PFIZER
XALKORI®

1 NAME OF THE MEDICINAL PRODUCT

XALKORI 200 MG HARD CAPSULES

XALKORI 250 MG HARD CAPSULES

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains either 200 mg or 250 mg of Crizotinib.

Crizotinib 200 mg hard capsule is a size 1, white opaque/pink opaque hard gelatin capsule, containing a white to pale yellow powder with CRZ 200 printed on the body in black ink and Pfizer (logo) printed on the cap in black ink.

Crizotinib 250 mg hard capsule is a size 0, pink opaque/pink opaque hard gelatin capsule, containing a white to pale yellow powder with CRZ 250 printed on the body in black ink and Pfizer (logo) printed on the cap in black ink.

3 PHARMACEUTICAL FORM

Hard gelatin capsules.

4 INDICATIONS AND USAGE

4.1 ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer

Crizotinib is indicated for the treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive.

5 DOSAGE AND ADMINISTRATION

5.1 Patient Selection

Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK or ROS1 positivity in tumor specimens *[*see *Clinical Studies (13)]*.

5.2 ALK and ROS1 Testing

An accurate and validated assay for either ALK or ROS1 is necessary for the selection of patients for treatment with XALKORI *[*see *Clinical Studies (13)].*

Either ALK-positive or ROS1-positive NSCLC status should be established prior to initiation of Crizotinib therapy.

Assessment should be performed by laboratories with demonstrated proficiency in the specific technology being utilized *[*see *Warnings and Precautions (7)]*.

5.3 Recommended Dosing for ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer

The recommended dose of XALKORI for patients with NSCLC is 250 mg orally, twice daily, with or without food, until disease progression or no longer tolerated by the patient.

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.

5.4 Dosage Modifications for Adverse Reactions

Recommended Dosage Reductions

ALK- or ROS1-positive metastatic NSCLC
The recommended dose reductions for adverse reactions in patients with metastatic NSCLC are:

- 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 orally once daily

Recommended Dosage Modifications for Patients with NSCLC

Recommended dosage modifications for hematologic and non-hematologic adverse reactions for patients with NSCLC are provided in Tables 1 and 2.

Table 1. Patients with NSCLC: XALKORI Dosage Modification – Hematologic Toxicities[a]

Severity of Adverse Reaction[b]	**XALKORI Dosage Modification**
Grade 3	Withhold until recovery to Grade 2 or less, then resume at the same dosage.
Grade 4	Withhold until recovery to Grade 2 or less, then resume at next lower dosage.

[a] Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
[b] Grade based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

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.

Table 2. Patients with NSCLC: XALKORI Dosage Modification – Non-Hematologic Toxicities

Severity of Adverse Reaction[a]	**XALKORI Dosage Modification**
Hepatotoxicity *[*see *Warnings and Precautions (7.1)]*	
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 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 next lower dosage.
ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 1.5 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue.
Interstitial Lung Disease (Pneumonitis) *[*see *Warnings and Precautions (7.2)]*	
Any grade drug-related interstitial lung disease/pneumonitis	Permanently discontinue.
QT Interval Prolongation *[*see *Warnings and Precautions (7.3)]*	

Severity of Adverse Reaction[a]	XALKORI Dosage Modification
QT corrected for heart rate (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 next lower dosage.
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 *[*see *Warnings and Precautions (7.5)]*	
Bradycardia[b] (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 antihypertensive 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 medication 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.
Severe Visual Loss *[*see *Warnings and Precautions (7.6)]*	
Visual Loss (Grade 4 Ocular Disorder)	Discontinue during evaluation of severe Visual loss.

[a] Grade based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
[b] Heart rate less than 60 beats per minute (bpm).
[c] Permanently discontinue for recurrence.

5.5 Dosage Modifications for Moderate and Severe Hepatic Impairment

ALK- or ROS1-positive metastatic NSCLC
The recommended dose of XALKORI in patients with pre-existing moderate hepatic impairment [any aspartate aminotransferase (AST) and total bilirubin greater than 1.5 times the upper limit of normal (ULN) and less than or equal to 3 times ULN] is 200 mg orally twice daily.

The recommended dose of XALKORI in patients with pre-existing severe hepatic impairment (any AST and total bilirubin greater than 3 times ULN) is 250 mg orally once daily *[*see *Use in Specific Populations (10.6), Clinical Pharmacology (11.3)]*.

5.6 Dosage Modification for Severe Renal Impairment

ALK- or ROS1-positive metastatic NSCLC

The recommended dosage of XALKORI in patients with severe renal impairment [creatinine clearance (CL_{cr}) less than 30 mL/min, calculated using the modified Cockcroft-Gault equation] not requiring dialysis is 250 mg orally once daily *[*see *Use in Specific Populations (10.7), Clinical Pharmacology (11.3)]*.

5.7 Dosage Modification for Concomitant Use of Strong CYP3A Inhibitors

ALK- or ROS1-positive metastatic NSCLC
Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the dose of XALKORI to 250 mg orally once daily *[*see *Drug Interactions (9.1)]*. After discontinuation of a strong CYP3A inhibitor, resume the XALKORI dose used prior to initiating the strong CYP3A inhibitor.

6 CONTRAINDICATIONS

Hypersensitivity to Crizotinib or to any of the excipients listed in section 14.

7 WARNINGS AND PRECAUTIONS

7.1 Hepatotoxicity

Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of the 1719 patients treated with XALKORI for NSCLC across clinical trials *[*see *Adverse Reactions (8.1)]*. Concurrent elevations in ALT or AST ≥3 times the ULN and total bilirubin ≥2 times the ULN, with normal alkaline phosphatase, occurred in <1% of patients treated with XALKORI. Increased ALT or AST >5 times the ULN occurred in 11% and 6% of patients, respectively. One percent (1.0%) of patients required permanent discontinuation due to elevated transaminases. Increased transaminases generally occurred within the first 2 months of treatment.

Monitor liver function tests, including ALT, AST, and total bilirubin, every 2 weeks during the first 2 months of treatment, then once a month, and as clinically indicated, with more frequent repeat testing for increased liver transaminases, alkaline phosphatase, or total bilirubin in patients who develop increased transaminases. Withhold, reduce dose, or permanently discontinue XALKORI for hepatotoxicity as recommended *[*see *Dosage and Administration (5.4)]*.

7.2 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with XALKORI. Across clinical trials in patients with NSCLC (n=1719), 2.9% of XALKORI-treated patients had ILD of any grade, 1% had Grade 3 or 4 ILD, and 0.5% had fatal ILD *[*see *Adverse Reactions (8.1)]*. Interstitial lung disease generally occurred within 3 months after the initiation of XALKORI.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue XALKORI in patients diagnosed with drug-related ILD/pneumonitis *[*see *Dosage and Administration (5.4)]*.

7.3 QT Interval Prolongation

QTc prolongation can occur in patients treated with XALKORI. Across clinical trials in patients with NSCLC, 2.1% of 1616 patients had QTcF (corrected QT for heart rate by the Fridericia method) greater than or equal to 500 ms and 5% of 1582 patients had an increase from baseline QTcF greater than or equal to 60 ms by automated machine-read evaluation of ECGs.

Avoid use of XALKORI in patients with congenital long QT syndrome. Monitor ECGs and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval. Withhold, reduce dose, or permanently discontinue XALKORI for QT/QTc interval prolongation as recommended *[*see *Dosage and Administration (5.4), Clinical Pharmacology (11.2)]*.

7.4 Cardiac Failure

In clinical studies with crizotinib and during post-marketing surveillance in adult patients, severe, life-threatening, or fatal adverse reactions of cardiac failure were reported.

Patients with or without pre-existing cardiac disorders, receiving crizotinib, should be monitored for signs and symptoms of heart failure (dyspnoea, oedema, rapid weight gain from fluid retention). Dosing interruption, dose reduction, or discontinuation should be considered as appropriate if such symptoms are observed.

7.5 Bradycardia

Symptomatic bradycardia can occur in patients receiving XALKORI. Across clinical trials in patients with NSCLC, bradycardia occurred in 13% of 1719 patients treated with XALKORI. Grade 3 syncope occurred in 2.4% of XALKORI-treated patients and in 0.6% of the chemotherapy-treated patients *[*see *Adverse Reactions (8.1)]*.

Avoid using XALKORI in combination with other medications known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. If bradycardia occurs, re-evaluate for the use of concomitant medications known to cause bradycardia. Withhold, reduce dose, or permanently discontinue XALKORI for bradycardia as recommended *[*see *Dosage and Administration (5.4)]*.

7.6 Severe Visual Loss

Across all clinical trials in patients with NSCLC, the incidence of Grade 4 visual field defect with visual loss was 0.2% of 1719 patients *[*see *Adverse Reactions (8.1)]*. Optic atrophy and optic nerve disorder have been reported as potential causes of visual loss.

Discontinue XALKORI in any patient with new onset of severe visual loss (best corrected vision less than 20/200 in one or both eyes). Perform an 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 visual loss and for other visual symptoms as clinically warranted *[see Dosage and Administration (5.4), Adverse Reactions (8.1)]*.

There is insufficient information to characterize the risks of resumption of XALKORI in patients who develop visual symptoms or visual loss. A decision to resume XALKORI should consider the potential benefits versus risks to the patient.

7.7 Embryo-Fetal Toxicity

Based on its mechanism of action, XALKORI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of Crizotinib in pregnant rats during organogenesis at exposures similar to those observed with the maximum recommended human dose

resulted in embryotoxicity and fetotoxicity. Advise pregnant women of the potential risk to a fetus *[*see *Use in Specific Populations (10.1), Nonclinical Toxicology (12.1)]*.

8 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hepatotoxicity *[*see *Warnings and Precautions (7.1)]*
- Interstitial Lung Disease/Pneumonitis *[*see *Warnings and Precautions (7.2)]*
- QT Interval Prolongation *[*see *Warnings and Precautions (7.3)]*
- Cardiac Failure *[*see *Warnings and Precautions (7.4)]*
- Bradycardia *[*see *Warnings and Precautions (7.5)]*
- Severe Visual Loss *[*see *Warnings and Precautions (7.6)]*

8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in the Warnings and Precautions reflect exposure to XALKORI in 1719 patients with NSCLC who received XALKORI 250 mg twice daily enrolled on Studies 1 (including an additional 109 patients who crossed over from the control arm), 2, 3, a single arm trial (n=1063) of ALK-positive NSCLC, and an additional ALK-positive NSCLC expansion cohort of a dose finding study (n=154).

ALK- or ROS1-Positive Metastatic NSCLC

The data described below is based primarily on 343 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg orally twice daily from 2 open-label, randomized, active-controlled trials (Studies 1 and 2). The safety of XALKORI was also evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study (Study 3).

The most common adverse reactions (≥25%) of XALKORI in patients with NSCLC are vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy.

Previously Untreated ALK-Positive Metastatic NSCLC – Study 1 (PROFILE 1014)

The data in Table 3 are derived from 340 patients with ALK-positive metastatic NSCLC who had not received previous systemic treatment for advanced disease who received treatment in a randomized, multicenter, open-label, active-controlled trial (Study 1). Patients in the XALKORI arm (n=171) received XALKORI 250 mg orally twice daily until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. A total of 169 patients in the chemotherapy arm received pemetrexed 500 mg/m^2 with cisplatin 75 mg/m^2 (n=91) or carboplatin at a dose calculated to produce an AUC of 5 or 6 mg × min/mL (n=78). Chemotherapy was given by intravenous infusion every 3 weeks for up to 6 cycles, in the absence of dose-limiting chemotherapy-related toxicities. After 6 cycles, patients remained on study with no additional anticancer treatment, and tumor assessments continued until documented disease progression.

The median duration of study treatment was 10.9 months for patients in the XALKORI arm and 4.1 months for patients in the chemotherapy arm. Median duration of treatment was 5.2 months for patients who

received XALKORI after cross over from chemotherapy. Across the 340 patients who were treated in Study 1, the median age was 53 years; 16% of patients were older than 65 years. A total of 62% of patients were female and 46% were Asian.

Serious adverse events were reported in 34% of patients treated with XALKORI. The most frequent serious adverse events reported in patients treated with XALKORI were dyspnea (4.1%) and pulmonary embolism (2.9%). Fatal adverse events in XALKORI-treated patients occurred in 2.3% patients, consisting of septic shock, acute respiratory failure, and diabetic ketoacidosis.

Dose reductions due to adverse reactions were required in 6% of XALKORI-treated patients. The most frequent adverse reactions that led to dose reduction in these patients were nausea (1.8%) and elevated transaminases (1.8%).

Permanent discontinuation of XALKORI treatment for adverse reactions was 8%. The most frequent adverse reactions that led to permanent discontinuation in XALKORI-treated patients were elevated transaminases (1.2%), hepatotoxicity (1.2%), and ILD (1.2%).

Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities in XALKORI-treated patients.

Table 3. Adverse Reactions Reported at a Higher Incidence (≥5% Higher for All Grades or ≥2% Higher for Grades 3-4) with XALKORI than Chemotherapy in Study 1[†]

Adverse Reaction	XALKORI (N=171)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=169)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Cardiac				
Bradycardia[a]	14	1	1	0
Electrocardiogram QT prolonged	6	2	2	0
Eye				
Vision disorder[b]	71	1	10	0
Gastrointestinal				
Diarrhea	61	2	13	1
Vomiting	46	2	36	3
Constipation	43	2	30	0
Abdominal pain[c]	26	0	12	0
Dyspepsia	14	0	2	0
Dysphagia	10	1	2	1
Esophagitis[d]	6	2	1	0
General				
Edema[e]	49	1	12	1
Pyrexia	19	0	11	1
Infections				
Upper respiratory infection[f]	32	0	12	1
Investigations				
Increased weight	8	1	2	0
Musculoskeletal and Connective Tissue				
Pain in extremity	16	0	7	0
Muscle spasm	8	0	2	1
Nervous System				

Adverse Reaction	XALKORI (N=171)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=169)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Dysgeusia	26	0	5	0
Headache	22	1	15	0
Dizziness[g]	18	0	10	1

[†]Adverse reactions were graded using NCI CTCAE version 4.0.
Includes cases reported within the clustered terms:
[a] Bradycardia (Bradycardia, Sinus bradycardia).
[b] Vision Disorder (Diplopia, Photophobia, Photopsia, Reduced visual acuity, Blurred vision, Vitreous floaters, Visual impairment).
[c] Abdominal pain (Abdominal discomfort, Abdominal pain, Lower abdominal pain, Upper abdominal pain, Abdominal tenderness).
[d] Esophagitis (Esophagitis, Esophageal ulcer).
[e] Edema (Edema, Peripheral edema, Face edema, Generalized edema, Local swelling, Periorbital edema).
[f] Upper respiratory infection (Nasopharyngitis, Pharyngitis, Rhinitis, Upper respiratory tract infection).
[g] Dizziness (Balance disorder, Dizziness, Postural dizziness, Presyncope).

Additional adverse reactions occurring at an overall incidence between 1% and 60% in patients treated with XALKORI included nausea (56%), decreased appetite (30%), fatigue (29%), neuropathy (21%; gait disturbance, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, polyneuropathy, sensory disturbance), rash (11%), renal cyst (5%), ILD (1%; ILD, pneumonitis), syncope (1%), and decreased blood testosterone (1%; hypogonadism).

Clinically relevant adverse reactions in <1% of patients who received XALKORI included photosensitivity (0.3%).

Table 4. Laboratory Abnormalities with Grades 3 - 4 Occurring in ≥4% of XALKORI-Treated Patients in Study 1

Laboratory Abnormality	XALKORI		Chemotherapy	
	Any Grade (%)	Grade 3-4 (%)	Any Grade (%)	Grade 3-4 (%)
Hematology				
Neutropenia	52	11	59	16
Lymphopenia	48	7	53	13
Chemistry				
Increased ALT	79	15	33	2
Increased AST	66	8	28	1
Hypophosphatemia	32	10	21	6

Additional laboratory test abnormality in patients treated with XALKORI was an increase in creatinine (Any Grade: 99%; Grade 3: 2%; Grade 4: 0%) compared to the chemotherapy arm (Any Grade: 92%; Grade 3: 0%; Grade 4: 1%).

Previously Treated ALK-Positive Metastatic NSCLC - Study 2 (PROFILE 1007)

The data in Table 5 are derived from 343 patients with ALK-positive metastatic NSCLC enrolled in a randomized, multicenter, active-controlled, open-label trial (Study 2). Patients in the XALKORI arm (n=172) received XALKORI 250 mg orally twice daily until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. A total of 171 patients in the chemotherapy arm received pemetrexed 500 mg/m^2 (n=99) or docetaxel 75 mg/m^2 (n=72) by intravenous infusion every 3 weeks until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Patients in the chemotherapy arm received pemetrexed unless they had received pemetrexed as part of first-line or maintenance treatment.

The median duration of study treatment was 7.1 months for patients who received XALKORI and 2.8 months for patients who received chemotherapy. Across the 347 patients who were randomized to study treatment (343 received at least 1 dose of study treatment), the median age was 50 years; 14% of patients were older than 65 years. A total of 56% of patients were female and 45% of patients were Asian.

Serious adverse reactions were reported in 37% of patients treated with XALKORI and 23% of patients in the chemotherapy arm. The most frequent serious adverse reactions reported in patients treated with XALKORI were pneumonia (4.1%), pulmonary embolism (3.5%), dyspnea (2.3%), and ILD (2.9%). Fatal adverse reactions in XALKORI-treated patients in Study 2 occurred in 5% of patients, consisting of: acute respiratory distress syndrome, arrhythmia, dyspnea, pneumonia, pneumonitis, pulmonary embolism, ILD, respiratory failure, and sepsis.

Dose reductions due to adverse reactions were required in 16% of XALKORI-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with XALKORI were increased ALT (8%) including some patients with concurrent increased AST, QTc prolongation (2.9%), and neutropenia (2.3%).

XALKORI was discontinued for adverse reactions in 15% of patients. The most frequent adverse reactions that led to discontinuation of XALKORI were ILD (1.7%), increased ALT and AST (1.2%), dyspnea (1.2%), and pulmonary embolism (1.2%).

Tables 5 and 6 summarize common adverse reactions and laboratory abnormalities in XALKORI-treated patients.

Table 5. Adverse Reactions Reported at a Higher Incidence (≥5% Higher for All Grades or ≥2% Higher for Grades 3-4) with XALKORI than Chemotherapy in Study 2[†]

Adverse Reaction	**XALKORI (N=172)**		**Chemotherapy (Pemetrexed or Docetaxel) (N=171)**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Nervous System				
Dysgeusia	26	0	9	0
Dizziness[a]	22	1	8	0
Syncope	3	3	0	**0**
Eye				
Vision disorder[b]	60	0	9	0
Cardiac				
Electrocardiogram QT prolonged	5	3	0	0
Bradycardia[c]	5	0	0	0
Investigations				
Decreased weight	10	1	4	0
Gastrointestinal				
Diarrhea	60	0	19	1
Nausea	55	1	37	1
Vomiting	47	1	18	0
Constipation	42	2	23	0
Dyspepsia	8	0	3	0
Infections				
Upper respiratory infection[d]	26	0	13	1
Respiratory, Thoracic and Mediastinal				
Pulmonary embolism[e]	6	5	2	2

Adverse Reaction	XALKORI (N=172)		Chemotherapy (Pemetrexed or Docetaxel) (N=171)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
General				
Edema[f]	31	0	16	0

[†]Adverse reactions were graded using NCI CTCAE version 4.0.
Includes cases reported within the clustered terms:
[a] Dizziness (Balance disorder, Dizziness, Postural dizziness).
[b] Vision Disorder (Diplopia, Photophobia, Photopsia, Blurred vision, Reduced visual acuity, Visual impairment, Vitreous floaters).
[c] Bradycardia (Bradycardia, Sinus bradycardia).
[d] Upper respiratory infection (Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Upper respiratory tract infection).
[e] Pulmonary embolism (Pulmonary artery thrombosis, Pulmonary embolism).
[f] Edema (Face edema, Generalized edema, Local swelling, Localized edema, Edema, Peripheral edema, Periorbital edema).

Additional adverse reactions occurring at an overall incidence between 1% and 30% in patients treated with XALKORI included decreased appetite (27%), fatigue (27%), neuropathy (19%; dysesthesia, gait disturbance, hypoesthesia, muscular weakness, neuralgia, peripheral neuropathy, paresthesia, peripheral sensory neuropathy, polyneuropathy, burning sensation in skin), rash (9%), ILD (4%; acute respiratory distress syndrome, ILD, pneumonitis), renal cyst (4%), esophagitis (2%), hepatic failure (1%), and decreased blood testosterone (1%; hypogonadism).

Clinically relevant adverse reactions in <1% of patients who received XALKORI included photosensitivity (0.4%).

Table 6. Laboratory Abnormalities with Grades 3-4 Occurring in ≥4% of XALKORI-Treated Patients in Study 2

Laboratory Abnormality	XALKORI		Chemotherapy	
	Any Grade (%)	Grade 3-4 (%)	Any Grade (%)	Grade 3-4 (%)
Hematology				
Lymphopenia	51	9	60	25
Neutropenia	49	12	28	12
Chemistry				
Increased ALT	76	17	38	4
Increased AST	61	9	33	0
Hypophosphatemia	28	5	25	6
Hypokalemia	18	4	10	1
Additional laboratory test abnormality in patients treated with XALKORI was an increase in creatinine (Any Grade: 96%; Grade 3: 1%; Grade 4: 0%) compared to the chemotherapy arm (Any Grade: 72%; Grade 3: 0%; Grade 4: 0%).				

ROS1-Positive Metastatic NSCLC - Study 3 (PROFILE 1001)

The safety profile of XALKORI from Study 3, which was evaluated in 50 patients with ROS1-positive metastatic NSCLC, was generally consistent with the safety profile of XALKORI evaluated in patients with ALK-positive metastatic NSCLC (n=1669). Vision disorders occurred in 92% of patients in Study 3; 90% were Grade 1 and 2% were Grade 2. The median duration of exposure to XALKORI was 34.4 months.

Description of Selected Adverse Reactions in Patients with Metastatic NSCLC

Vision disorders:

Vision disorders, most commonly visual impairment, photopsia, blurred vision, or vitreous floaters, occurred in 63% of 1719 patients. The majority (95%) of these patients had Grade 1 visual adverse reactions. There were 0.8% of patients with Grade 3 and 0.2% of patients with Grade 4 visual impairment.

Based on the Visual Symptom Assessment Questionnaire (VSAQ-ALK), patients treated with XALKORI in Studies 1 and 2 reported a higher incidence of visual disturbances compared to patients treated with chemotherapy. The onset of vision disorder generally was within the first week of drug administration. The majority of patients on the XALKORI arms in Studies 1 and 2 (>50%) reported visual disturbances which occurred at a frequency of 4-7 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 in the VSAQ-ALK questionnaire.

Neuropathy:
Neuropathy, most commonly sensory in nature, occurred in 25% of 1719 patients. Most events (95%) were Grade 1 or Grade 2 in severity.

Renal cysts:
Renal cysts were experienced by 3.0% of 1719 patients.

The majority of renal cysts in XALKORI-treated patients were complex. Local cystic invasion beyond the kidney occurred, in some cases with imaging characteristics suggestive of abscess formation. However, across clinical trials no renal abscesses were confirmed by microbiology tests.

Renal toxicity:
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 (n=1499) in patients with ALK-positive advanced NSCLC who received XALKORI in clinical trials. No clinically relevant changes occurred in median eGFR from 12 to 104 weeks of treatment. Median eGFR slightly increased (83.02 mL/min/1.73 m^2) 4 weeks after the last dose of XALKORI. Overall, 76% of patients had a decrease in eGFR to <90 mL/min/1.73 m^2, 38% had a decrease to eGFR to <60 mL/min/1.73 m^2, and 3.6% had a decrease to eGFR to <30 mL/min/1.73 m^2.

8.2 Postmarketing Experience

The following additional adverse reaction has been identified during postapproval use of XALKORI. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Investigations: Increased blood creatine phosphokinase

9 DRUG INTERACTIONS

9.1 Effect of Other Drugs on XALKORI

Strong or Moderate CYP3A Inhibitors

Concomitant use of crizotinib with strong CYP3A inhibitors increases crizotinib plasma concentrations *[*see *Clinical Pharmacology (11.3)]*, which may increase the risk of adverse reactions of XALKORI. Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the XALKORI dosage *[*see *Dosage and Administration (5.7)]*. Avoid grapefruit or grapefruit juice which may also increase plasma concentrations of crizotinib. Use caution with concomitant

use of moderate CYP3A inhibitors.

Strong CYP3A Inducers

Concomitant use of crizotinib with strong CYP3A inducers decreases crizotinib plasma concentrations *[*see *Clinical Pharmacology (11.3)]* which may decrease the efficacy of XALKORI. Avoid concomitant use of strong CYP3A inducers.

9.2 Effect of XALKORI on Other Drugs

CYP3A Substrates

Concomitant use of crizotinib increases plasma concentrations of CYP3A substrates *[*see *Clinical Pharmacology (11.3)],* which may increase the risk of adverse reactions of these substrates. Avoid concomitant use of XALKORI with CYP3A substrates where minimal concentration changes may lead to serious adverse reactions. If concomitant use of XALKORI is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

9.3 Drugs That Prolong the QT Interval

XALKORI can prolong the QT/QTc interval. Avoid concomitant use of XALKORI with drugs that prolong the QT interval *[*see *Warnings and Precautions (7.3), Clinical Pharmacology (11.2)]*.

9.4 Drugs That Cause Bradycardia

XALKORI can cause bradycardia. Avoid concomitant use of XALKORI with drugs that cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) *[*see *Warnings and Precautions (7.5)]*.

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, XALKORI can cause fetal harm when administered to a pregnant woman *[*see *Clinical Pharmacology (11.1)]*. There are no available data on the use of XALKORI during pregnancy. In animal reproduction studies, oral administration of crizotinib in pregnant rats during organogenesis at exposures similar to those expected with the maximum recommended human dose resulted in embryotoxicity and fetotoxicity *(*see *Data)*. Advise pregnant women of the potential risk to fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data
Crizotinib was administered to pregnant rats and rabbits during organogenesis to study the effects on embryo-fetal development. Post-implantation loss was increased at doses ≥50 mg/kg/day (approximately 0.6 times the recommended human dose based on AUC) in rats. No teratogenic effects were observed in

rats at doses up to the maternally toxic dose of 200 mg/kg/day (approximately 2.7 times the recommended human dose based on AUC) or in rabbits at doses of up to 60 mg/kg/day (approximately 1.6 times the recommended human dose based on AUC), though fetal body weights were reduced at these doses.

10.2 Lactation

Risk Summary

There is no information regarding the presence of crizotinib or its metabolites in human milk, or the effects on the breastfed child or on milk production. Because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with XALKORI and for 45 days after the final dose.

10.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating XALKORI *[*see *Use in Specific Population (10.1)]*.

Contraception

There are no adequate and well-controlled studies in pregnant women using crizotinib. Women of childbearing potential should be advised to avoid becoming pregnant while receiving crizotinib. 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.

Infertility

Based on reproductive organ findings in animals, XALKORI may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[*see *Non-clinical Toxicology (12.1)]*.

10.4 Pediatric Use

The safety and effectiveness of XALKORI in pediatric patients have not been established.

Juvenile Animal Toxicity Data

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 5.4 times the recommended human dose based on AUC). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

10.5 Geriatric Use

Of the total number of patients with ALK-positive metastatic NSCLC in clinical studies of XALKORI (n=1669), 16% were 65 years or older and 3.8% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Clinical studies of XALKORI in patients with ROS1-positive metastatic NSCLC did not include sufficient numbers of patients age 65 years and older to determine whether they respond differently from younger patients.

10.6 Hepatic Impairment

Crizotinib concentrations increased in patients with pre-existing moderate (any AST and total bilirubin greater than 1.5 times ULN and less than or equal to 3 times ULN) or severe (any AST and total bilirubin greater than 3 times ULN) hepatic impairment *[*see *Clinical Pharmacology (11.3)]*. Reduce XALKORI dosage in patients with moderate or severe hepatic impairment *[*see *Dosage and Administration (5.5)]*. No dose adjustment is recommended in patients with pre-existing mild hepatic impairment (AST > ULN and total bilirubin less than or equal to 1 times ULN or any AST and total bilirubin greater than 1 times ULN but less than or equal to1.5 times ULN).

10.7 Renal Impairment

Increased exposure to crizotinib occurred in patients with pre-existing severe renal impairment (CL_{cr} less than 30 mL/min calculated using the modified Cockcroft-Gault equation for adult patients and the Schwartz equation for pediatric patients) not requiring dialysis, therefore reduce dosage of XALKORI in these patients *[*see *Dosage and Administration (5.4)* and *Clinical Pharmacology (11.3)]*. No dose adjustment is recommended in patients with mild to moderate renal impairment (CL_{cr} 30 to 89 mL/min).

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS1 (c-ros), and Recepteur d'Origine Nantais (RON). Translocations can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins. Crizotinib demonstrated concentration-dependent inhibition of ALK, ROS1, and c-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed echinoderm microtubule-associated protein-like 4 (EML4)- or nucleophosmin (NPM)-ALK fusion proteins or c-Met.

11.2 Pharmacodynamics

Cardiac Electrophysiology

In an ECG substudy conducted in 52 patients with ALK-positive NSCLC, the maximum mean QTcF (corrected QT by the Fridericia method) change from baseline was 12.3 ms (2-sided 90% upper CI: 19.5 ms) following administration of XALKORI 250 mg orally twice daily. An exposure-QT analysis suggested a crizotinib plasma concentration-dependent increase in QTcF *[see Warnings and Precautions (7.3)]*.

11.3 Pharmacokinetics

Following XALKORI 250 mg twice daily, steady state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8. Steady-state observed minimum concentration (C_{min}) and AUC

increased in a greater than dose-proportional manner over the dose range of 200 mg to 300 mg twice daily (0.8 to 1.2 times the approved recommended dosage).

Absorption

A single crizotinib dose was absorbed with median time to achieve peak concentration of 4 to 6 hours, and the mean absolute bioavailability of crizotinib was 43% (range: 32% to 66%).

Effect of Food

A high-fat meal reduced crizotinib $AUC_{0\text{-}INF}$ and maximum observed plasma concentration (C_{max}) by approximately 14%.

Distribution

The geometric mean volume of distribution (V_{ss}) of crizotinib was 1772 L following a single intravenous dose.

Protein binding of crizotinib is 91% and is independent of drug concentration *in vitro*. Crizotinib is a substrate for P-glycoprotein (P-gp) *in vitro*. The blood-to-plasma concentration ratio is approximately 1.

Elimination

The mean apparent plasma terminal half-life of crizotinib was 42 hours following single doses of crizotinib in patients. The mean apparent clearance (CL/F) of crizotinib was lower at steady state (60 L/h) after 250 mg twice daily than after a single 250 mg oral dose (100 L/h).

Metabolism
Crizotinib is predominantly metabolized by CYP3A.

Excretion
Following administration of a single oral 250 mg dose of radiolabeled crizotinib dose to healthy subjects, 63% (53% as unchanged) of the administered dose was recovered in feces and 22% (2.3% as unchanged) in urine.

Specific Populations

No clinically significant difference in crizotinib pharmacokinetics were observed based on age, sex, or ethnicity (Asian, non-Asian). For patients <18 years of age, body weight has a significant effect on the pharmacokinetics of crizotinib, with lower crizotinib exposures observed in patients with higher body weight.

Patients with Hepatic Impairment
Steady-state mean crizotinib AUC and C_{max} decreased by 9% in patients with mild hepatic impairment (AST >ULN and total bilirubin ≤1 times ULN or any AST and total bilirubin >1 times ULN but ≤1.5 times ULN) compared to patients with normal hepatic function following XALKORI 250 mg orally twice daily.

Steady-state mean crizotinib AUC increased by 14% and C_{max} increased by 9% in patients with moderate hepatic impairment (any AST and total bilirubin >1.5 times ULN and ≤3 times ULN) following XALKORI

200 mg orally twice daily compared with patients with normal hepatic function following XALKORI 250 mg orally twice daily.

Mean crizotinib AUC decreased by 35% and C_{max} decreased by 27% in patients with severe hepatic impairment (any AST and total bilirubin >3 times ULN) following XALKORI 250 mg orally once daily compared with patients with normal hepatic function following XALKORI 250 mg orally twice daily *[*see *Dosage and Administration (5.5), Use in Specific Populations (10.6)]*.

Patients with Renal Impairment
Mild or moderate renal impairment (CL_{cr} of 60-89 ml/min or 30-59 ml/min, respectively, calculated using the modified Cockcroft-Gault equation) has no clinically significant effect on the exposure of crizotinib.

Following a single 250 mg dose, the mean $AUC_{0\text{-}INF}$ of crizotinib increased by 79% and the mean C_{max} increased by 34% in patients with severe renal impairment (CL_{cr} <30 mL/min) who did not require dialysis compared to those with normal renal function (CL_{cr} ≥90 mL/min). Similar changes in $AUC_{0\text{-}INF}$ and C_{max} were observed for the active metabolite of crizotinib *[*see *Dosage and Administration (5.6) and Use in Specific Populations (10.7)]*.

Drug Interaction Studies

Clinical Studies
Gastric Acid Reducing Agents: No clinically significant differences in crizotinib pharmacokinetics were observed when used concomitantly with esomeprazole, a proton pump inhibitor.

Strong CYP3A Inhibitors: Co-administration of a single 150 mg oral dose of crizotinib with ketoconazole, a strong CYP3A inhibitor, increased crizotinib $AUC_{0\text{-}INF}$ by 216% and C_{max} by 44% compared to crizotinib alone. Co-administration of XALKORI 250 mg orally once daily with itraconazole, a strong CYP3A inhibitor, increased crizotinib steady-state AUC by 57% and C_{max} by 33%, respectively, compared to crizotinib alone *[*see *Drug Interactions (9.1)]*.

Strong CYP3A Inducers: Co-administration of XALKORI 250 mg orally twice daily with rifampin, a strong CYP3A inducer, decreased crizotinib steady-state $AUC_{0\text{-}Tau}$ by 84% and C_{max} by 79%, compared to crizotinib alone *[*see *Drug Interactions (9.1)]*.

CYP3A Substrates: Co-administration of XALKORI 250 mg orally twice daily for 28 days increased $AUC_{0\text{-}INF}$ of oral midazolam (CYP3A substrate) 3.7-fold compared to midazolam alone *[*see *Drug Interactions (9.2)]*.

In Vitro Studies
CYP Enzymes: Crizotinib inhibits CYP2B6 *in vitro*. Crizotinib does not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Crizotinib does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A.

UDP-glucuronosyltransferase (UGT): Crizotinib does not inhibit UGT1A1, UGT1A4, UGT1A6, UGT1A9 or UGT2B7.

Transporters: Crizotinib inhibits P-gp, organic cation transporter (OCT) 1, and OCT2. Crizotinib does not inhibit organic anion transporting polypeptides (OATP) B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, or bile salt export pump transporter (BSEP).

12 NON-CLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with crizotinib have not been conducted.

Crizotinib was genotoxic in an *in vitro* micronucleus assay in Chinese Hamster Ovary cultures, in an *in vitro* human lymphocyte chromosome aberration assay, and in *in vivo* rat bone marrow micronucleus assays. Crizotinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay.

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 greater than or equal to 50 mg/kg/day for 28 days (greater than 1.7 times the recommended human dose 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 (approximately 10 times the recommended human dose based on body surface area) for 3 days.

13 CLINICAL STUDIES

13.1 ALK-or ROS1-Positive Metastatic Non Small Cell Lung Cancer

Previously Untreated ALK-Positive Metastatic NSCLC - Study 1 (PROFILE 1014; NCT01154140)

The efficacy of XALKORI for the treatment of patients with ALK-positive metastatic NSCLC, who had not received previous systemic treatment for advanced disease, was demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 1). Patients were required to have ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart fluorescence *in situ* hybridization (FISH) Probe Kit, prior to randomization. The major efficacy outcome measure was progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by independent radiology review (IRR) committee. Additional efficacy outcome measures included objective response rate (ORR) as assessed by IRR, DOR, and overall survival (OS). Patient-reported lung cancer symptoms were assessed at baseline and periodically during treatment.

Patients were randomized to receive XALKORI (n=172) or chemotherapy (n=171). Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0-1, 2), race (Asian, non-Asian), and brain metastases (present, absent). Patients in the XALKORI arm received XALKORI 250 mg orally twice daily until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Chemotherapy consisted of pemetrexed 500 mg/m^2 with cisplatin 75 mg/m^2 or carboplatin AUC of 5 or 6 mg × min/mL by intravenous infusion every 3 weeks for up to 6 cycles. Patients in the chemotherapy arm were not permitted to receive maintenance chemotherapy. At the time of documented disease progression, as per independent radiology review, patients randomized to chemotherapy were offered XALKORI.

The demographic characteristics of the overall study population were 62% female, median age of 53 years, baseline ECOG performance status 0 or 1 (95%), 51% White and 46% Asian, 4% current smokers, 32% past smokers, and 64% never smokers. The disease characteristics of the overall study population were metastatic disease in 98% of patients, 92% of patients' tumors were classified as adenocarcinoma histology, 27% of patients had brain metastases, and 7% received systemic chemotherapy as adjuvant or neoadjuvant therapy. At the time of the final analysis of overall survival, 84% of patients randomized to the

chemotherapy arm subsequently received XALKORI.

Study 1 demonstrated a statistically significant improvement in PFS in patients treated with XALKORI. There was no statistically significant difference in OS between patients treated with XALKORI and patients treated with chemotherapy. Table 7 and Figure 1 summarize the efficacy results. Exploratory patient-reported symptom measures of baseline and post-treatment dyspnea, cough, and chest pain suggested a delay in time to development of or worsening of dyspnea, but not cough or chest pain, in patients treated with XALKORI as compared to chemotherapy. The patient-reported delay in onset or worsening of dyspnea may be an overestimation, because patients were not blinded to treatment assignment.

Table 7. Previously Untreated ALK-Positive Metastatic NSCLC - Efficacy Results in Study 1

	XALKORI (N=172)	**Chemotherapy (N=171)**
Progression-Free Survival (Based on IRR)		
Number of Events (%)	100 (58%)	137 (80%)
Progressive Disease	89 (52%)	132 (77%)
Death	11 (6%)	5 (3%)
Median, Months (95% CI)	10.9 (8.3, 13.9)	7.0 (6.8, 8.2)
HR (95% CI)[a]	0.45 (0.35, 0.60)	
p-value[b]	<0.001	
Overall Survival		
Number of Events (%)	71 (41%)	81 (47%)
Median, Months (95% CI)	NR (45.8, NR)	47.5 (32.2, NR)
HR (95% CI)[a]	0.76 (0.55,1.05)	
p-value[b]	0.098	
Tumor Responses (Based on IRR)		
Objective Response Rate % (95% CI)	74% (67, 81)	45% (37, 53)
CR, n (%)	3 (1.7%)	2 (1.2%)
PR, n (%)	125 (73%)	75 (44%)
p-value[c]	<0.001	
Duration of Response		
Median, Months (95% CI)	11.3 (8.1, 13.8)	5.3 (4.1, 5.8)

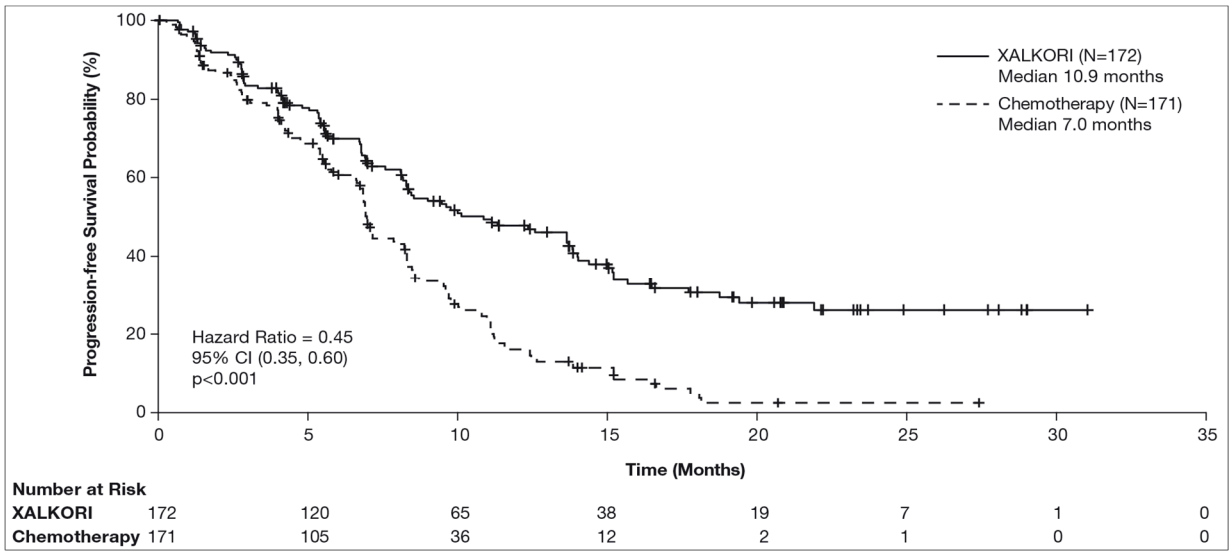
HR=hazard ratio; CI=confidence interval; IRR=independent radiology review; NR=not reached; CR=complete response; PR=partial response.

[a] Based on the Cox proportional hazards stratified analysis.

[b] Based on the stratified log-rank test.

[c] Based on the stratified Cochran-Mantel-Haenszel test.

Figure 1. Kaplan-Meier Curves of Progression-Free Survival as Assessed by IRR in Study 1



Previously Treated ALK-Positive Metastatic NSCLC - Study 2 (PROFILE 1007; NCT00932893)

The efficacy of XALKORI as monotherapy for the treatment of 347 patients with ALK-positive metastatic NSCLC, previously treated with 1 platinum-based chemotherapy regimen, were demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 2). The major efficacy outcome was PFS according to RECIST version 1.1 as assessed by IRR. Additional efficacy outcomes included ORR as assessed by IRR, DOR, and OS.

Patients were randomized to receive XALKORI 250 mg orally twice daily (n=173) or chemotherapy (n=174). Chemotherapy consisted of pemetrexed 500 mg/m^2 (if pemetrexed naïve; n=99) or docetaxel 75 mg/m^2 (n=72) intravenously (IV) every 21 days. Patients in both treatment arms continued treatment until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Randomization was stratified by ECOG performance status (0-1, 2), brain metastases (present, absent), and prior EGFR tyrosine kinase inhibitor treatment (yes, no). Patients were required to have ALK-positive NSCLC as identified by the FDA-approved assay, Vysis ALK Break-Apart FISH Probe Kit, prior to randomization.

The demographic characteristics of the overall study population were 56% female, median age of 50 years, baseline ECOG performance status 0 or 1 (90%), 52% White and 45% Asian, 4% current smokers, 33% past smokers, and 63% never smokers. The disease characteristics of the overall study population were metastatic disease in at least 95% of patients and at least 93% of patients' tumors were classified as adenocarcinoma histology. At the time of the final analysis of overall survival, 89% of patients randomized to the chemotherapy arm subsequently received XALKORI.

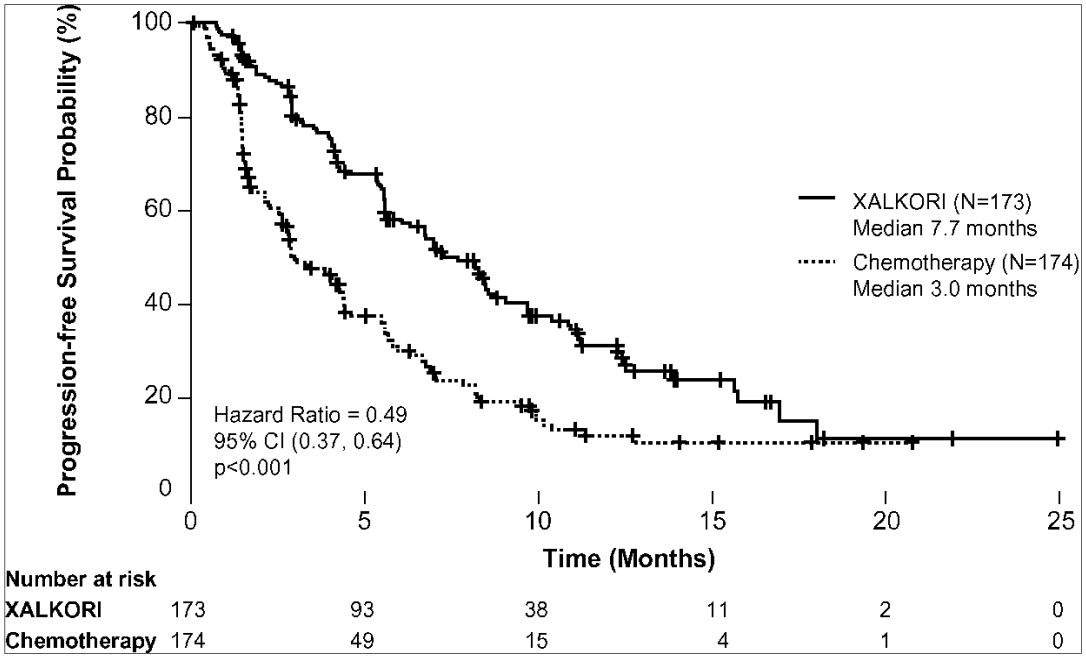
Study 2 demonstrated a statistically significant improvement in PFS in the patients treated with XALKORI. Table 8 and Figure 2 summarize the efficacy results.

Table 8. Previously Treated ALK-Positive Metastatic NSCLC - Efficacy Results in Study 2

	XALKORI (N=173)	Chemotherapy (N=174)
Progression-Free Survival (Based on IRR)		
Number of Events (%)	100 (58%)	127 (73%)
Progressive Disease	84 (49%)	119 (68%)
Death	16 (9%)	8 (5%)
Median, 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]	<0.001	
Overall Survival		
Number of Events (%)	116 (67%)	126 (72%)
Median, 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]	0.229	
Tumor Responses (Based on IRR)		
Objective Response Rate % (95% CI)	65% (58, 72)	20% (14, 26)
CR, n (%)	1 (0.6%)	0
PR, n (%)	112 (65%)	34 (20%)
p-value[d]	<0.001	
Duration of Response		
Median, Months (95% CI)	7.4 (6.1, 9.7)	5.6 (3.4, 8.3)

HR=hazard ratio; CI=confidence interval; IRR=independent radiology review; CR=complete response; PR=partial response.
[a] For pemetrexed, the median PFS was 4.2 months. For docetaxel, the median PFS was 2.6 months.
[b] Based on the Cox proportional hazards stratified analysis.
[c] Based on the stratified log-rank test.
[d] Based on the stratified Cochran-Mantel-Haenszel test.

Figure 2. Kaplan-Meier Curves of Progression-Free Survival as Assessed by IRR in Study 2



ROS1-Positive Metastatic NSCLC - Study 3 (PROFILE 1001; NCT00585195)

The efficacy and safety of XALKORI was investigated in a multicenter, single-arm study (Study 3), in which patients with ROS1-positive metastatic NSCLC received XALKORI 250 mg orally twice daily. Patients were required to have histologically-confirmed advanced NSCLC with a ROS1 rearrangement, age 18 years or older, ECOG performance status of 0, 1, or 2, and measurable disease. The efficacy outcome measures were ORR and DOR according to RECIST version 1.0 as assessed by IRR and investigator, with imaging performed every 8 weeks for the first 60 weeks.

Baseline demographic and disease characteristics were female (56%), median age of 53 years, baseline ECOG performance status of 0 or 1 (98%), White (54%), Asian (42%), past smokers (22%), never smokers (78%), metastatic disease (92%), adenocarcinoma (96%), no prior systemic therapy for metastatic disease (14%), and prior platinum-based chemotherapy for metastatic disease (80%). The ROS1 status of NSCLC tissue samples was determined by laboratory-developed break-apart FISH (96%) or RT-PCR (4%) clinical trial assays. For assessment by FISH, ROS1 positivity required that ≥15% of a minimum of 50 evaluated nuclei contained a ROS1 gene rearrangement.

Efficacy results are summarized in Table 9.

Table 9. ROS1-Positive Metastatic NSCLC - Results* in Study 3

Efficacy Parameters	**IRR (N=50)**	**Investigator-Assessed (N=50)**
Objective Response Rate (95% CI)	66% (51, 79)	72% (58, 84)
Complete Response, n	1	5
Partial Response, n	32	31
Duration of Response		
Median, Months (95% CI)	18.3 (12.7, NR)	NR (14.5, NR)

IRR=independent radiology review; CI=confidence interval; NR=not reached.
*As assessed by RECIST version 1.0.

14 LIST OF EXCIPIENTS

Colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate and hard gelatin capsule shells.

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.

15 SHELF LIFE

Please refer to the bottle label (for bottle packing) or carton box (for blister packing).

16 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

17 NATURE AND CONTENTS OF CONTAINER

Crizotinib is available in high-density polyethylene (HDPE) bottle of 60 capsules and polyvinyl chloride/aluminum foil (PVC/Alu) blister foil of 6 blister strips with 10 capsules each.

Some product strengths or pack sizes may not be available in your country.

18 MANUFACTURER

Manufactured by:
Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1,
79108 Freiburg Im Breisgau, Germany.

Date of Revision: 21 AUG 2024

XALKORI-0824