XALKORI

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XALKORI

1. NAME OF THE MEDICINAL PRODUCT

XALKORI

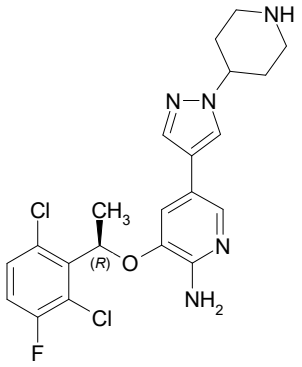
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

250 mg capsules
Hard gelatin capsule, size 0, pink opaque cap and body, with “Pfizer” on the cap and “CRZ 250” on the body.

200 mg capsules
Hard gelatin capsule, size 1, white opaque body and pink opaque cap, with “Pfizer” on the cap and “CRZ 200” on the body.

XALKORI (crizotinib) is an oral receptor tyrosine kinase inhibitor. The molecular formula for crizotinib is $C_{21}H_{22}Cl_2FN_5O$. The molecular weight is 450.34 Daltons. Crizotinib is described chemically as (*R*)-3-[1-(2, 6-Dichloro-3-fluorophenyl) ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl] pyridin-2-amine.

The chemical structure of crizotinib is shown below:



Crizotinib is a white to pale-yellow powder with a pKa of 9.4 (piperidinium cation) and 5.6 (pyridinium cation). The solubility of crizotinib in aqueous media decreases over the range pH 1.6 to pH 8.2 from greater than 10 mg/mL to less than 0.1 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7.4 is 1.65.

3. PHARMACEUTICAL FORM

Hard gelatin capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XALKORI is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an accurate and validated assay.

XALKORI is indicated for the treatment of patients with locally advanced or metastatic NSCLC that is ROS1-positive as detected by an accurate and validated assay.

4.2 Posology and method of administration

ALK and ROS1 Testing

Detection of either ALK-positive or ROS1-positive NSCLC is necessary for selection of patients for treatment with XALKORI because these are the only patients for whom benefit has been shown. Assessment for either ALK-positive or ROS1-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results.

Recommended Dosing

The recommended dose and schedule of XALKORI is 250 mg taken orally twice daily. Continue treatment as long as the patient is deriving clinical benefit from therapy. The recommended dose of XALKORI in patients with severe renal impairment (creatinine clearance <30 mL/min) not requiring dialysis is 250 mg orally, once daily (see Section 5.2).

XALKORI may be taken with or without food. Swallow capsules whole. If a dose of XALKORI is missed, make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of XALKORI, take the next dose at the regular time.

Dose Modification

Reduce dose as below for patients treated with crizotinib 250 mg orally twice daily, if one or more dose reductions are necessary, due to adverse reactions of Grade 3 or 4 severity, as defined by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0:

- First dose reduction: XALKORI 200 mg taken orally twice daily.
- Second dose reduction: XALKORI 250 mg taken orally once daily.
- Permanently discontinue if unable to tolerate XALKORI 250 mg taken once daily.

Dose reduction guidelines are provided in Tables 1 and 2. For patients treated with a lower dose of crizotinib than 250 mg twice daily, then use the recommendations in Table 1 and Table 2 accordingly.

Table 1. XALKORI Dose Modification – Hematologic Toxicities[a]

CTCAE Grade	XALKORI Dosing
Grade 3	Withhold until recovery to Grade 2 or less, then resume at the same dose schedule
Grade 4	Withhold until recovery to Grade 2 or less, then resume at next lower dose[b]

a Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
b For patients treated with 250 mg once daily or whose dose was reduced to 250 mg once daily, discontinue during evaluation.

Table 2. XALKORI Dose Modification – Non-hematologic Toxicities

Criteria	XALKORI Dosing
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 1.5 times ULN	Withhold until recovery to baseline or less than or equal to 3 times ULN, then resume at the next lower dose[a].
ALT or AST elevation greater than 3 times ULN with concurrent total bilirubin elevation greater than 1.5 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue.
Any Grade drug-related interstitial lung disease/pneumonitis	Permanently discontinue.
QTc greater than 500 ms on at least 2 separate electrocardiograms (ECGs)	Withhold until recovery to baseline or to a QTc less than 481 ms, then resume at the next lower dose[a].
QTc greater than 500 ms or greater than or equal to 60 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue.
Bradycardia[a] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to asymptomatic bradycardia or to a heart rate of 60

	bpm or above.
Bradycardia[b,c] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medications is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring.
Visual Loss (Grade 4 Ocular Disorder)	Discontinue during evaluation of severe vision loss.

a For patients treated with 250 mg once daily or whose dose was reduced to 250 mg once daily, discontinue during evaluation.
b Heart rate less than 60 beats per minute (bpm).
c Permanently discontinue for recurrence.

Monitor complete blood counts including differential white blood cell counts monthly and as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs.

4.3 Contraindications

Use of XALKORI is contraindicated in patients with hypersensitivity to crizotinib or to any of the excipients.

4.4 Special warnings and precautions for use

Cardiac failure

Across clinical studies (n=1,669), 19 (1.1%) patients treated with crizotinib had any grade cardiac failure, 8 (0.5%) patients had Grade 3 or 4, and 3 (0.2%) patients had fatal outcome. The reporting rate of crizotinib and cardiac failure from post-marketing experience was 0.27%. Patients receiving XALKORI should be monitored for signs and symptoms of cardiac failure such as edema, dyspnea, and chest pain. Dosing interruption, dose reduction, or discontinuation should be considered as appropriate if such symptoms are observed.

Hepatotoxicity

Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of 1,722 patients treated with XALKORI across clinical trials. Concurrent elevations in ALT and/or AST ≥3×ULN and total bilirubin ≥2×ULN without significant elevations of alkaline phosphatase (≤2×ULN) have been observed in less than 1% of patients treated with XALKORI. Increases to Grade 3 or 4 ALT or AST elevations were observed in 187 (11%) and 95 (6%) of patients, respectively. Seventeen (1%) patients required permanent discontinuation from treatment associated with elevated transaminases suggesting that these events were generally manageable by dosing modifications as defined in Table 2 (see Section 4.2). Transaminase elevations generally occurred within the first 2 months of treatment.

Liver function tests including ALT, AST, and total bilirubin should be monitored every 2 weeks during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3, or 4 elevations. For patients who develop

transaminase elevations, temporarily suspend, dose reduce, or permanently discontinue XALKORI as described in Table 2 (see Section 4.2).

Interstitial lung disease (Pneumonitis)

XALKORI has been associated with severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis in clinical trials at a frequency of 26 (2%) of 1,722 patients treated with XALKORI. Across studies in patients with ALK-positive NSCLC (N=1,669), 49 (3%) patients treated with crizotinib had any grade ILD, 18 (1%) patients had Grade 3 or 4, and 8 (<1%) patients had fatal outcome. According to IRC assessment, 20 (1.2%) patients had ILD/pneumonitis, including 10 (<1%) patients with fatal cases. These cases generally occurred within 3 months after the initiation of treatment.

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Other potential causes of ILD/pneumonitis should be excluded. XALKORI should be permanently discontinued in patients diagnosed with treatment-related ILD/pneumonitis (see Section 4.2).

QT interval prolongation

QTc prolongation has been observed in clinical studies in patients treated with XALKORI (see Sections 4.8 and 5.2) which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de Pointes) or sudden death. The benefits and potential risks of crizotinib should be considered before beginning therapy in patients with pre-existing bradycardia, who have a history of or predisposition for QTc prolongation, who are taking antiarrhythmics or other medicinal products that are known to prolong QT interval and in patients with relevant pre-existing cardiac disease and/or electrolyte disturbances. XALKORI should be administered with caution in these patients and periodic monitoring of ECGs, electrolytes and renal function is required. When using XALKORI, ECG and electrolytes (e.g., calcium, magnesium, potassium) should be obtained as close as possible prior to the first dose and periodic monitoring with ECGs and electrolytes is recommended, especially at the beginning of treatment in case of vomiting, diarrhea, dehydration or impaired renal function. Correct electrolytes as necessary. Avoid use of XALKORI in patients with congenital long QT syndrome. Permanently discontinue XALKORI in patients who develop QTc greater than 500 ms or greater than or equal to 60 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Withhold XALKORI in patients who develop QTc greater than 500 ms on at least 2 separate ECGs until recovery to a QTc less than or equal to 480 ms, then resume XALKORI at a reduced dose as described in Table 2 (see Sections 4.2 and 5.2).

Bradycardia

All-causality bradycardia was reported in clinical studies in 12% of patients treated with crizotinib, and it was usually asymptomatic. Symptomatic bradycardia (e.g., syncope, dizziness, hypotension) can occur in patients receiving XALKORI. The full effect of crizotinib on pulse rate may not develop until several weeks after start of treatment. Avoid using XALKORI in combination with other bradycardic agents (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, such as verapamil and diltiazem, clonidine, digoxin) to the extent possible, due to the increased risk of symptomatic bradycardia (syncope, dizziness, hypotension). Monthly monitoring of pulse rate and blood pressure is recommended. In cases of symptomatic bradycardia that is not life-threatening, hold XALKORI until recovery

to asymptomatic bradycardia or to a heart rate of 60 bpm or above, re-evaluate the use of concomitant medications, and adjust the dose of XALKORI. Permanently discontinue for life-threatening bradycardia due to XALKORI; however, if associated with concomitant medications known to cause bradycardia or hypotension, hold XALKORI until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, and if concomitant medications can be adjusted or discontinued, restart XALKORI at 250 mg once daily with frequent monitoring (see Sections 4.2 and 4.8).

Neutropenia and leukopenia

In clinical studies with crizotinib in patients with either ALK-positive or ROS1-positive NSCLC, Grade 3 or 4 neutropenia has been very commonly (12%) reported. Grade 3 or 4 leukopenia has been commonly (3%) reported (see Section 4.8). Less than 0.5% of patients experienced febrile neutropenia in clinical studies with crizotinib. Complete blood counts including differential white blood cell counts should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs (see Section 4.2).

Renal impairment

If patients have severe renal impairment not requiring peritoneal dialysis or hemodialysis, the dose of crizotinib should be adjusted (see Sections 4.2 and 5.2).

Visual effects

In clinical studies with crizotinib in patients with either ALK-positive or ROS1-positive NSCLC (N=1722), Grade 4 visual field defect with vision loss has been reported in 4 (0.2%) patients. Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss. In patients with new onset of severe visual loss (best corrected visual acuity less than 6/60 in one or both eyes), crizotinib treatment should be discontinued (see Section 4.2). Ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate for new onset of severe visual loss, should be performed. There is insufficient information to characterize the risks of resumption of crizotinib in patients with a severe visual loss. A decision to resume crizotinib should consider the potential benefit to the patient.

Ophthalmological evaluation is recommended if vision disorder persists or worsens in severity (see Section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Crizotinib is a substrate of CYP3A4/5 and also a moderate inhibitor of CYP3A. *In vitro* studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP3A.

Agents that may increase crizotinib plasma concentrations

Co-administration of crizotinib with strong CYP3A inhibitors may increase crizotinib plasma concentrations (see Section 5.2). The concomitant use of strong CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole,

nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of crizotinib and should be avoided. Exercise caution with concomitant use of moderate CYP3A inhibitors.

Agents that may decrease crizotinib plasma concentrations

Co-administration of crizotinib with strong CYP3A inducers may decrease crizotinib plasma concentrations (see Section 5.2). The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort should be avoided.

Agents whose plasma concentrations may be altered by crizotinib

Crizotinib has been identified as an inhibitor of CYP3A both *in vitro* and *in vivo* (see Section 5.2). Caution should be exercised in administering crizotinib in combination with drugs that are predominantly metabolized by CYP3A, particularly those CYP3A substrates that have narrow therapeutic indices, including but not limited to alfentanil, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus.

Co-administration of crizotinib should be avoided with CYP3A substrates that have narrow therapeutic indices and are associated with life-threatening arrhythmias, including but not limited to dihydroergotamine, ergotamine, and pimozide.

4.6 Fertility, pregnancy and lactation

Fertility

Based on non-clinical safety findings, male and female fertility may be compromised by treatment with XALKORI (see Section 5.3). Both men and women should seek advice on fertility preservation before treatment.

Pregnancy

XALKORI may cause fetal harm when administered to a pregnant woman. XALKORI was not shown to be teratogenic in pregnant rats or rabbits. Reduced fetal body weights were considered adverse effects in the rat and rabbit at 200 and 60 mg/kg/day, respectively (approximately equivalent to human clinical exposure based on area under the plasma concentration-time curve [AUC]).

There are no adequate and well-controlled studies in pregnant women using XALKORI. Women of childbearing potential should be advised to avoid becoming pregnant while receiving XALKORI. Women of childbearing potential who are receiving this drug, or partners of women of childbearing potential receiving this drug, should use adequate contraceptive methods during therapy and for at least 90 days after completing therapy.

Female patients taking XALKORI during pregnancy or who become pregnant while taking XALKORI should be apprised of the potential hazard to a fetus. Male patients taking XALKORI should also be apprised of the potential hazard to a fetus if their partner is or should become pregnant.

Lactation

It is not known whether XALKORI and its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from exposure to XALKORI, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

No studies on the effect of XALKORI on the ability to drive and use machines have been performed. However, caution should be exercised when driving or operating machinery by patients who experience vision disorder, dizziness, or fatigue while taking XALKORI (see Section 4.8).

4.8 Undesirable effects

Summary of Safety Profile

The data described below reflect exposure to XALKORI in 1,669 patients with ALK-positive advanced NSCLC who participated in randomized Phase 3 Studies 1007 or 1014 or in single-arm Studies 1001 or 1005, and in 53 patients with ROS1-positive advanced NSCLC who participated in single-arm Study 1001, for a total of 1,722 patients (see Section 5.1). These patients received a starting oral dose of 250 mg twice daily continuously. In Study 1014, the median duration of study treatment was 47 weeks for patients in the XALKORI arm (N = 171); the median duration of treatment was 23 weeks for patients who crossed over from the chemotherapy arm to receive XALKORI treatment (N = 109). In Study 1007, the median duration of study treatment was 48 weeks for patients in the XALKORI arm (N = 172). For ALK-positive NSCLC patients in Studies 1001 (N = 154) and 1005 (N = 1,063), the median duration of treatment was 57 and 45 weeks, respectively. For ROS1-positive NSCLC patients in Study 1001 (N = 53), the median duration of treatment was 101 weeks.

The most serious adverse reactions in 1,722 patients with either ALK-positive or ROS1-positive advanced NSCLC were hepatotoxicity, ILD/pneumonitis, neutropenia and QT interval prolongation (see Section 4.4). The most common adverse reactions (≥25%) in patients with either ALK-positive or ROS1-positive NSCLC were vision disorder, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, dizziness, and neuropathy.

In 1,722 patients with either ALK-positive or ROS1-positive NSCLC treated with XALKORI, all-causality adverse events associated with dosing interruptions or dose reductions occurred in 763 (44%) and 259 (15%) patients, respectively. All-causality adverse events associated with permanent treatment discontinuation occurred in 302 (18%) patients.

Table 3 presents adverse drug reactions (ADRs) experienced by ALK-positive NSCLC patients who participated in randomized Phase 3 Studies 1007 or 1014 or in single-arm Studies 1001 or 1005 (N=1,669), and in ROS1-positive NSCLC patients who participated in single-arm Study 1001 (N=53), for a total dataset of 1,722 patients (see Section 5.1). Adverse drug reactions are

listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC.*

Table 3. ADRs by System Organ Class (SOC) and Council for International Organizations of Medical Sciences (CIOMS) frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC (Pooled ROS1-Positive NSCLC and ALK-Positive NSCLC; n=1,722)*

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Frequency not known (cannot be estimated from the available data)
Blood and Lymphatic System Disorders	Neutropenia[a] Leukopenia[b] Anemia[c]			
Metabolism and Nutrition Disorders	Decreased appetite	Hypophosphatemia		
Nervous System Disorders	Neuropathy[d] Dizziness[e] Dysgeusia			
Eye Disorders	Vision disorder[f]			
Cardiac Disorders	Bradycardia[g]	Electrocardiogram QT prolonged Syncope Cardiac failure[h]		
Respiratory, Thoracic and Mediastinal Disorders		Interstitial lung disease[i]		
Gastrointestinal Disorders	Vomiting Diarrhea Nausea Constipation Abdominal pain[j]	Esophagitis[k] Dyspepsia	Gastrointestinal perforation[l]	
Hepatobiliary Disorders	Elevated transaminases[m]	Blood alkaline phosphatase increased	Hepatic failure	
Skin and Subcutaneous Tissue Disorders	Rash			
Renal and Urinary Disorders		Renal cyst[n] Blood creatinine increased[o]		
General Disorders and Administration Site Conditions	Edema[p] Fatigue			
Investigations		Blood testosterone decreased[q]		Blood creatine phosphokinase increased**

* The frequency categories of adverse drug reactions were based on the data cutoff date of 30 Nov 2013 for patients with ALK-positive NSCLC, and based on the data cutoff date of 30 Nov 2014 for patients with ROS1-positive NSCLC.

** Adverse reaction identified post-marketing. Creatine phosphokinase was not a standard laboratory test in the crizotinib clinical trials.

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above. Terms actually reported in the studies up to the data cutoff date and contributing to the relevant adverse drug reaction are indicated in parentheses, as listed below.

a. Neutropenia (Febrile neutropenia, Neutropenia, Neutrophil count decreased).
b. Leukopenia (Leukopenia, White blood cell count decreased).
c. Anemia (Anemia, Hemoglobin decreased, Hypochromic anemia).
d. Neuropathy (Burning sensation, Dysesthesia, Formication, Gait disturbance, Hyperesthesia, Hypoesthesia, Hypotonia, Motor dysfunction, Muscle atrophy, Muscular weakness, Neuralgia, Neuritis, Neuropathy peripheral, Neurotoxicity, Paraesthesia, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal nerve palsy, Polyneuropathy, Sensory disturbance, Skin burning sensation).
e. Dizziness (Balance disorder, Dizziness, Dizziness postural, Presyncope).
f. Vision disorder (Diplopia, Halo vision, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual brightness, Visual field defect, Visual impairment, Vitreous floaters).
g. Bradycardia (Bradycardia, Heart rate decreased, Sinus bradycardia).
h. Cardiac failure (Cardiac failure, Cardiac failure congestive, Ejection fraction decreased, Left ventricular failure, Pulmonary edema). Across clinical studies (n=1,669), 19 (1.1%) patients treated with crizotinib had any grade cardiac failure, 8 (0.5%) patients had Grade 3 or 4, and 3 (0.2%) patients had fatal outcome.
i. Interstitial lung disease (Acute respiratory distress syndrome, Alveolitis, Interstitial lung disease, Pneumonitis).
j. Abdominal pain (Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness).
k. Esophagitis (Esophagitis, Esophageal ulcer).
l. Gastrointestinal perforation (Gastrointestinal perforation, Intestinal perforation).
m. Elevated transaminases (Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Liver function test abnormal, Transaminases increased).
n. Renal cyst (Renal abscess, Renal cyst, Renal cyst hemorrhage, Renal cyst infection).
o. Blood creatinine increased (Blood creatinine increased, Creatinine renal clearance decreased).
p. Edema (Face edema, Generalised edema, Local swelling, Localized edema, Edema, Edema peripheral, Periorbital edema).
q. Blood testosterone decreased (Blood testosterone decreased, Hypogonadism, Secondary hypogonadism).

Description of Selected Adverse Reactions

Visual Effects

In clinical trials of patients with either ALK-positive or ROS1-positive advanced NSCLC (N = 1722), Grade 4 visual field defect with vision loss has been reported in 4 (0.2%) patients. Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss (see Section 4.4). All-causality vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 1,084 (63%) of 1,722 patients treated with XALKORI. Of the 1,084 patients who experienced vision disorder, 95% of these patients had events that were mild in severity. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity. Seven (0.4%) patients had temporary treatment discontinuation and 2 (0.1%) patients had a dose reduction associated with vision disorder. There were no permanent discontinuations associated with vision disorder for any of the 1,722 patients treated with XALKORI.

Based on the Visual Symptom Assessment Questionnaire (VSAQ-ALK), patients treated with XALKORI in Study 1007 and Study 1014 reported a higher incidence of visual disturbances compared to patients treated with chemotherapy. The onset of vision disorders generally occurred during the first week of drug administration. The majority of patients in the

XALKORI arm in Study 1007 and Study 1014 (>50%) reported visual disturbances, which occurred at a frequency of 4 to 7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured by the VSAQ-ALK questionnaire.

In patients with new onset of Grade 4 visual loss, crizotinib treatment should be discontinued and ophthalmological evaluation should be performed. Ophthalmological evaluation is recommended if vision disorder persists or worsens in severity (see Sections 4.2 and 4.4).

Gastrointestinal Effects

Nausea (57%), diarrhea (54%), vomiting (51%), and constipation (43%) were the most commonly reported all-causality gastrointestinal events. Most events were mild to moderate in severity. Median times to onset for nausea and vomiting were 3 days, and these events declined in frequency after 3 weeks of treatment. Supportive care should include the use of antiemetic medications. In clinical trials, the most commonly used antiemetic medications were ondansetron and prochlorperazine. Median times to onset for diarrhea and constipation were 13 and 17 days, respectively. Supportive care for diarrhea and constipation should include the use of standard antidiarrheal and laxative medications, respectively.

Nervous System Effects

All-causality neuropathy, as defined in Table 3, was experienced by 435 (25%) of 1,722 patients treated with XALKORI and was primarily Grade 1 or 2 in severity. Dizziness and dysgeusia were also very commonly reported and were primarily Grade 1 in severity.

Bradycardia

In clinical trials of patients with either ALK-positive or ROS1-positive advanced NSCLC, all--causality bradycardia was experienced by 219 (13%) of 1,722 patients treated with XALKORI. Most events were mild in severity. A total of 259 (16%) of 1,666 patients with at least 1 post-baseline vital sign assessment had a pulse rate <50 bpm. The use of concomitant medications associated with bradycardia should be carefully evaluated. Patients who develop symptomatic bradycardia should be managed as recommended in the Dose Modification and Warnings and Precautions sections (see Sections 4.2 and 4.4).

Renal Cysts

All-causality complex renal cysts were experienced by 52 (3%) of 1,722 patients treated with XALKORI. There were no reports of clinically relevant abnormal urinalyses or renal impairment in these cases, although local cystic invasion beyond the kidney was observed in some patients. Periodic monitoring with imaging and urinalysis should be considered in patients who develop renal cysts.

Laboratory Abnormalities/Testing

Hematologic Laboratory Abnormalities

In clinical studies of XALKORI in patients with either ALK-positive or ROS1-positive advanced NSCLC, shifts to Grade 3 or 4 decreases in leukocytes and neutrophils were observed

in 64 (4%) and 226 (13%) patients, respectively. Complete blood counts including differential white blood cell counts should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs. In patients who develop hematologic laboratory abnormalities, see Dose Modification section (see Section 4.2).

Hepatic Laboratory Abnormalities

In clinical studies of XALKORI in patients with either ALK-positive or ROS1-positive advanced NSCLC, shifts to Grade 3 or 4 ALT, AST, and alkaline phosphatase were observed in 187 (11%), 95 (6%), and 33 (2%) patients, respectively. Patients should be monitored for hepatotoxicity and managed as recommended in Warnings and Precautions section (see Section 4.4).

Renal Laboratory Abnormalities

In clinical studies of crizotinib in patients with ALK-positive advanced NSCLC, the estimated glomerular filtration rate (eGFR) decreased from a baseline median of 96.42 mL/min/1.73 m^2 (n=1681) to a median of 80.23 mL/min/1.73 m^2 at 2 weeks of treatment (n=1499). Median eGFR appeared to be relatively stable from 12 weeks of treatment (78.06 mL/min/1.73 m^2, n=1338) through 104 weeks of treatment (75.45 mL/min/1.73 m^2, n=315) and increased to 83.02 mL/min/1.73 m^2 at 28 days after the last dose of crizotinib (n=123).

Shifts to eGFR Grade 4 (15 to <30 mL/min/1.73 m^2) or to eGFR Grade 5 (<15 mL/min/1.73 m^2) were observed in 3% and <1% of patients, respectively.

4.9 Overdose

Treatment of overdose with crizotinib should consist of general supportive measures. There is no antidote for XALKORI.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Crizotinib is a selective small-molecule inhibitor of the ALK receptor tyrosine kinase (RTK) and its oncogenic variants (i.e., ALK fusion events and selected ALK mutations). Crizotinib is also an inhibitor of the Hepatocyte Growth Factor Receptor (HGFR, c-Met) RTK, ROS1 (c-ros), and Recepteur d'Origine Nantais (RON) RTKs. Crizotinib demonstrated concentration-dependent inhibition of the kinase activity of ALK, ROS1, and c-Met in biochemical assays and inhibited phosphorylation and modulated kinase-dependent phenotypes in cell-based assays. Crizotinib demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumor cell lines exhibiting ALK fusion events (including echinoderm microtubule-associated protein-like 4[EML]4-ALK and nucleophosmin [NPM]-ALK), ROS1 fusion events, or exhibiting amplification of the ALK or MET gene locus.

Crizotinib demonstrated antitumor efficacy, including marked cytoreductive antitumor activity, in mice bearing tumor xenografts that expressed ALK fusion proteins. The antitumor efficacy of crizotinib was dose-dependent and correlated to pharmacodynamic inhibition of phosphorylation of ALK fusion proteins (including EML4-ALK and NPM-ALK) in tumors

in vivo. Crizotinib also demonstrated marked antitumor activity in mouse xenograft studies, where tumors were generated using a panel of NIH-3T3 cell lines engineered to express key ROS1 fusions identified in human tumors. The antitumor efficacy of crizotinib was dose-dependent and demonstrated a correlation with inhibition of ROS1 phosphorylation *in vivo*.

Pediatric Population

The safety and efficacy of XALKORI in pediatric patients has not been established. Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 3 times human clinical exposure based on AUC). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

Clinical Studies

Previously Untreated ALK-positive Advanced NSCLC – Randomized Phase 3 Study 1014

The use of single-agent XALKORI for the first-line treatment of ALK-positive advanced NSCLC in patients with or without brain metastases was investigated in a multicenter, multinational, randomized, open-label Phase 3 Study 1014. The primary objective of this study was to demonstrate that XALKORI was superior to first-line standard-of-care platinum-based chemotherapy (pemetrexed-cisplatin or pemetrexed-carboplatin) in prolonging Progression-free Survival (PFS) as assessed by independent radiology review (IRR) in patients with ALK-positive advanced NSCLC who had not received previous systemic treatment for advanced disease. Secondary objectives were to compare measures of clinical efficacy including Objective Response Rate (ORR) as assessed by IRR, Duration of Response (DR), Overall Survival (OS), Intracranial Time to Progression (IC-TTP) as assessed by IRR, and Patient-Reported Outcomes (PRO).

The full analysis population for Study 1014 included 343 patients with ALK-positive advanced NSCLC as identified by Fluorescence *In Situ* Hybridization (FISH) prior to randomization. One hundred seventy-two (172) patients were randomized to the XALKORI arm (171 patients received XALKORI 250 mg orally twice daily) and 171 patients were randomized to the chemotherapy arm (169 patients received chemotherapy; 91 patients were treated with pemetrexed/cisplatin and 78 patients were treated with pemetrexed/carboplatin).

Chemotherapy consisted of pemetrexed 500 mg/m^2 in combination with cisplatin 75 mg/m^2 or carboplatin at a dose calculated to produce AUC of 5 or 6 mg•min/mL. Chemotherapy was given by intravenous infusion every 3 weeks for up to 6 cycles. The median duration of study treatment was 47 weeks in the XALKORI arm and 18 weeks in the chemotherapy arm. Patients could continue XALKORI treatment beyond the time of Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression, as assessed by IRR, at the discretion of the investigator if the patient was still experiencing clinical benefit. Patients in the chemotherapy arm who completed 6 cycles were to continue in the study without further treatment, but have ongoing tumor assessments until RECIST-defined disease progression as determined by IRR. Patients in the chemotherapy arm who had RECIST-defined progression of disease as assessed by IRR had the option to receive XALKORI. One hundred forty-four (84%) patients received XALKORI after the randomization phase (128 patients through the crossover process and 16 patients as follow-up therapy).

Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs. 2), race (Asian vs. non-Asian), and brain metastases (present vs. absent).

Baseline demographic and disease characteristics were similar between the XALKORI and chemotherapy treatment arms with regard to gender (female: 61% vs. 63% for XALKORI vs. chemotherapy, respectively), median age (52 years vs. 54 years), race (White: 53% vs. 50%, and Asian: 45% vs. 47%); smoking status (current smokers: 6% vs. 3%, former-smokers: 33% vs. 32%, and never smokers: 62% vs. 65%), metastatic disease (98% in both treatment arms), tumor histology (adenocarcinoma: 92% vs. 93%), performance status (ECOG 0 or 1: 94% vs. 95%, and ECOG 2: 6% vs. 5%), and brain metastases (present 26% vs. 28%).

XALKORI significantly prolonged PFS compared to chemotherapy as assessed by IRR. There was a numerical improvement in OS in the patients treated with crizotinib, although this improvement was not statistically significant. Efficacy data from randomized Phase 3 Study 1014 are summarized in Table 4, and the Kaplan-Meier curves for PFS and OS are shown in Figures 1 and 2, respectively.

Table 4. Efficacy Results from Randomized Phase 3 Study 1014 (Full Analysis Population) in Patients with Previously Untreated ALK-positive Advanced NSCLC*

Response Parameter	**XALKORI (N = 172)**	**Chemotherapy (N = 171)**
Progression-Free Survival (Based on IRR)		
Number with event, n (%)	100 (58%)	137 (80%)
Median PFS in months (95% CI)	10.9 (8.3, 13.9)	7.0[a] (6.8, 8.2)
HR (95% CI)[b]	0.45 (0.35, 0.60)	
p-value[c]	<0.0001	
Overall Survival[d]		
Number of deaths, n (%)	71 (41%)	81 (47%)
Median OS in months (95% CI)	NR (45.8, NR)	47.5 (32.2, NR)
HR (95% CI)[b]	0.76 (0.55, 1.05)	
p-value[c]	0.0489	
12-Month survival probability,[d] % (95% CI)	83.5 (77.0, 88.3)	78.4 (71.3, 83.9)
18-Month survival probability,[d] % (95% CI)	71.5 (64.0, 77.7)	66.6 (58.8, 73.2)
48-Month survival probability,[d] % (95% CI)	56.6 (48.3, 64.1)	49.1 (40.5, 57.1)
Objective Response Rate (based on IRR)		
Objective Response Rate % (95% CI)	74% (67, 81)	45%[e] (37, 53)
p-value[f]	<0.0001	
Duration of Response		
Months[g] (95% CI)	11.3 (8.1, 13.8)	5.3 (4.1, 5.8)

Abbreviations: N/n=number of patients; CI = confidence interval; HR=hazard ratio; IRR=independent radiology review; NR = not reached; PFS = progression-free survival; OS = overall survival.

* PFS, Objective Response Rate and Duration of Response are based on the data cutoff date of 30 November 2013; OS is based on the last patient last visit date of 30 November 2016, and is based on a median follow up of approximately 46 months.

a. Median PFS times were 6.9 months (95% CI: 6.6, 8.3) for pemetrexed/cisplatin (HR = 0.49; p-value <0.0001 for crizotinib compared with pemetrexed/cisplatin) and 7.0 months (95% CI: 5.9, 8.3) for pemetrexed/carboplatin (HR = 0.45; p-value <0.0001 for crizotinib compared with pemetrexed/carboplatin).

b. Based on the Cox proportional hazards stratified analysis.

c. Based on the stratified log-rank test (1-sided).

d. Updated based on final OS analysis. OS analysis was not adjusted for the potentially confounding effects of cross over (144 [84%] patients in the chemotherapy arm received subsequent crizotinib treatment).
e. ORRs were 47% (95% CI: 37, 58) for pemetrexed/cisplatin (p-value < 0.0001 compared with crizotinib) and 44% (95% CI: 32, 55) for pemetrexed/carboplatin (p-value <0.0001 compared with crizotinib).
f. Based on the stratified Cochran-Mantel-Haenszel test (2-sided).
g. Estimated using the Kaplan-Meier method.

Figure 1. Kaplan-Meier Curves for Progression-free Survival (Based on IRR) by Treatment Arm in Randomized Phase 3 Study 1014 (Full Analysis Population) in Patients with Previously Untreated ALK-positive Advanced NSCLC

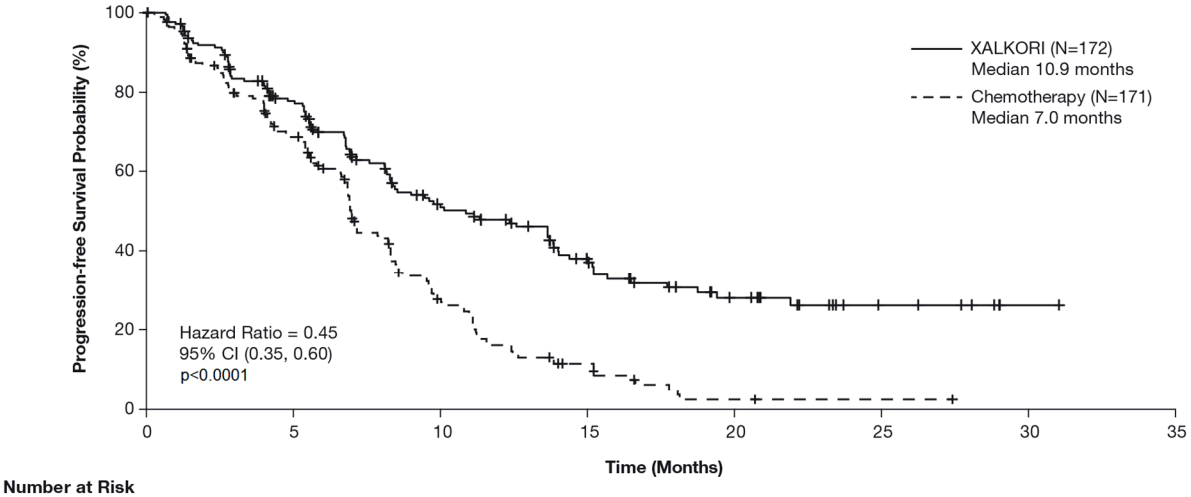
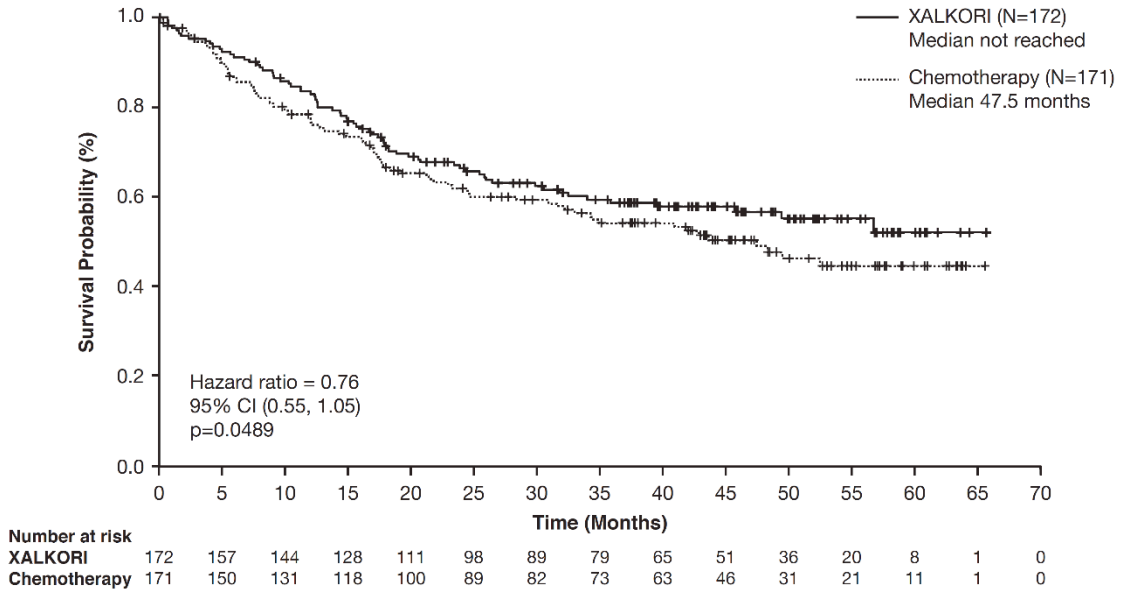


Figure 2. Kaplan-Meier Curves for Overall Survival by Treatment Arm in Randomized Phase 3 Study 1014 (Full Analysis Population) in Patients with Previously Untreated ALK-positive Advanced NSCLC



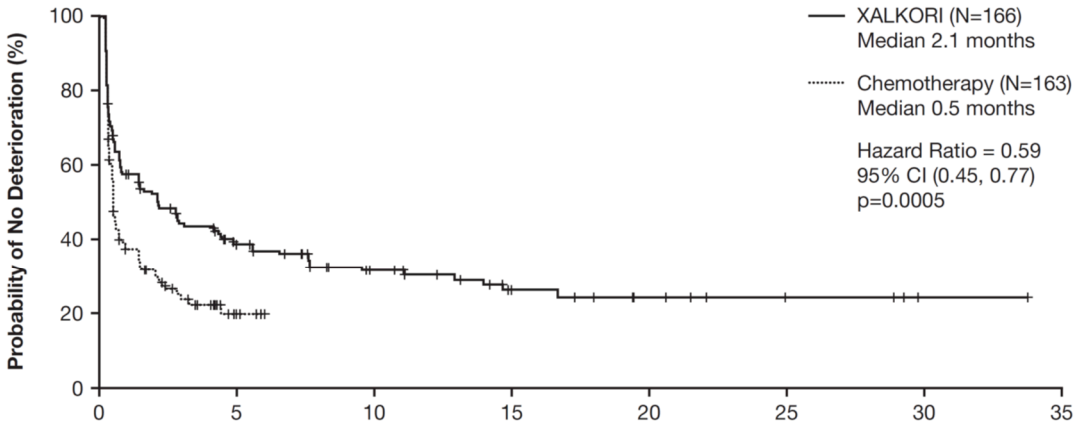
Based on IRR assessment, a total of 9 (23.1%) of the 39 patients in the XALKORI arm and 12 (30.0%) of the 40 patients in the chemotherapy arm with previously treated baseline brain

metastases experienced progression of intracranial lesions or developed new intracranial lesions. For patients with previously treated baseline brain metastases, the median intracranial TTP (IC-TTP) was 15.7 months in the XALKORI arm and 12.5 months in the chemotherapy arm (HR = 0.45 [95% CI: 0.19, 1.07]; 1-sided p-value=0.0315). A total of 16 (12.1%) of the 132 patients in the XALKORI arm and 14 (10.7%) of the 131 patients in the chemotherapy arm without baseline brain metastases developed new intracranial lesions. For patients without baseline brain metastases, the median IC-TTP was not reached in either the XALKORI or the chemotherapy arms (HR = 0.69 [95% CI: 0.33, 1.45]; 1-sided p-value=0.1617).

Patient-reported symptoms and global QOL was collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13) at baseline (Day 1), Day 7 and Day 15 of Cycle 1, and Day 1 of each subsequent treatment cycle. A total of 166 patients in the XALKORI arm and 163 patients in the chemotherapy arm had completed the EORTC QLQ-C30 and LC-13 questionnaires at baseline and at least 1 post-baseline visit.

Time to Deterioration (TTD) was pre-specified as the time from randomization to the first occurrence of a ≥10-point increase in scores from baseline in symptoms of pain (EORTC QLQ-LC13 pain in chest), cough (EORTC QLQ-LC13 cough), or dyspnea (EORTC QLQ-LC13 dyspnea). The median TTD in patient-reported pain in chest, dyspnea, or cough as a composite endpoint was 2.1 months (95% CI: 0.8 months, 4.2 months) in the XALKORI arm compared to 0.5 months (95% CI: 0.4 months, 0.7 months) in the chemotherapy arm. Treatment with XALKORI was associated with a significantly longer TTD in the symptoms of pain in chest, dyspnea, or cough compared to chemotherapy (hazard ratio 0.59; 95% CI: 0.45, 0.77; Hochberg-adjusted log-rank 2-sided p-value =0.0005).

Figure 3. Kaplan-Meier Plot of Time to Deterioration in Pain (in Chest), Dyspnea, or Cough (Composite Endpoint) by Treatment Arm (Patient-reported Outcome Evaluable Population) in Patients with Previously Untreated ALK-positive Advanced NSCLC



Number at Risk								
XALKORI	166	49	29	15	9	4	1	0
Chemotherapy	163	5	0	0	0	0	0	0

The change from baseline scores was found to be significantly different between the 2 treatment arms, with a significantly greater improvement observed in global quality of life in the XALKORI arm compared to the chemotherapy arm (overall difference in change from baseline scores 13.8; p-value <0.0001).

Previously Treated ALK-positive Advanced NSCLC-randomized Phase 3 Study 1007

The use of single-agent XALKORI in the treatment of ALK-positive advanced NSCLC with or without brain metastases was investigated in a multicenter, multinational, randomized, open-label Phase 3 study (Study 1007). The primary objective of this study was to demonstrate that XALKORI 250 mg orally twice daily was superior to standard-of-care chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2) intravenously (IV) every 21 days in prolonging Progression-free Survival (PFS) in patients with ALK-positive advanced NSCLC who had received 1 prior chemotherapy regimen. Patients were required to have ALK-positive NSCLC as identified by FISH prior to randomization. Patients randomized to chemotherapy could cross over to receive XALKORI in Study 1005 upon RECIST-defined disease progression confirmed by IRR. The primary efficacy endpoint was PFS with disease progression events determined by IRR. Secondary endpoints included ORR as determined by IRR, DR, OS, and PRO. The full analysis population for Study 1007 included 347 patients with ALK-positive advanced NSCLC. One hundred seventy-three (173) patients were randomized to the XALKORI arm (172 patients received XALKORI) and 174 patients were randomized to the chemotherapy arm (99 [58%] patients received pemetrexed and 72 [42%] patients received docetaxel). Randomization was stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and prior EGFR tyrosine kinase inhibitor treatment (yes, no). The median duration of study treatment was 31 weeks in the XALKORI arm as compared to 12 weeks in the chemotherapy arm.

Patients could continue treatment as assigned beyond the time of RECIST-defined disease progression, as assessed by IRR, at the discretion of the investigator if the patient was still experiencing clinical benefit. Fifty-eight of 84 (69%) patients treated with XALKORI and 17 of 119 (14%) patients treated with chemotherapy continued treatment for at least 3 weeks after objective disease progression.

Baseline demographic and disease characteristics for patients in this study were similar between the XALKORI and chemotherapy arms with regard to gender (female: 57% vs. 55% for XALKORI vs. chemotherapy, respectively), median age (51 years vs. 49 years), race (White: 52% in both treatment arms, and Asian: 46% vs. 45%), smoking status (current smokers: 3% vs. 5%, former-smokers: 34% vs. 31%, and never smokers: 62% vs. 64%), metastatic disease (95% vs. 91%), tumor histology (adenocarcinoma: 94% vs. 92%), performance status (ECOG 0 or 1: 89% vs. 91%, ECOG 2: 11% vs. 9%), and brain metastases (present: 35% in both treatment arms).

XALKORI significantly prolonged PFS compared to chemotherapy as assessed by IRR. Efficacy data from randomized Phase 3 Study 1007 are summarized in Table 5, and the Kaplan-Meier curve for PFS is shown in Figure 4.

Table 5. Efficacy Results from Randomized Phase 3 Study 1007 (Full Analysis Population) in Patients with Previously Treated ALK-positive Advanced NSCLC*

Response Parameter	XALKORI (N = 173)	Chemotherapy (N = 174)
Progression-free Survival (Based on IRR)		
Number of events, n (%)	100 (58%)	127 (73%)
Median PFS in months (95% CI)	7.7 (6.0, 8.8)	3.0[a] (2.6, 4.3)
HR (95% CI)[b]	0.49 (0.37, 0.64)	
P-value[c]	<0.0001	
Overall Survival[d]		
Number of deaths, n (%)	116 (67%)	126 (72%)
Median OS in months (95% CI)	21.7(18.9, 30.5)	21.9 (16.8, 26.0)
HR (95% CI)[b]	0.85 (0.66, 1.10)	
P-value[c]	0.1145	
Objective Response Rate (Based on IRR)		
Objective response rate % (95% CI)	65% (58,72)	20%[e] (14,26)
P-value[f]	<0.0001	
Duration of Response		
Median[g], months (95% CI)	7.4 (6.1, 9.7)	5.6 (3.4, 8.3)

Abbreviations: N/n=number of patients; CI = confidence interval; HR = Hazard Ratio; IRR = independent radiology review; PFS=progression-free survival; OS=overall survival.

* PFS, Objective Response Rate and Duration of Response are based on the data cutoff date of 30 March 2012; OS is based on the data cutoff date of 31 August 2015.

a Median PFS times were 4.2 months (95% CI: 2.8, 5.7) for pemetrexed (HR = 0.59; p-value=0.0004 for XALKORI compared with pemetrexed) and 2.6 months (95% CI: 1.6, 4.0) for docetaxel (HR = 0.30; p-value <0.0001 for XALKORI compared with docetaxel).

b Based on the Cox proportional hazards stratified analysis.

c Based on the stratified log-rank test (1-sided).

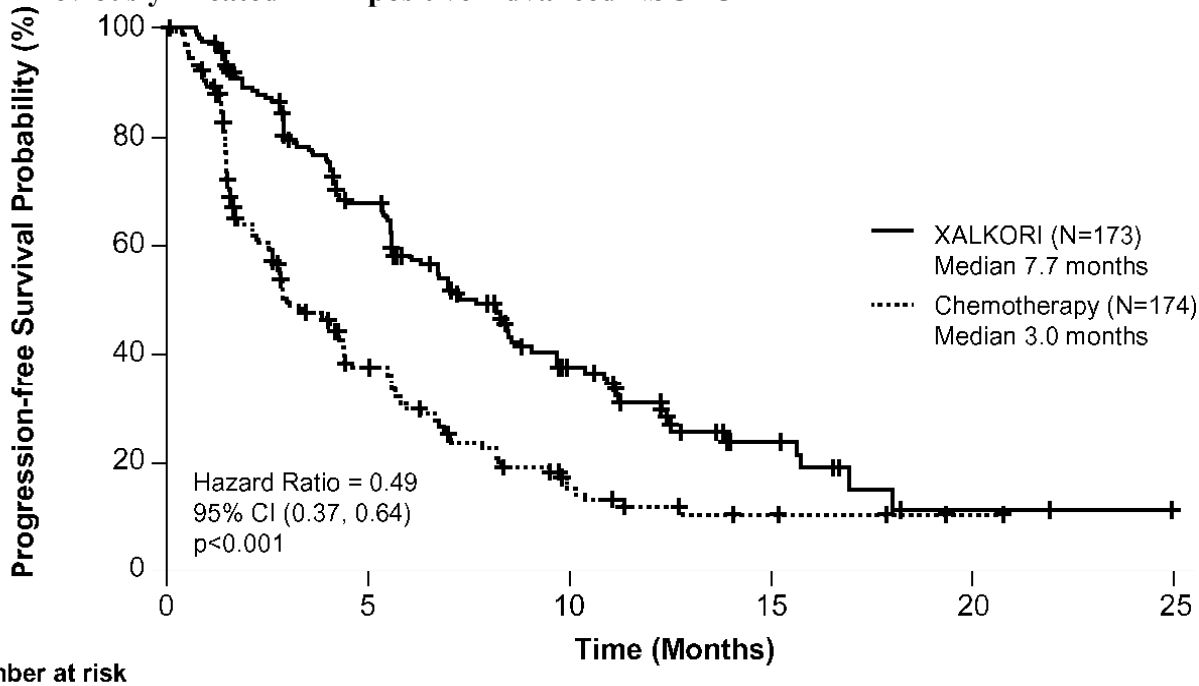
d Updated based on final OS analysis. OS analysis was not adjusted for the potentially confounding effects of cross over.

e ORRs were 29% (95% CI: 21, 39) for pemetrexed (p-value <0.0001 compared with XALKORI) and 7% (95% CI: 2, 16) for docetaxel (p-value <0.0001 compared with XALKORI).

f Based on the stratified Cochran-Mantel-Haenszel test (2-sided).

g Estimated using the Kaplan-Meier method.

Figure 4. Kaplan-Meier Curves for Progression-free Survival (Based on IRR) by Treatment Arm in Randomized Phase 3 Study 1007 (Full Analysis Population) in Patients with Previously Treated ALK-positive Advanced NSCLC



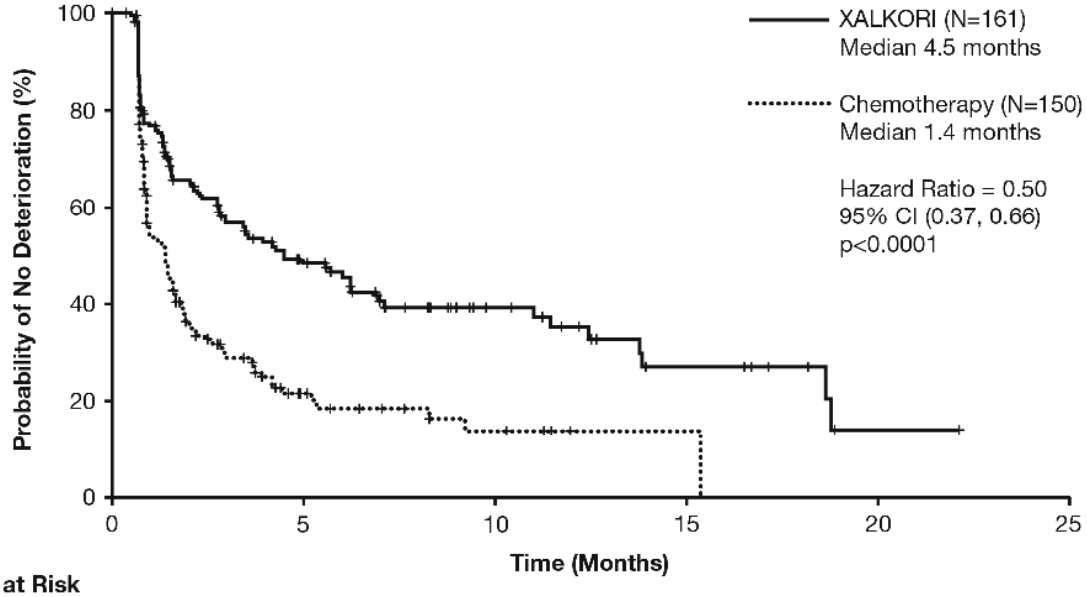
Number at risk						
XALKORI	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

Patient-reported symptoms and global QOL was collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13) at baseline (Day 1 Cycle 1) and Day 1 of each subsequent treatment cycle. A total of 162 patients in the XALKORI arm and 151 patients in the chemotherapy arm had completed the EORTC QLQ-C30 and LC13 questionnaires at baseline and at least 1 post-baseline visit.

TTD was pre-specified as the time from randomization to the first occurrence of a ≥10-point increase in scores from baseline in symptoms of pain (EORTC QLQ-LC13 pain in chest), cough (EORTC QLQ-LC13 cough), or dyspnea (EORTC QLQ-LC13 dyspnea). The median TTD in patient-reported pain in chest, dyspnea, or cough as a composite endpoint was 4.5 months (95% CI: 3.0 months, 6.9 months) in the XALKORI arm compared to 1.4 months (95% CI: 1.0 months, 1.6 months) in the chemotherapy arm. Treatment with XALKORI was associated with a significantly longer TTD in the symptoms of pain in chest, dyspnea, or cough compared to chemotherapy (hazard ratio 0.50; 95% CI: 0.37, 0.66; Hochberg-adjusted log-rank p-value <0.0001).

The change from baseline scores was found to be significantly different between the 2 treatment arms, with a significantly greater improvement observed in global quality of life in the XALKORI arm compared to the chemotherapy arm (overall difference in change from baseline scores 9.84; p-value <0.0001).

Figure 5. Kaplan-Meier Plot of Time to Deterioration in Pain (in Chest), Dyspnea, or Cough (Composite Endpoint) by Treatment Arm (Patient-reported Outcome Evaluable Population) in Patients with Previously Treated ALK-positive Advanced NSCLC



Single-arm Studies in ALK-positive Advanced NSCLC

The use of single-agent XALKORI in the treatment of ALK-positive advanced NSCLC with or without brain metastases was investigated in 2 multicenter, multinational, single-arm studies (Studies 1001 and 1005). Patients enrolled into these studies had received prior systemic therapy, with the exception of 16 patients in Study 1001 and 3 patients in Study 1005 who had no prior systemic treatment for locally advanced or metastatic disease. The primary efficacy endpoint in both studies was ORR according to RECIST. Secondary endpoints included Time to Tumor Response (TTR), DR, PFS, and OS. Patients received XALKORI 250 mg orally twice daily.

In Study 1001 (n = 119) the demographic characteristics were 50% female; median age 51 years; baseline ECOG performance status of 0 or 1 (87%) or 2 (12%), 62% White and 29% Asian; and <1% current smokers, 27% former-smokers, and 72% never smokers. The disease characteristics were 96% metastatic, 98% adenocarcinoma histology, and 13% with no prior systemic therapy for metastatic disease.

In Study 1005 (n = 934) the demographic characteristics were 57% female; median age 53 years baseline ECOG performance status of 0/1 (82%) or 2/3 (18%), 52% White and 44% Asian; and 4% current smokers, 30% former-smokers, and 66% never smokers. The disease characteristics were 92% metastatic, 94% adenocarcinoma histology.

In Study 1001, patients with advanced NSCLC were required to have ALK-positive tumors prior to entering the clinical trial. ALK-positive NSCLC was identified using a number of local clinical trial assays. One hundred nineteen patients with ALK-positive advanced NSCLC were enrolled into Study 1001 at the time of data cutoff for the PFS and ORR analyses. The median duration of treatment was 32 weeks. There were 2 complete responses and 69 partial responses for an ORR of 61%. The median DR was 48 weeks. Fifty-five percent of objective tumor

responses were achieved during the first 8 weeks of treatment. Study 1001 OS data were updated based on 154 ALK-positive advanced NSCLC patients. The median OS at the time of data cutoff was 28.9 months (95% CI: 21.1, 40.1).

In Study 1005, patients with advanced NSCLC were required to have ALK-positive tumors prior to entering the clinical trial. For most patients, ALK-positive NSCLC was identified by FISH. Nine hundred thirty-four patients with ALK-positive advanced NSCLC were treated with crizotinib in Study 1005 at the time of data cutoff for the PFS and ORR analyses. The median duration of treatment for these patients was 23 weeks. Patients could continue treatment as assigned beyond the time of RECIST-defined disease progression at the discretion of the investigator if the benefit/risk assessment justified continuation of treatment. Seventy-seven of 106 patients (73%) continued XALKORI treatment for at least 3 weeks after objective disease progression.

Seven hundred sixty-five patients with ALK-positive advanced NSCLC from Study 1005 were both evaluable for response and identified by the same FISH assay used in randomized Phase 3 Study 1007. There were 8 complete responses and 357 partial responses for an ORR of 48%. The median DR was 47 weeks. Eighty-three percent of objective tumor responses were achieved within the first 12 weeks of treatment. Study 1005 OS data were updated based on 905 ALK-positive advanced NSCLC patients identified by the same FISH assay used in randomized Phase 3 Study 1007. The median OS at the time of data cutoff was 21.5 months (95% CI: 19.3, 23.6).

Efficacy data from Studies 1001 and 1005 are provided in Table 6.

Table 6. ALK-positive Advanced NSCLC Efficacy Results from Studies 1001 and 1005

Efficacy Parameter	**Study 1001**	**Study 1005**
	N = 119[a]	**N = 765[a]**
ORR[b] [% (95% CI)]	61 (52, 70)	48 (44, 51)
TTR [median (range)] weeks	7.7 (4, 40)	6.1 (3, 49)
DR[c] [median (95% CI)] weeks	48.1 (36, not reached)	47.3 (36, 54)
PFS[c] [median (95% CI)] months	10.0 (8.2, 14.7)	7.8 (6.9, 9.5)[d]
	N = 154[e]	**N = 905[e]**
Number of deaths, n (%)	83 (54%)	504 (56%)
OS[c] [median (95% CI)] months	28.9 (21.1, 40.1)	21.5 (19.3, 23.6)

Abbreviations: N/n=number of patients; CI = confidence interval: ORR = objective response rate; TTR = time to tumor response; DR=duration of response; PFS = progression-free survival; OS = overall survival.

a. Per data cutoff dates 15 September 2010 (Study 1001) and 15 February 2012 (Study 1005).
b. Three patients were not evaluable for response in Study 1001, and 42 patients were not evaluable for response in Study 1005.
c. Estimated using the Kaplan-Meier method.
d. PFS data from Study 1005 included 807 patients in the safety analysis population who were identified by the FISH assay (per data cutoff date 15 February 2012).
e. Per data cutoff date 30 November 2013.

ROS1-Positive Advanced NSCLC

The use of single-agent XALKORI in the treatment of ROS1-positive advanced NSCLC was investigated in multicenter, multinational, single-arm Study 1001. A total of 53 ROS1-positive advanced NSCLC patients were enrolled in the study at the time of data cutoff, including 46 patients with previously treated ROS1-positive advanced NSCLC and 7 patients who had no

prior systemic treatment. The primary efficacy endpoint was ORR according to RECIST. Secondary endpoints included TTR, DR, PFS, and OS. Patients received XALKORI 250 mg orally twice daily.

The demographic characteristics were 57% female; median age 55 years; baseline ECOG performance status of 0 or 1 (98%) or 2 (2%), 57% White and 40% Asian; 25% former-smokers, and 75% never smokers. The disease characteristics were 94% metastatic, 96% adenocarcinoma histology, and 13% with no prior systemic therapy for metastatic disease.

In Study 1001, patients were required to have ROS1-positive advanced NSCLC prior to entering the clinical trial. For most patients, ROS1-positive NSCLC was identified by FISH. The median duration of treatment was 22.4 months (95% CI: 15.0, 35.9). There were 6 complete responses and 32 partial responses for an ORR of 72% (95% CI: 58%, 83%). The median DR was 24.7 months (95% CI: 15.2, 45.3). Fifty percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median PFS at the time of data cutoff was 19.3 months (95% CI: 15.2, 39.1). The median OS at the time of data cutoff was 51.4 months (95% CI: 29.3, NR).

Efficacy data from ROS1-positive advanced NSCLC patients from Study 1001 are provided in Table 7.

Table 7. ROS1-positive Advanced NSCLC Efficacy Results from Study 1001

Efficacy Parameter	**Study 1001**
	N=53[a]
ORR [% (95% CI)]	72 (58, 83)
TTR [median (range)] weeks	8 (4, 104)
DR[b] [median (95% CI)] months	24.7 (15.2, 45.3)
PFS[b] [median (95% CI)] months	19.3 (15.2, 39.1)
OS[b] [median (95% CI)] months	51.4 (29.3, NR)

Abbreviations: N=number of patients; CI=confidence interval: ORR=objective response rate; NR=not reached; TTR=time to tumor response; DR=duration of response; OS=overall survival; PFS=progression-free survival. OS is based on a median follow up of approximately 63 months.

a. Per data cutoff date 30 June 2018.
b. Estimated using the Kaplan-Meier method.

ROS1-positive Advanced NSCLC - A8081063

Study A8081063 is an open-label, single-arm phase II study designed to evaluate the efficacy and safety of crizotinib in East Asian patients with ROS1-positive and ALK-negative advanced/metastatic NSCLC, in which patients received XALKORI 250 mg orally twice daily. ROS1 rearrangements were determined for study enrollment using the Amoy RT-PCR assay. ALK testing was completed locally using 1 of 3 protocol-allowed methods (FISH, IHC, or RT-PCR). The study population was restricted to those who were treatment-naïve or had received no more than 3 prior systemic treatment regimens for advanced-stage disease, who had an ECOG performance status of 0 or 1, and who would have been expected to receive treatment with crizotinib in the study for a reasonable period of time. For patients with brain metastases, the metastases must have been neurologically stable. The primary endpoint was ORR by IRR. Secondary measures of clinical efficacy included DOR, time to tumor response (TTR), disease control rate (DCR), PFS, and OS. Tumor assessments (CT or MRI scan) were performed every 8 weeks (bone scans every 12 weeks, if required); after 8 cycles, assessments were every 12 weeks.

All patients were Asian (100%). Patients had a median age of 52 years and most were female (58%). Most patients were <65 years of age (84%) and did not have a history of smoking (72%). Most patients had an ECOG performance status of 1 (73%) at study entry. Most patients had a histological classification of adenocarcinoma (98%) and metastatic disease (95%) at baseline.

Efficacy results are summarized in Table 8.

Table 8. A8081063 ROS1-positive Advanced NSCLC - Efficacy Results*

Efficacy Parameters	**IRR (N=127)**	**Investigator-Assessed (N=127)**
Objective Response Rate (95% CI)	69.3% (60.5, 77.2)	64.6% (55.6, 72.8)
Complete Response, n	14	1
Partial Response, n	74	81
Duration of Response		
Median, Months (95% CI)	NR (8.5, NR)	ND

IRR=independent radiology review; CI=confidence interval; ND=not done; NR=not reached.
*As assessed by RECIST version 1.1.

Elderly (see also Sections 4.2 and 5.2)

Of 171 ALK-positive NSCLC patients treated with XALKORI in randomized Phase 3 Study 1014, 22 (13%) were 65 years or older, and of 109 ALK-positive patients treated with XALKORI who crossed over from the chemotherapy arm, 26 (24%) were 65 years or older. Of 172 ALK-positive patients treated with XALKORI in randomized Phase 3 Study 1007, 27 (16%) were 65 years or older. Of 154 and 1,063 ALK-positive NSCLC patients in single-arm studies 1001 and 1005, 22 (14%) and 173 (16%) were 65 years or older, respectively. In ALK-positive NSCLC patients, the frequency of adverse reactions was generally similar for patients <65 years of age and patients ≥65 years of age with the exception of edema and constipation, which were reported with greater frequency in Study 1014 among patients treated with XALKORI ≥65 years of age. No overall differences in efficacy were observed in comparison with younger patients. Of the 53 ROS1-positive NSCLC patients in single-arm Study 1001, 15 (28%) were 65 years or older.

5.2 Pharmacokinetic properties

Absorption

Following oral single-dose administration in the fasted state, crizotinib is absorbed with median time to achieve peak concentration of 4 to 6 hours. Following crizotinib 250 mg twice daily, steady-state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8. The absolute bioavailability of crizotinib was determined to be 43% (range: 32% to 66%) following the administration of a single 250 mg oral dose.

A high-fat meal reduced crizotinib area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}) and maximum observed plasma concentration (C_{max}) by approximately 14% when a 250 mg single dose was given to healthy volunteers. XALKORI can be administered with or without food (see Section 4.2).

Distribution

The geometric mean volume of distribution (V_{ss}) of crizotinib was 1,772 L following intravenous administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma.

Binding of crizotinib to human plasma proteins *in vitro* is 91% and is independent of drug concentration. *In vitro* studies suggested that crizotinib is a substrate for P-glycoprotein (P-gp). The blood-to-plasma concentration ratio is approximately 1.

Metabolism

In vitro studies demonstrated that CYP3A4/5 were the major enzymes involved in the metabolic clearance of crizotinib. The primary metabolic pathways in humans were oxidation of the piperidine ring to crizotinib lactam and *O*-dealkylation, with subsequent Phase 2 conjugation of *O*-dealkylated metabolites.

In vitro studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP2B6 and CYP3A.

Elimination

Following single doses of crizotinib, the apparent plasma terminal half-life of crizotinib was 42 hours in patients.

Following the administration of a single 250 mg radiolabeled crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in feces and urine, respectively. Unchanged crizotinib represented approximately 53% and 2.3% of the administered dose in feces and urine, respectively.

The mean apparent clearance (CL/F) of crizotinib was lower at steady-state (60 L/h) after 250 mg twice daily than that after a single 250 mg oral dose (100 L/h), which was likely due to autoinhibition of CYP3A by crizotinib after multiple dosing.

Drug Interactions

Co-administration of XALKORI and CYP3A Substrates

Crizotinib has been identified as an inhibitor of CYP3A both *in vitro* and *in vivo*. Following 28 days of crizotinib dosing at 250 mg taken twice daily in cancer patients, the oral midazolam AUC_{inf} was 3.7-fold (90% CI: 2.63-5.07) those seen when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A (see Section 4.5).

Co-administration of XALKORI and CYP3A Inhibitors

Co-administration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib AUC_{inf} and C_{max} values that were approximately 3.2-fold and 1.4-fold, respectively, than those seen when crizotinib was administered alone. Coadministration of crizotinib (250 mg once daily) with itraconazole (200 mg once daily), a

strong CYP3A inhibitor, resulted in 57% and 33% increases in crizotinib steady-state area under the plasma concentration-time curve from 0 hour to time tau, the dosing interval (AUC_{tau}) and C_{max}, respectively, compared to when crizotinib was given alone (see Section 4.5).

Co-administration of XALKORI and CYP3A Inducers

Co-administration of crizotinib (250 mg twice daily) with rifampin (600 mg once daily), a strong CYP3A inducer, resulted in 84% and 79% decreases in crizotinib steady-state AUC_{tau} and C_{max}, respectively, compared to when crizotinib was given alone (see Section 4.5).

Co-administration of XALKORI with Agents that Increase Gastric pH

The aqueous solubility of crizotinib is pH dependent, with low (acidic) pH resulting in higher solubility. Administration of a single 250 mg crizotinib dose following treatment with esomeprazole 40 mg once daily for 5 days resulted in an approximately 10% decrease in crizotinib total exposure (AUC_{inf}) and no change in peak exposure (C_{max}); the extent of the change in total exposure was not clinically meaningful. Therefore, starting dose adjustment is not required when crizotinib is co-administered with agents that increase gastric pH (such as proton-pump inhibitors, H_2 blockers, or antacids).

Co-administration with Other CYP Substrates

In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of drugs that are substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

Crizotinib is an inhibitor of CYP2B6 *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are predominantly metabolized by CYP2B6.

In vitro studies in human hepatocytes indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated induction of the metabolism of drugs that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A.

Co-administration with UGT Substrates

In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of drugs that are substrates for uridine diphosphate glucuronosyltransferase (UGT) 1A1, UGT1A4, UGT1A6, UGT1A9 or UGT2B7.

Co-administration with Drugs that are Substrates of Transporters

Crizotinib is an inhibitor of P-glycoprotein (P-gp) *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are substrates of P-gp.

Crizotinib is an inhibitor of OCT1 and OCT2 *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are substrates of OCT1 or OCT2.

In vitro, crizotinib did not inhibit the human hepatic uptake transport proteins organic anion transporting polypeptide (OATP)1B1 or OATP1B3, or the renal uptake transport proteins organic anion transporter (OAT)1 or OAT3 at clinically relevant concentrations. Therefore, clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the hepatic or renal uptake of drugs that are substrates for these transporters.

Effect on Other Transport Proteins

In vitro, crizotinib is not an inhibitor of the bile salt export pump transporter (BSEP) at clinically relevant concentrations.

Pharmacokinetics in Special Patient Groups

Hepatic Impairment: Crizotinib is extensively metabolized in the liver. Patients with mild (either AST >ULN and total bilirubin ≤ULN or any AST and total bilirubin >ULN but ≤1.5×ULN), moderate (any AST and total bilirubin >1.5×ULN and ≤3×ULN), or severe (any AST and total bilirubin >3×ULN) hepatic impairment or normal (AST and total bilirubin ≤ULN) hepatic function, who were matched controls for mild or moderate hepatic impairment, were enrolled in an open-label, non-randomized clinical study (Study 1012), based on NCI classification.

Following crizotinib 250 mg twice daily dosing, patients with mild hepatic impairment (N=10) showed similar systemic crizotinib exposure at steady state compared to patients with normal hepatic function (N=8), with geometric mean ratios for area under the plasma concentration-time curve as daily exposure at steady state (AUC_{daily}) and C_{max} of 91.1% and 91.2%, respectively. No starting dose adjustment is recommended for patients with mild hepatic impairment.

Following crizotinib 200 mg twice daily dosing, patients with moderate hepatic impairment (N=8) showed higher systemic crizotinib exposure compared to patients with normal hepatic function (N=9) at the same dose level, with geometric mean ratios for AUC_{daily} and C_{max} of 150% and 144%, respectively. However, the systemic crizotinib exposure in patients with moderate hepatic impairment at the dose of 200 mg twice daily was comparable to that observed from patients with normal hepatic function at a dose of 250 mg twice daily, with geometric mean ratios for AUC_{daily} and C_{max} of 114% and 109%, respectively.

The systemic crizotinib exposure parameters AUC_{daily} and C_{max} in patients with severe hepatic impairment (N=6) receiving a crizotinib dose of 250 mg once daily were approximately 64.7% and 72.6%, respectively, of those from patients with normal hepatic function receiving a dose of 250 mg twice daily.

An adjustment of the dose of crizotinib is recommended when administering crizotinib to patients with moderate or severe hepatic impairment (see Section 4.4).

Renal Impairment: Patients with mild (CL_{cr} 60-89 mL/min) and moderate (CL_{cr} 30-59 mL/min) renal impairment were enrolled in single-arm Studies 1001 and 1005. The effect of renal function, as measured by baseline CL_{cr} on observed crizotinib steady-state trough concentrations ($C_{trough,ss}$) was evaluated. In Study 1001, the adjusted geometric mean of plasma $C_{trough,ss}$ in mild (N = 35) and moderate (N = 8) renal impairment patients were 5.1% and 11% higher, respectively, than those in patients with normal renal function. In Study 1005, the

adjusted geometric mean $C_{trough,ss}$ of crizotinib in mild (N = 191) and moderate (N = 65) renal impairment groups were 9.1% and 15% higher, respectively, than those in patients with normal renal function. In addition, the population pharmacokinetic analysis from Studies 1001, 1005 and 1007 indicated CL_{cr} did not have a clinically meaningful effect on the pharmacokinetics of crizotinib.

Due to the small size of the increases in crizotinib exposure (5%-15%), no starting dose adjustment is recommended for patients with mild or moderate renal impairment. After a single 250-mg dose in subjects with severe renal impairment (CL_{cr} <30 mL/min) not requiring peritoneal dialysis or hemodialysis, crizotinib AUC_{inf} and C_{max} increased by 79% and 34%, respectively, compared to those with normal renal function. An adjustment of the dose of crizotinib is recommended when administering crizotinib to patients with severe renal impairment not requiring peritoneal dialysis or hemodialysis (see Sections 4.2 and 4.4).

Ethnicity: Based on the population pharmacokinetic analysis from Studies 1001, 1005 and 1007, the predicted area under the plasma concentration-time curve at steady-state (AUC_{ss}) (95% CI) was 23% to 37% higher in Asian patients (N = 523) than in non-Asian patients (N = 691).

In studies in patients with ALK-positive advanced NSCLC (N=1,669), the following adverse reactions were reported with an absolute difference of ≥10% in Asian patients (N=753) than in non-Asian patients (N=916): elevated transaminases, decreased appetite, neutropenia, and leukopenia. No adverse drug reactions were reported with an absolute difference of ≥15%.

Age: Based on the population pharmacokinetic analysis from Studies 1001, 1005 and 1007, age has no effect on crizotinib pharmacokinetics (see Sections 4.2 and 5.1).

Body Weight and Gender: Based on the population pharmacokinetic analysis from Studies 1001, 1005 and 1007, there was no clinically meaningful effect of body weight or gender on crizotinib pharmacokinetics.

Cardiac Electrophysiology

The QT interval prolongation potential of crizotinib was assessed in patients with either ALK-positive or ROS1-positive NSCLC who received XALKORI 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady-state to evaluate the effect of crizotinib on QT intervals. Thirty-four of 1,619 patients (2.1%) with at least 1 post-baseline ECG assessment were found to have QTcF (corrected QT by the Fridericia method) ≥500 msec and 79 of 1,585 patients (5.0%) with a baseline and at least 1 post-baseline ECG assessment had an increase from baseline QTcF ≥60 msec by automated machine-read evaluation of ECG (see Section 4.4).

An ECG substudy using blinded manual ECG measurements was conducted in 52 ALK-positive NSCLC patients who received crizotinib 250 mg twice daily. A central tendency analysis indicated that a QTc effect ≥20 msec can be excluded. A pharmacokinetic/pharmacodynamic analysis suggested a relationship between crizotinib plasma concentration and QTc. In addition, a decrease in heart rate was found to be associated with increasing crizotinib plasma concentration (see Section 4.4).

5.3 Preclinical safety data

Genotoxicity

Crizotinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay. Crizotinib was aneugenic in an *in vitro* micronucleus assay in Chinese Hamster Ovary cells and in an *in vitro* human lymphocyte chromosome aberration assay. Small increases of structural chromosomal aberrations at cytotoxic concentrations were seen in human lymphocytes. In the rat bone marrow *in vivo*, increases in micronuclei were only seen at doses significantly exceeding the expected human exposure. Increases in micronuclei were observed in rats at 250 mg/kg/day (approximately 4 times the AUC at the recommended human dose).

Carcinogenicity

Carcinogenicity studies with crizotinib have not been performed.

Fertility

No specific studies with crizotinib have been conducted in animals to evaluate the effect on fertility; however, crizotinib is considered to have the potential to impair reproductive function and fertility in humans based on findings in repeat-dose toxicity studies in the rat. Findings observed in the male reproductive tract included testicular pachytene spermatocyte degeneration in rats given $\geqslant$50 mg/kg/day for 28 days (approximately equivalent to human clinical exposure based on AUC). Findings observed in the female reproductive tract included single-cell necrosis of ovarian follicles of a rat given 500 mg/kg/day for 3 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

XALKORI capsules are supplied as printed hard-shell capsules containing 250 mg or 200 mg of crizotinib together with colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate, and hard gelatin capsule shells as inactive ingredients.

The pink opaque capsule shell components contain gelatin, titanium dioxide, and red iron oxide. The white opaque capsule shell components contain gelatin and titanium dioxide. The printing ink contains shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

6.2 Special precautions for storage

Store below 30°C.

6.3 Nature and contents of container

250 mg capsules
Hard gelatin capsule with pink opaque cap and body, printed with black ink “Pfizer” on the cap, “CRZ 250” on the body; available in:
Bottles of 60 capsules, Blisters of 10’s and 60’s.

200 mg capsules
Hard gelatin capsule with pink opaque cap and white opaque body, printed with black ink "Pfizer" on the cap, "CRZ 200" on the body; available in:
Bottles of 60 capsules, Blisters of 10's and 60's.

6.4 Patient counseling information

Inform patients of the symptoms of hepatotoxicity, and that they should be reported immediately (see Section 4.4).

Advise patients to immediately report any new or worsening pulmonary symptoms (see Section 4.4).

Inform patients that symptoms of bradycardia including dizziness, lightheadedness, and syncope can occur while taking XALKORI. Advise patients to report these symptoms and to inform their physician about the use of any heart or blood pressure medications (see Section 4.4).

Inform patients that nausea, diarrhea, vomiting, and constipation are the most commonly reported gastrointestinal adverse events occurring in patients who received XALKORI. Nausea and vomiting began most commonly during the first few days of treatment (see Section 4.8).

Inform patients that visual changes, such as perceived flashes of light, blurry vision, light sensitivity, and floaters are commonly reported adverse events and may occur while driving or operating machinery. The onset of visual disorders most commonly occurs during the first week of treatment (see Section 4.8).

Inform patients to avoid grapefruit or grapefruit juice while taking XALKORI. Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products (see Section 4.5).

Advise patients to take XALKORI with or without food and swallow XALKORI capsules whole.

If a patient misses a dose, advise the patient to take it as soon as remembered unless it is less than 6 hours until the next dose, in which case, advise the patient not to take the missed dose. If a patient vomits after taking a dose of XALKORI, advise the patient not to take an extra dose, but to take the next dose at the regular time.

Inform patients of childbearing potential to use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. Advise patients to inform their doctor if they or their partners are pregnant or think they may be pregnant. Also advise patients not to breastfeed while taking XALKORI (see Section 4.6).

7. PRODUCT OWNER

Pfizer Inc
New York,
United States

Package leaflet: Information for the user

XALKORI 200 mg hard capsules
XALKORI 250 mg hard capsules
crizotinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What XALKORI is and what it is used for

XALKORI is an anticancer medicine containing the active substance crizotinib used to treat adults with a type of lung cancer called non-small cell lung cancer, that presents with a specific rearrangement or defect in either a gene called anaplastic lymphoma kinase (ALK) or a gene called ROS1.

XALKORI can be prescribed to you for treatment if your disease is at a locally advanced or metastatic stage of lung cancer.

XALKORI may slow or stop the growth of lung cancer. It may help shrink tumors.

If you have any questions about how XALKORI works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take XALKORI

Do not take XALKORI
- If you are allergic to crizotinib or any of the other ingredients of this medicine (listed in Section 6, “What XALKORI contains”).

Warnings and precautions
Talk to your doctor before taking XALKORI:

- If you have moderate or severe liver disease.
- If you have ever had any other lung problems. Some lung problems may get worse during treatment with XALKORI, as XALKORI may cause inflammation of the lungs

during treatment. Symptoms may be similar to those from lung cancer. Tell your doctor right away if you have any new or worsening symptoms including difficulty in breathing, shortness of breath, or cough with or without mucous, or fever.
- If you have been told that you have an abnormality of your heart tracing after an electrocardiogram (ECG) known as prolonged QT interval.
- If you have reduced heart rate.
- If you have vision disorders (seeing flashes of light, blurred vision, and double vision).
- If you have severe kidney disease.
- If you have existing heart conditions such as heart failure.
- If you have a history of low white blood cell counts.
- If you are currently treated with any of the medicines listed in section "Other medicines and XALKORI".

Talk to your doctor right away after having taken XALKORI:
- If you are experiencing fever, chills, shortness of breath, fast heartbeat, swelling, chest pain or partial or complete loss of vision (in one or both eyes).

Children and adolescents
Treatment of children and adolescents with this medicine is not recommended. The indication does not cover children and adolescents.

Other medicines and XALKORI
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including herbal medicines and medicine obtained over the counter.

In particular, the following medicines may increase the risk of side effects with XALKORI:
- Clarithromycin, telithromycin, troleandomycin, antibiotics used to treat bacterial infections.
- Ketoconazole, itraconazole, voriconazole, used to treat fungal infections.
- Atazanavir, ritonavir, nelfinavir, saquinavir, indinavir, used to treat HIV infections/AIDS.
- Nefazodone, used to treat depression.

The following medicines or herbal products may reduce the effectiveness of XALKORI:
- Phenytoin, carbamazepine or phenobarbital, anti-epileptics used to treat seizures or fits.
- Rifabutin, rifampin, used to treat tuberculosis.
- St. John's wort (*Hypericum perforatum*), a herbal product.

XALKORI may increase side effects associated with the following medicines:
- Alfentanil and other short acting opiates such as fentanyl (painkillers used for surgical procedures).
- Quinidine, digoxin, verapamil, diltiazem used to treat heart problems.
- Medicines for high blood pressure called beta-blockers such as atenolol, propranolol, labetalol.
- Pimozide, used to treat mental illness.
- Metformin, used to treat diabetes.
- Procainamide, used to treat cardiac arrhythmia.
- Cyclosporine, sirolimus and tacrolimus used in transplant patients.
- Ergot alkaloids (e.g., ergotamine, dihydroergotamine), used to treat migraine.
- Dabigatran, anticoagulant used to slow down clotting of the blood.
- Colchicine, used to treat gout.

- Pravastatin, used to reduce cholesterol levels.
- Clonidine used to treat hypertension.
- Bupropion, used to treat depression and smoking cessation.
- Efavirenz, used to treat HIV infection.

These medicines *should be avoided* during your treatment with XALKORI.

XALKORI with food and drink
You can take XALKORI with or without food; however, you should avoid drinking grapefruit juice or eating grapefruit while on treatment with XALKORI as they may change the amount of XALKORI in your body.

Pregnancy and breastfeeding
Talk to your doctor or pharmacist before taking this medicine if you are pregnant, may become pregnant or are breastfeeding.

It is recommended that women avoid becoming pregnant and that men do not father children during treatment with XALKORI because this medicine could harm the baby. If there is any possibility that the person taking this medicine may become pregnant or father a child, they must use adequate contraception during treatment, and for at least 90 days after completing therapy.

Do not breastfeed during treatment with XALKORI. XALKORI could harm a breastfed baby.

If you or your partner are pregnant or breastfeeding, think you or your partner may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
You should take special care when driving and using machines as patients taking XALKORI may experience visual disturbances, dizziness, and tiredness.

XALKORI contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 200 mg or 250 mg capsule, that is to say essentially 'sodium-free'.

3. How to take XALKORI

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- The recommended dose is one capsule of 250 mg taken orally twice daily (total amount 500 mg).
- Take the capsule once in the morning and once in the evening.
- Take the capsules at about the same time each day.
- You can take the capsules with or without food always avoiding grapefruit.
- Swallow the capsules whole and do not crush, dissolve or open the capsules.

If necessary, your doctor may decide to reduce the dose to 200 mg to be taken orally twice daily (total amount 400 mg) and if further dose reduction is necessary, to reduce it to 250 mg to be taken orally once daily. Your doctor may decide to permanently discontinue your treatment if you are unable to tolerate XALKORI 250 mg taken orally once daily.

If you take more XALKORI than you should
If you accidentally take too many capsules, tell your doctor or pharmacist right away. You may require medical attention.

If you forget to take XALKORI
What to do if you forget to take a capsule depends on how long it is until your next dose.

- If your next dose is in **6 hours or more**, take the missed capsule as soon as you remember. Then take the next capsule at the usual time.
- If your next dose is in **less than 6 hours**, skip the missed capsule. Then take the next capsule at the usual time.

Tell your doctor about the missed dose at your next visit.

Do not take a double dose (two capsules at the same time) to make up for a forgotten capsule.

If you vomit after taking a dose of XALKORI, do not take an extra dose; just take your next dose at your regular time.

If you stop taking XALKORI
It is important to take XALKORI every day, as long as your doctor prescribes it to you. If you are not able to take the medicine as your doctor prescribed, or you feel you do not need it anymore, contact your doctor right away.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet.

Some side effects could be serious. You should immediately contact your doctor if you experience any of the following serious side effects (see also section 2 “What you need to know before you take XALKORI”):

- **Liver failure**
  Tell your doctor right away if you feel more tired than usual, your skin and whites of your eyes turn yellow, your urine turns dark or brown (tea color), you have nausea, vomiting, or decreased appetite, you have pain on the right side of your stomach, you have itching, or if you bruise more easily than usual. Your doctor may do blood tests to check your liver function, and if the results are abnormal, your doctor may decide to reduce the dose of XALKORI or stop your treatment.

- **Lung inflammation**
  Tell your doctor right away if you experience difficulty in breathing, especially if associated with cough or fever.

- **Reduction in the number of white blood cells (including neutrophils)**
  Tell your doctor right away if you experience fever or signs of an infection such as chills, sweats, sore throat or cough. Your doctor may do blood tests and if the results are abnormal, your doctor may decide to reduce the dose of XALKORI.

- **Light-headedness, fainting, or chest discomfort**
  Tell your doctor right away if you experience these symptoms which could be signs of changes in the electrical activity (seen on electrocardiogram) or abnormal rhythm of the heart. Your doctor may perform electrocardiograms to check there are no problems with your heart during treatment with XALKORI.

- **Partial or complete loss of vision in one or both eyes**
  Tell your doctor right away if you experience any loss of vision or any change in vision such as difficulty seeing out of one or both eyes. Your doctor may stop XALKORI treatment and refer you to an ophthalmologist.

Other side effects of XALKORI may include:

Very common side effects (may affect more than 1 in 10 people)
- Visual effects (seeing flashes of light, blurred vision, or double vision, often beginning soon after starting treatment with XALKORI).
- Stomach upset, including vomiting, diarrhea, nausea.
- Edema (excess fluid in body tissue, causing swelling of the hands and feet).
- Constipation.
- Abnormalities in liver blood tests.
- Decreased appetite.
- Tiredness.
- Dizziness.
- Neuropathy (feeling of numbness or pins and needles in the joints or extremities).
- Alteration in sense of taste.
- Pain in the abdomen.
- Reduction in the number of red blood cells (anemia).
- Skin rash.
- Reduced heart rate.
- Reduction in the number of white blood cells (leukopenia and/or neutropenia).

*Common side effect*s (may affect up to 1 in 10 people)
- Indigestion.
- Increased blood levels of creatinine (may indicate that kidneys are not functioning properly).
- Increased levels of the enzyme alkaline phosphatase in the blood (an indicator of organ malfunction or injury, particularly liver, pancreas, bone, thyroid gland, or gall bladder).
- Hypophosphatemia (low blood phosphate levels that can cause confusion or muscle weakness).
- Closed pouches of fluid within the kidneys (kidney cysts).
- Fainting.
- Inflammation of the esophagus (swallowing tube).
- Decreased levels of testosterone, a male sex hormone.
- Heart failure.
- Abnormality in the beating of the heart.

- Inflammation of the lung.

*Uncommon side effect*s (may affect up to 1 in 100 people)
- Hole (perforation) in stomach or intestine.
- Failure of the liver.

Side effects identified post-marketing (frequency not known)
- Increased blood levels of tests that check for muscle damage (high creatine phosphokinase levels).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store XALKORI

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the bottle or blister foil and carton after "EXP".
- Store below 30°C.
- Do not use any pack that is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What XALKORI contains
- The active substance in XALKORI is crizotinib.
  XALKORI 200 mg: each capsule contains 200 mg crizotinib
  XALKORI 250 mg: each capsule contains 250 mg crizotinib

- The other ingredients are (see also section 2 "XALKORI contains sodium"):
  Capsule content: colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate.
  Capsule shell (pink): gelatin, titanium dioxide, and red iron oxide.
  Capsule shell (white): gelatin, and titanium dioxide.
  Printing ink: shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

What XALKORI looks like and contents of the pack
XALKORI 200 mg is supplied as hard gelatin capsules with pink cap and white body, printed with black ink "Pfizer" on the cap, "CRZ 200" on the body.

XALKORI 250 mg is supplied as hard gelatin capsules with pink cap and body, printed with black ink "Pfizer" on the cap, "CRZ 250" on the body.

It is available in blister packs of 10 and 60 hard capsules and in plastic bottles of 60 hard capsules.

Not all pack sizes may be marketed.

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