13 (7.6)	9 (5.3)	5 (3.0)	3 (1.8)
Nausea	94 (55.0)	85 (49.7)	99 (58.6)	94 (55.6)
Stomatitis	11 (6.4)	11 (6.4)	17 (10.1)	16 (9.5)
Vomiting	78 (45.6)	68 (39.8)	57 (33.7)	50 (29.6)
General disorders and administration site conditions	**127 (74.3)**	**87 (50.9)**	**109 (64.5)**	**85 (50.3)**
Asthenia	22 (12.9)	14 (8.2)	41 (24.3)	34 (20.1)
Chest pain	17 (9.9)	0	13 (7.7)	0
Fatigue	49 (28.7)	41 (24.0)	65 (38.5)	55 (32.5)
Mucosal inflammation	1 (0.6)	1 (0.6)	9 (5.3)	9 (5.3)
Oedema peripheral	80 (46.8)	54 (31.6)	10 (5.9)	4 (2.4)
Pyrexia	32 (18.7)	0	17 (10.1)	0
Infections and infestations	**50 (29.2)**	**0**	**18 (10.7)**	**0**
Nasopharyngitis	22 (12.9)	0	5 (3.0)	0
Upper respiratory tract infection	35 (20.5)	0	13 (7.7)	0
Investigations	**88 (51.5)**	**62 (36.3)**	**51 (30.2)**	**42 (24.9)**
Alanine aminotransferase increased	54 (31.6)	52 (30.4)	20 (11.8)	18 (10.7)
Aspartate aminotransferase increased	40 (23.4)	38 (22.2)	16 (9.5)	15 (8.9)
Electrocardiogram QT prolonged	10 (5.8)	0	3 (1.8)	0
Neutrophil count decreased	8 (4.7)	8 (4.7)	17 (10.1)	17 (10.1)
Platelet count decreased	1 (0.6)	1 (0.6)	18 (10.7)	18 (10.7)
Weight decreased	11 (6.4)	0	6 (3.6)	0
Weight increased	14 (8.2)	0	4 (2.4)	0
White blood cell count decreased	9 (5.3)	9 (5.3)	12 (7.1)	12 (7.1)
Metabolism and nutrition disorders	**61 (35.7)**	**38 (22.2)**	**66 (39.1)**	**60 (35.5)**
Decreased appetite	50 (29.2)	38 (22.2)	57 (33.7)	51 (30.2)
Hypoalbuminaemia	14 (8.2)	0	2 (1.2)	0
Hypomagnesaemia	2 (1.2)	1 (0.6)	12 (7.1)	10 (5.9)
Musculoskeletal and connective tissue disorders	**67 (39.2)**	**9 (5.3)**	**46 (27.2)**	**0**
Arthralgia	14 (8.2)	0	11 (6.5)	0
Back pain	23 (13.5)	0	21 (12.4)	0
Bone pain	10 (5.8)	0	4 (2.4)	0

System Organ Class Preferred Term	Crizotinib (N=171) n (%)		Chemotherapy (N=169) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Any AEs	**168 (98.2)**	**166 (97.1)**	**165 (97.6)**	**153 (90.5)**
Muscle spasms	14 (8.2)	9 (5.3)	2 (1.2)	0
Musculoskeletal pain	15 (8.8)	0	7 (4.1)	0
Pain in extremity	27 (15.8)	0	12 (7.1)	0
Nervous system disorders	**86 (50.3)**	**66 (38.6)**	**52 (30.8)**	**31 (18.3)**
Dizziness	27 (15.8)	19 (11.1)	15 (8.9)	7 (4.1)
Dysgeusia	45 (26.3)	41 (24.0)	9 (5.3)	8 (4.7)
Headache	36 (21.1)	9 (5.3)	25 (14.8)	4 (2.4)
Neuropathy peripheral	2 (1.2)	2 (1.2)	11 (6.5)	10 (5.9)
Paraesthesia	19 (11.1)	13 (7.6)	7 (4.1)	6 (3.6)
Peripheral sensory neuropathy	5 (2.9)	5 (2.9)	10 (5.9)	9 (5.3)
Psychiatric disorders	**23 (13.5)**	**9 (5.3)**	**22 (13.0)**	**3 (1.8)**
Anxiety	6 (3.5)	0	9 (5.3)	0
Insomnia	19 (11.1)	9 (5.3)	15 (8.9)	3 (1.8)
Respiratory, thoracic and mediastinal disorders	**54 (31.6)**	**0**	**47 (27.8)**	**0**
Cough	35 (20.5)	0	28 (16.6)	0
Dyspnoea	23 (13.5)	0	23 (13.6)	0
Haemoptysis	10 (5.8)	0	6 (3.6)	0
Skin and subcutaneous tissue disorders	**31 (18.1)**	**24 (14.0)**	**38 (22.5)**	**34 (20.1)**
Alopecia	12 (7.0)	4 (2.3)	17 (10.1)	15 (8.9)
Pruritus	6 (3.5)	5 (2.9)	10 (5.9)	9 (5.3)
Rash	18 (10.5)	16 (9.4)	19 (11.2)	18 (10.7)

Abbreviation: MedDRA=medical dictionary for regulatory activities.
The MedDRA preferred term of syncope is reported under the system organ class of cardiac disorders.
MedDRA (v16.1) coding dictionary applied.

Serious Adverse Events (SAEs)

SAEs by preferred term and by system organ class (all-causality and treatment-related) are summarized in Table 21.

All causality SAEs were reported for 58 (33.9%) subjects in crizotinib arm and 47 (27.8%) subjects in chemotherapy arm. Most commonly reported all causality SAEs (≥2% of subjects in either treatment arm) were vomiting (1.2% in crizotinib and 2.4% in chemotherapy), disease progression (8.8% in crizotinib and 0.6% in chemotherapy), dyspnea (4.1% in crizotinib and 2.4% in chemotherapy), pleural effusion (1.2% in crizotinib and 3.0% in

chemotherapy) and pulmonary embolism (2.1% in crizotinib and 4.1% in chemotherapy), and convulsion (0% in crizotinib, 3.0% in chemotherapy).

Treatment-related SAEs were reported for 18 (10.5%) subjects in crizotinib arm and 15 (8.9%) subjects in chemotherapy arm. Most commonly reported (≥1% of subjects in either treatment arm) treatment-related SAEs were febrile neutropenia (none in crizotinib and 1.2% in chemotherapy), diarrhoea (1.2% in crizotinib and 0.6% in chemotherapy), nausea (1.8% in crizotinib and 0.6% in chemotherapy), oesophagitis (1.8% in crizotinib and none in chemotherapy), vomiting (1.2% in crizotinib and 2.4% in chemotherapy), general physical health deterioration (none in crizotinib and 1.2% in chemotherapy), pyrexia (0.6% in crizotinib and 1.2% in chemotherapy), dehydration (none in crizotinib and 1.2% in chemotherapy), renal cyst (1.2% in crizotinib and none in chemotherapy), pulmonary embolism (none in crizotinib and 1.2% in chemotherapy).

Table 21: Treatment-Emergent Serious Adverse Events Reported in Subjects by System Organ Class and Preferred Term (All Causalities and Treatment-Related) - Safety Analysis Set

System Organ Class Preferred Term	Crizotinib (N=171) n (%)		Chemotherapy (N=169) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Any AEs	**58 (33.9)**	**18 (10.5)**	**47 (27.8)**	**15 (8.9)**
Blood and lymphatic system disorders	**0**	**0**	**3 (1.8)**	**3 (1.8)**
Anaemia	0	0	1 (0.6)	1 (0.6)
Febrile neutropenia	0	0	2 (1.2)	2 (1.2)
Cardiac disorders	**4 (2.3)**	**0**	**7 (4.1)**	**2 (1.2)**
Atrial fibrillation	1 (0.6)	0	1 (0.6)	0
Atrioventricular block	1 (0.6)	0	0	0
Cardiac arrest	0	0	1 (0.6)	0
Cardiac tamponade	2 (1.2)	0	0	0
Cardiotoxicity	0	0	1 (0.6)	1 (0.6)
Pericardial effusion	0	0	1 (0.6)	0
Pericarditis	0	0	1 (0.6)	0
Syncope	0	0	2 (1.2)	1 (0.6)
Gastrointestinal disorders	**11 (6.4)**	**9 (5.3)**	**7 (4.1)**	**6 (3.6)**
Abdominal pain	1 (0.6)	1 (0.6)	0	0
Constipation	0	0	1 (0.6)	1 (0.6)
Diarrhoea	2 (1.2)	2 (1.2)	1 (0.6)	1 (0.6)
Dysphagia	0	0	1 (0.6)	0
Haemorrhoids	1 (0.6)	0	0	0
Intestinal obstruction	2 (1.2)	1 (0.6)	0	0

System Organ Class Preferred Term	Crizotinib (N=171) n (%)		Chemotherapy (N=169) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Any AEs	**58 (33.9)**	**18 (10.5)**	**47 (27.8)**	**15 (8.9)**
Nausea	3 (1.8)	3 (1.8)	1 (0.6)	1 (0.6)
Oesophageal ulcer	1 (0.6)	1 (0.6)	0	0
Oesophagitis	3 (1.8)	3 (1.8)	0	0
Vomiting	2 (1.2)	2 (1.2)	4 (2.4)	4 (2.4)
General disorders and administration site conditions	**17 (9.9)**	**2 (1.2)**	**5 (3.0)**	**3 (1.8)**
Chest pain	0	0	1 (0.6)	0
Disease progression	15 (8.8)	0	1 (0.6)	0
Fatigue	1 (0.6)	1 (0.6)	0	
General physical health deterioration	0	0	2 (1.2)	2 (1.2)
Oedema peripheral	1 (0.6)	0	0	0
Pyrexia	1 (0.6)	1 (0.6)	2 (1.2)	2 (1.2)
Hepatobiliary disorders	**2 (1.2)**	**1 (0.6)**	**2 (1.2)**	**0**
Bile duct obstruction	0	0	1 (0.6)	0
Cholecystitis	1 (0.6)	0	0	0
Cholecystitis acute	0	0	1 (0.6)	0
Drug-induced liver injury	1 (0.6)	1 (0.6)	0	0
Infections and infestations	**15 (8.8)**	**1 (0.6)**	**3 (1.8)**	**0**
Abdominal abscess	1 (0.6)	1 (0.6)	0	0
Bronchitis	0	0	1 (0.6)	0
Cellulitis	2 (1.2)	0	0	0
Hepatitis B	1 (0.6)	0	0	0
Lower respiratory tract infection	2 (1.2)	0	0	0
Lung infection	1 (0.6)	0	0	0
Periodontitis	1 (0.6)	0	0	0
Pneumonia	3 (1.8)	0	1 (0.6)	0
Pulmonary sepsis	1 (0.6)	0	0	0
Respiratory tract infection	1 (0.6)	0	1 (0.6)	0
Sepsis	1 (0.6)	0	0	0
Septic shock	2 (1.2)	0	0	0
Upper respiratory tract infection	1 (0.6)	0	0	0
Urinary tract infection	1 (0.6)	0	0	0
Injury, poisoning and procedural complications	**0**	**0**	**2 (1.2)**	**0**
Overdose	0	0	1 (0.6)	0

System Organ Class Preferred Term	Crizotinib (N=171) n (%)		Chemotherapy (N=169) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Any AEs	**58 (33.9)**	**18 (10.5)**	**47 (27.8)**	**15 (8.9)**
Rib fracture	0	0	1 (0.6)	0
Investigations	**1 (0.6)**	**1 (0.6)**	**0**	**0**
Alanine aminotransferase increased	1 (0.6)	1 (0.6)	0	0
Aspartate aminotransferase increased	1 (0.6)	1 (0.6)	0	0
Metabolism and nutrition disorders	**4 (2.3)**	**2 (1.2)**	**3 (1.8)**	**3 (1.8)**
Decreased appetite	2 (1.2)	1 (0.6)	0	0
Dehydration	0	0	2 (1.2)	2 (1.2)
Diabetic ketoacidosis	1 (0.6)	0	0	0
Hypokalaemia	1 (0.6)	0	0	0
Hyponatraemia	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)
Hypoproteinaemia	1 (0.6)	0	1 (0.6)	0
Musculoskeletal and connective tissue disorders	**4 (2.3)**	**0**	**2 (1.2)**	**0**
Arthritis	1 (0.6)	0	0	0
Bone pain	1 (0.6)	0	0	0
Muscle spasms	0	0	1 (0.6)	0
Muscular weakness	1 (0.6)	0	0	0
Osteonecrosis	1 (0.6)	0	0	0
Rotator cuff syndrome	0	0	1 (0.6)	0
Spinal column stenosis	1 (0.6)	0	0	0
Nervous system disorders	**6 (3.5)**	**1 (0.6)**	**7 (4.1)**	**1 (0.6)**
Altered state of consciousness	1 (0.6)	0	0	0
Central nervous system lesion	1 (0.6)	0	0	0
Convulsion	0	0	5 (3.0)	1 (0.6)
Headache	2 (1.2)	1 (0.6)	0	0
Loss of consciousness	1 (0.6)	0	0	0
Multiple sclerosis	1 (0.6)	0	0	0
Partial seizures	0	0	1 (0.6)	0
Transient ischaemic attack	0	0	1 (0.6)	0
Psychiatric disorders	**1 (0.6)**	**0**	**1 (0.6)**	**0**
Completed suicide	0	0	1 (0.6)	0
Hypomania	1 (0.6)	0	0	0
Renal and urinary disorders	**3 (1.8)**	**2 (1.2)**	**2 (1.2)**	**1 (0.6)**
Haematuria	0	0	1 (0.6)	0

System Organ Class Preferred Term	Crizotinib (N=171) n (%)		Chemotherapy (N=169) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Any AEs	**58 (33.9)**	**18 (10.5)**	**47 (27.8)**	**15 (8.9)**
Renal cyst	2 (1.2)	2 (1.2)	0	0
Renal failure acute	0	0	1 (0.6)	1 (0.6)
Urinary retention	1 (0.6)	0	0	0
Respiratory, thoracic and mediastinal disorders	**16 (9.4)**	**3 (1.8)**	**19 (11.2)**	**2 (1.2)**
Acute respiratory failure	1 (0.6)	0	0	0
Asthma	0	0	1 (0.6)	0
Dyspnoea	7 (4.1)	1 (0.6)	4 (2.4)	0
Haemoptysis	0	0	2 (1.2)	0
Hydropneumothorax	0	0	1 (0.6)	0
Interstitial lung disease	1 (0.6)	1 (0.6)	0	0
Lung infiltration	0	0	1 (0.6)	0
Pleural effusion	2 (1.2)	0	5 (3.0)	0
Pleurisy	0	0	1 (0.6)	0
Pneumonitis	1 (0.6)	1 (0.6)	0	0
Pulmonary embolism	5 (2.9)	0	7 (4.1)	2 (1.2)
Pulmonary oedema	0	0	1 (0.6)	0
Vascular disorders	**2 (1.2)**	**0**	**1 (0.6)**	**0**
Deep vein thrombosis	1 (0.6)	0	1 (0.6)	0
Orthostatic hypotension	1 (0.6)	0	0	0

Abbreviation: MedDRA=medical dictionary for regulatory activities.
The MedDRA preferred term of syncope is reported under the system organ class of cardiac disorders.
MedDRA (v16.1) coding dictionary applied.

Permanent discontinuations due to AEs

All withdrawals due to AEs regardless of causality by system organ class and preferred terms are summarized in Table 22. Permanent discontinuations from study treatment were similar between the 2 treatment arms; 21 (12.3%) subjects in the crizotinib arm and 24 (14.2%) subjects in the chemotherapy arm.

Table 22: Treatment-Emergent All Causality Adverse Events Associated With Permanent Discontinuation From Treatment by Treatment Arm - Safety Analysis Population

System Organ Class Preferred Term	Crizotinib (N=171) n (%)	Chemotherapy (N=169)[a] n (%)
Any AE associated with permanent treatment discontinuation;	21 (12.3)	24 (14.2)
Blood and lymphatic system disorders	**0**	**1 (0.6)**
Febrile neutropenia	0	1 (0.6)
Cardiac disorders	**0**	**3 (1.8)**
Cardiac arrest	0	1 (0.6)
Cardiotoxicity	0	1 (0.6)
Syncope	0	1 (0.6)
Gastrointestinal disorders	**2 (1.2)**	**2 (1.2)**
Abdominal pain	0	1 (0.6)
Intestinal obstruction	1 (0.6)	0
Nausea	1 (0.6)	0
Vomiting	0	1 (0.6)
General disorders and administration site conditions	**7 (4.1)**	**3 (1.8)**
Disease progression	7 (4.1)	1 (0.6)
Fatigue	0	2 (1.2)
Hepatobiliary disorders	**2 (1.2)**	**1 (0.6)**
Bile duct obstruction	0	1 (0.6)
Drug-induced liver injury	1 (0.6)	0
Hepatocellular injury	1 (0.6)	0
Infections and infestations	**2 (1.2)**	**0**
Pulmonary sepsis	1 (0.6)	0
Septic shock	1 (0.6)	0
Investigations	**2 (1.2)**	**5 (3.0)**
Alanine aminotransferase increased	2 (1.2)	1 (0.6)
Blood creatinine increased	0	2 (1.2)
Platelet count decreased	0	2 (1.2)
Musculoskeletal and connective tissue disorders	**0**	**1 (0.6)**
Arthralgia	0	1 (0.6)
Metabolism and nutrition disorders	**1 (0.6)**	**0**
Diabetic ketoacidosis	1 (0.6)	0
Psychiatric disorders	**0**	**2 (1.2)**
Completed suicide	0	1 (0.6)
Depression	0	1 (0.6)
Renal and urinary disorders	**1 (0.6)**	**2 (1.2)**
Azotaemia	0	1 (0.6)
Renal cyst	1 (0.6)	0

System Organ Class Preferred Term	Crizotinib (N=171) n (%)	Chemotherapy (N=169)[a] n (%)
Renal failure acute	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	**4 (2.3)**	**4 (2.4)**
Acute respiratory failure	1 (0.6)	0
Dyspnoea	0	1 (0.6)
Haemoptysis	0	1 (0.6)
Interstitial lung disease	1 (0.6)	0
Pleural effusion	1 (0.6)	0
Pneumonitis	1 (0.6)	0
Pulmonary embolism	0	2 (1.2)

Abbreviation: MedDRA=medical dictionary for regulatory activities.
MedDRA (v16.1) coding dictionary applied.

Deaths:

Grade 5 all-causality AEs were reported for 20 (11.7%) subjects in the crizotinib arm and 4 (2.4%) subjects in the chemotherapy arm (before crossover). The most commonly reported Grade 5 all-causality AE in the crizotinib arm was Disease progression (16 [9.4%] subjects). No Grade 5 all-causality AEs in the crizotinib arm or in the chemotherapy arm (while on chemotherapy) were considered to be treatment-related (Table 23).

Table 23: Treatment-Emergent Adverse Events Associated With Death on Study (Grade 5) by Treatment Arm - All-Causality and Treatment-Related (All Cycles) - Safety Analysis Population

MedDRA Preferred Term	Crizotinib (N=171)		Chemotherapy (N=169)[a]	
	All-Causality n (%)	Treatment-Related n (%)	All-Causality n (%)	Treatment-Related n (%)
Any Grade 5 AE:	20 (11.7)	0	4 (2.4)	0
Disease progression	16 (9.4)[b]	0	1 (0.6)	0
Septic shock	2 (1.2)	0	0	0
Acute respiratory failure	1 (0.6)	0	0	0
Diabetic ketoacidosis	1 (0.6)	0	0	0
Cardiac arrest	0	0	1 (0.6)	0
Completed suicide	0	0	1 (0.6)	0
Haemoptysis	0	0	1 (0.6)	0

MedDRA Version 16.1 coding dictionary applied.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; n/N=number of subjects.

[a] Only includes data before crossover to crizotinib for those subjects who crossed over to receive crizotinib treatment.

[b] Two subjects are included although the Grade 5 events of Disease progression occurred >28 days after the last dose of crizotinib (29 days and 185 days, respectively).

Clinical laboratory and other safety evaluations

Abnormal values in the clinical laboratory data that the investigator determined to be clinically significant were reported as AEs that were summarized in previous sections. Other safety parameters (blood pressure, ECGs, and MUGA scans/Echocardiograms, and ophthalmologic evaluations) did not reveal any new safety concerns. Due to the low number of subjects with results for DXA analysis and hypogonadism laboratory parameters, no clear conclusion can be made.

CONCLUSIONS:

- Crizotinib treatment resulted in a statistically significant, robust, and clinically meaningful improvement in IRR-assessed PFS as compared with platinum-based chemotherapy in the treatment of subjects with previously untreated ALK-positive, advanced non-squamous NSCLC (median PFS 10.9 months vs 7.0 months; HR: 0.454; 1-sided p-value <0.0001).
- Crizotinib treatment resulted in a clinically and statistically significant improvement in IRR-assessed ORR compared with chemotherapy (74% vs 45%; 2-sided p-value <0.0001), with objective responses that were rapid in onset (median TTR 6 weeks) and durable (median DR estimate 49.0 weeks).

- Crizotinib treatment resulted in a clinically and statistically significant improvement in TTP compared with chemotherapy (median 13.6 months vs 7.0 months; HR: 0.441; 1-sided p-value <0.0001). This improvement in TTP was also observed when only extracranial lesions were evaluated (HR: 0.387; 1-sided p-value <0.0001). There was a numerical improvement in IC-TTP in the crizotinib arm (HR: 0.595; 1-sided p-value=0.0347).
- With only 26% of OS events, median OS was not reached in either treatment arm. There was a numerical improvement in OS in the crizotinib arm (HR: 0.821; 1-sided p-value=0.1804). The 1-year and 18-month survival probabilities were similar between the treatment arms; for crizotinib they were 84% and 69%, respectively, and for chemotherapy they were 79% and 67%, respectively. These OS analyses were not adjusted for the potentially confounding effects of crossover, as 120 chemotherapy subjects (70.2%) received subsequent crizotinib treatment.
- Crizotinib had a distinct side effect profile that was generally tolerable and manageable by dosing interruption, dose reduction, and/or standard medical therapy.
- Crizotinib treatment significantly delayed TTD in the composite endpoint of lung cancer symptoms that included pain in chest, cough, or dyspnea (HR: 0.615; 2-sided p-value=0.0017).
- Crizotinib treatment resulted in statistically significantly (2-sided p-value<0.05) greater overall improvement from baseline in patient-reported key lung cancer symptoms of coughing, dyspnea, and pain in chest, physical functioning, global quality of life, and general health status as compared with the chemotherapy arm.