XALKORI® (crizotinib) 250 mg capsules is an oral medicine that inhibits the anaplastic lymphoma kinase (ALK) and ROS1 receptor tyrosine kinases.1,2

XALKORI was the first ALK inhibitor and first and only ROS1 inhibitor approved in the U.S. and is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test.

To date, over 10,000 patients have been treated with XALKORI in the U.S.3

ALK IN LUNG CANCER

Originally discovered as an oncogenic driver in a type of lymphoma, ALK gene alterations were also found to be among key drivers of tumor development in cancers such as NSCLC and rare sarcomas.4 By inhibiting ALK, XALKORI blocks signaling in a number of cell pathways that are believed to be critical for the growth and survival of tumor cells.4,5

In ALK-positive lung cancer, a normally dormant gene named ALK is fused with another gene, predominantly EML4. This genetic alteration creates the ALK fusion gene and ultimately, the production of the ALK fusion protein, which is responsible for tumor growth.4,5 Epidemiology studies suggest that approximately 3 to 5 percent of NSCLC tumors are ALK-positive.5

Only biomarker testing can determine which patients have ALK-positive metastatic NSCLC. In the U.S., the Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular), the Ventana ALK (D5F3) CDx Assay and FoundationOne® CDx are the FDA-approved tests for detecting ALK.

ROS1 IN LUNG CANCER

Another gene that can rearrange or combine with other genes is called ROS1. Sometimes the ROS1 gene can attach to another gene, changing the way each gene normally functions. This ROS1 gene rearrangement can contribute to cancer-cell growth and tumor survival. This change occurs in approximately one to 2 percent of NSCLC cases. Of the estimated 1.8 million new cases of NSCLC worldwide each year, roughly 18,000 may be driven by oncogenic ROS1 fusions.2,7-9

In the U.S., the FDA approved companion diagnostic (CDx) to identify mNSCLC ROS1-positive patients eligible for treatment with XALKORI is the Ion Torrent™ Oncomine™ Dx Target Test, a Next Generation Sequencing (NGS) diagnostic test for NSCLC.*

NSCLC CLINICAL STUDIES

PROFILE 1014 studied XALKORI 250 mg twice daily in previously untreated patients with ALK-positive metastatic NSCLC versus standard platinum-based chemotherapy regimens. This Phase 3 study enrolled 343 participants from clinical sites globally.10 Patients in the chemotherapy arm of the study received one of the following standard-of-care chemotherapy regimens based on the choice of the investigator: either pemetrexed 500 mg/m² with cisplatin 75 mg/m² or carboplatin AUC of 5 or 6 min/mL by intravenous infusion every 3 weeks for up to 6 cycles. 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.

• In PROFILE 1014, XALKORI demonstrated significantly prolonged progression-free survival (PFS) of 10.9 months (95% CI, 8.3 to 13.9) (n=172) compared to 7.0 months (95% CI, 6.8 to 8.2) with chemotherapy (n=171) in previously untreated patients with ALK-positive metastatic NSCLC (hazard ratio, 0.45; 95% CI: 0.35 to 0.60; P<0.001).
• XALKORI also demonstrated significantly higher objective response rate (ORR) when compared to standard platinum-based chemotherapy regimens. XALKORI demonstrated an ORR of 74% (95% CI, 67 to 81) compared to an ORR of 45% (95% CI, 37 to 53) for the chemotherapy arm (P<0.001).

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NSCLC CLINICAL STUDIES (CONTINUED)

• Median duration of response was 11.3 months (95% CI, 8.1 to 13.8) with XALKORI and 5.3 months (95% CI, 4.1 to 5.8) with chemotherapy.

• With the majority of patients still in follow up for survival at the time of the PFS analysis, and over two-thirds of the patients randomized to the chemotherapy arm of the study subsequently crossing over to XALKORI, median OS was not reached in either treatment arm (hazard ratio, 0.82; 95% CI, 0.54 to 1.26; \( P=0.36 \)). The OS analysis conducted at the time of the PFS analysis did not suggest a difference in survival between arms.

• Safety data for PROFILE 1014 is based on 340 patients (including n=171 in the XALKORI arm and n=169 in the chemotherapy arm). Serious adverse events were reported in 58 patients (34%) 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% of patients, consisting of septic shock, acute respiratory failure and diabetic ketoacidosis.
  – Common adverse reactions (all grades) occurring in ≥25% and more commonly (≥5%) in patients treated with XALKORI vs chemotherapy were vision disorder (71% vs 10%), diarrhea (61% vs. 13%), edema (49% vs 12%), vomiting (46% vs 36%), constipation (43% vs 30%), upper respiratory infection (32% vs 12%), dysgeusia (26% vs 5%), and abdominal pain (26% vs 12%). Grade 3/4 reactions occurring at a ≥2% higher incidence with XALKORI vs chemotherapy were QT prolongation (2% vs 0%), esophagitis (2% vs 0%), and constipation (2% vs 0%).
  – In patients treated with XALKORI vs chemotherapy, the following occurred: elevation of ALT (any grade [79% vs 33%] or Grade 3/4 [15% vs 2%]); elevation of AST (any grade [66% vs 28%] or Grade 3/4 [8% vs 1%]); neutropenia (any grade [52% vs 59%] or Grade 3/4 [11% vs 16%]); lymphopenia (any grade [48% vs 53%] or Grade 3/4 [7% vs 13%]); hypophosphatemia (any grade [32% vs 21%] or Grade 3/4 [10% vs 6%]).
  – In patients treated with XALKORI vs chemotherapy, renal cysts occurred (5% vs 1%).
  – Nausea (56%), decreased appetite (30%), fatigue (29%) and neuropathy (21%) also occurred in patients taking XALKORI.

PROFILE 1001 is a multicenter, single-arm Phase 1 study that included a cohort of 50 patients with ROS1-positive metastatic NSCLC treated with 250 mg of XALKORI orally twice daily. In the clinical trial, tumors were tested for ROS1 rearrangement by laboratory-developed break-apart fluorescence in situ hybridization (FISH) (96%) or RT-PCR (4%) clinical trial assays.

• The efficacy outcome measures were objective response rate (ORR) and duration of response as assessed by independent radiology review (IRR) and investigator.
  – The ORR was 66% (95% CI, 51 to 79) as assessed by IRR. There was one complete response and 32 partial responses.
  – The median duration of response as assessed by IRR was 18.3 months (95% CI, 12.7 months, not reached).

• Additionally, the safety profile of XALKORI in ROS1-positive metastatic NSCLC was generally consistent with that observed in patients with ALK-positive metastatic NSCLC. Vision disorders occurred in 92% of patients in the ROS1 study; 90% of patients had Grade 1 vision disorders and 2% had Grade 2.

SAFETY PROFILE

IMPORTANT SAFETY INFORMATION (CONTINUES ON NEXT PAGE)

Hepatotoxicity: Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of patients treated with XALKORI across clinical trials (n=1719). Transaminase elevations generally occurred within the first 2 months. 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 transaminase elevations. Permanently discontinue for ALT/AST elevation >3 times ULN with concurrent total bilirubin elevation >1.5 times ULN (in the absence of cholestasis or hemolysis); otherwise, temporarily suspend and dose-reduce XALKORI as indicated.
SAFETY PROFILE (CONTINUED)

IMPORTANT SAFETY INFORMATION (CONTINUED)

Interstitial Lung Disease (Pneumonitis): Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur. Across clinical trials (n=1719), 2.9% of XALKORI-treated patients had any grade ILD, 1.0% had Grade 3/4, and 0.5% had fatal ILD. ILD generally occurred within 3 months after initiation of treatment. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes and permanently discontinue XALKORI in patients with drug-related ILD/pneumonitis.

QT Interval Prolongation: QTc prolongation can occur. Across clinical trials (n=1616), 2.1% of patients had QTcF (corrected QT by the Fridericia method) ≥500 ms and 5.0% had an increase from baseline QTcF ≥60 ms by automated machine-read evaluation of ECGs. Avoid use 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 prolong the QT interval. Permanently discontinue XALKORI in patients who develop QTc >500 ms or ≥60 ms change from baseline with Torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia. Withhold XALKORI in patients who develop QTc >500 ms on at least 2 separate ECGs until recovery to a QTc ≤480 ms, then resume at a reduced dose.

Bradycardia: Symptomatic bradycardia can occur. Across clinical trials, bradycardia occurred in 12.7% of patients treated with XALKORI (n=1719). Avoid use in combination with other agents known to cause bradycardia. Monitor heart rate and blood pressure regularly. 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, 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. If concomitant medications can be adjusted or discontinued, restart XALKORI at 250 mg once daily with frequent monitoring.

Severe Visual Loss: Across clinical trials, the incidence of Grade 4 visual field defect with vision loss was 0.2% (n=1719). Discontinue XALKORI in patients with new onset of severe visual loss (best corrected vision less than 20/200 in one or both eyes). Perform an ophthalmological evaluation. There is insufficient information to characterize the risks of resumption of XALKORI in patients with a severe visual loss; a decision to resume should consider the potential benefits to the patient.

Vision Disorders: Most commonly visual impairment, photopsia, blurred vision or vitreous floaters, occurred in 63.1% of 1719 patients. The majority (95%) of these patients had Grade 1 visual adverse reactions. 0.8% of patients had Grade 3 or 0.2% had Grade 4 visual impairment. 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 on daily activities.

Embryo-Fetal Toxicity: XALKORI can cause fetal harm when administered to a pregnant woman. Advise of the potential risk to the fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for at least 45 days (females) or 90 days (males) respectively, following the final dose of XALKORI.

ROS1-positive Metastatic NSCLC: Safety was evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study, and was generally consistent with the safety profile of XALKORI evaluated in patients with ALK-positive metastatic NSCLC. Vision disorders occurred in 92% of patients in the ROS1 study; 90% of patients had Grade 1 vision disorders and 2% had Grade 2.

Adverse Reactions: Safety was evaluated in a phase 3 study in previously untreated patients with ALK-positive metastatic NSCLC randomized to XALKORI (n=171) or chemotherapy (n=169). Serious adverse events were reported in 34% of patients treated with XALKORI, the most frequent were dyspnea (4.1%) and pulmonary embolism (2.9%). Fatal adverse events in XALKORI-treated patients occurred in 2.3% of patients, consisting of septic shock, acute respiratory failure, and diabetic ketoacidosis. Common adverse reactions (all grades) occurring in ≥25% and more commonly (≥5%) in patients treated with XALKORI vs chemotherapy were vision disorder (71% vs 10%), diarrhea (61% vs 13%), edema (49% vs 12%), vomiting (46% vs 36%), constipation (43% vs 30%), upper respiratory infection (32% vs 12%), dysgeusia (26% vs 5%), and abdominal pain (26% vs 12%). Grade 3/4 reactions occurring at a ≥2% higher incidence with XALKORI vs chemotherapy were QT prolongation (2% vs 0%), esophagitis (2% vs 0%), and constipation (2% vs 0%). In patients treated with XALKORI vs chemotherapy, the following occurred: elevation of ALT (any grade [79% vs 33%] or Grade 3/4 [15% vs 2%]); elevation of AST (any grade [66% vs 28%] or Grade 3/4 [8% vs 1%]); neutropenia (any grade [52% vs 59%] or Grade 3/4 [11% vs 16%]); lymphopenia (any grade [48% vs 53%] or Grade 3/4 [7% vs 13%]); hypophosphatemia (any grade [32% vs 21%] or Grade 3/4 [10% vs 6%]). In patients treated with XALKORI vs chemotherapy, renal cysts occurred (5% vs 1%). Nausea (56%), decreased appetite (30%), fatigue (29%), and neuropathy (21%) also occurred in patients taking XALKORI.

Continues on next page
SAFETY PROFILE (CONTINUED)

IMPORTANT SAFETY INFORMATION (CONTINUED)

Drug Interactions: Exercise caution with concomitant use of moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice which may increase plasma concentrations of crizotinib. Avoid concomitant use of strong CYP3A inducers and inhibitors. Avoid concomitant use of CYP3A substrates with narrow therapeutic range in patients taking XALKORI. If concomitant use of CYP3A substrates with narrow therapeutic range is required in patients taking XALKORI, dose reductions of the CYP3A substrates may be required due to adverse reactions.

Lactation: Because of the potential for adverse reactions in breastfed infants, advise females not to breastfeed during treatment with XALKORI and for 45 days after the final dose.

Hepatic Impairment: Crizotinib concentrations increased in patients with pre-existing moderate (any AST and total bilirubin >1.5x ULN and ≤3x ULN) or severe (any AST and total bilirubin >3x ULN) hepatic impairment. Reduce XALKORI dose in patients with moderate or severe hepatic impairment. The recommended dose of XALKORI in patients with pre-existing moderate hepatic impairment is 200 mg orally twice daily or with pre-existing severe hepatic impairment is 250 mg orally once daily.

Renal Impairment: Decreases in estimated glomerular filtration rate occurred in patients treated with XALKORI. Administer XALKORI at a starting dose of 250 mg taken orally once daily in patients with severe renal impairment (CLcr <30 mL/min) not requiring dialysis.

Please see full Prescribing Information for XALKORI.

For more information about XALKORI please visit www.XALKORI.com.

CONTACT & ADDITIONAL INFORMATION

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Phone: (212) 733-6213

For more information about XALKORI trials currently ongoing and enrolling, please visit www.clinicaltrials.gov or www.pfizercancertrials.com.

REFERENCES


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Indications and Usage

This document contains information about the use and dosing of XALKORI, a medication approved for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive.

Dosage and Administration

The recommended dose of XALKORI is 250 mg orally twice daily until disease progression or no longer tolerated by the patient. Dose reduction guidelines are provided in Tables 1 and 2.

Warnings and Precautions

Hepatotoxicity: Fatal hepatotoxicity occurred in 0.1% of patients. Monitor periodic liver testing. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. Bradycardia: XALKORI can cause bradycardia. Monitor heart rate and blood pressure regularly.

Adverse Reactions

The most common adverse reactions (≥25%) are vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, and upper respiratory infection. Dizziness is also a frequently reported adverse reaction.

Use in Specific Populations

Pregnancy, lactation, and use in patients with renal or hepatic impairment are discussed in this section. Special considerations for use in children and patients with specific medical conditions are also provided.

How Supplied/Storage and Handling

XALKORI capsules are available in strengths of 250 mg and 200 mg. The capsules should be stored at room temperature and protected from humidity.

Full Prescribing Information

This section includes additional details about the use, dosage, administration, warnings, precautions, and adverse reactions of XALKORI. It is important to consult this information for complete and up-to-date prescribing details.

Using this information in your medical practice can help ensure that patients receive the appropriate treatment and that any potential risks are managed effectively.
Table 2. XALKORI Dose Modification – Non-Hematologic Toxicities (cont'd)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>XALKORI Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade drug-related interstitial lung disease/pneumonitis</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>QT corrected for heart rate (QTc) greater than 500 ms or at least 2 separate electrocardiograms (ECGs)</td>
<td>Withheld until recovery to baseline or to a QTc less than 481 ms, then resume at reduced dose.</td>
</tr>
<tr>
<td>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</td>
<td>Permanently discontinue.</td>
</tr>
<tr>
<td>Bradycardiaa (symptomatic, may be severe and medically significant, medical intervention indicated)</td>
<td>Withheld 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.</td>
</tr>
<tr>
<td>Visual Loss (Grade 4 Ocular Disorder)</td>
<td>Discontinue during evaluation of severe vision loss.</td>
</tr>
</tbody>
</table>

5.3 QT Interval Prolongation

QTc prolongation can occur in patients treated with XALKORI. Across clinical trials, 34 of 1616 patients (2.1%) had QTc (corrected QT for heart rate by the Fridericia method) greater than or equal to 500 ms and 79 of 1582 patients (5.0%) had an increase from baseline QTc 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, bradycardia, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval. 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 or 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 Dosage and Administration (2.3) and Clinical Pharmacology (12.2)].

5.4 Bradycardia

Symptomatic bradycardia can occur in patients receiving XALKORI. Across clinical trials, bradycardia occurred in 219 (12.7%) of 1719 patients treated with XALKORI. Grade 3 syncope occurred in 2.4% of XALKORI-treated patients and in 0.6% of the chemotheraphy-treated patients.

Avoid using XALKORI in combination with other agents 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. 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 Dosage and Administration (2.3) and Adverse Reactions (6)].

5.5 Severe Visual Loss

Across all clinical trials, the incidence of Grade 4 visual field defect with vision loss was 0.2% (4/1719). Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss. Discontinue XALKORI in patients 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 onset of new severe visual loss. There is insufficient information to characterize the risks of resumption of XALKORI in patients with a severe visual loss; a decision to resume XALKORI should consider the potential benefits to the patient.

5.6 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. Advise females of reproductive potential to use effective contraception during treatment with XALKORI and for at least 45 days following the final dose [see Use in Specific Populations (8.1, 8.3)].

XALKORI may cause fetal harm when administered to a pregnant woman. Advise female patients with male partners of reproductive potential to use condoms during treatment with XALKORI and for at least 90 days after the final dose [see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)].

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hepatotoxicity [see Warnings and Precautions (5.1)]
- Interstitial Lung Disease (Pneumonitis) [see Warnings and Precautions (5.2)]
- QT Interval Prolongation [see Warnings and Precautions (5.3)]
- Bradycardia [see Warnings and Precautions (5.4)]
- Severe Visual Loss [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials may not directly be 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 section reflect exposure to XALKORI in 1719 patients who received XALKORI 250 mg twice daily enrolled in 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) [see Warnings and Precautions (5)].

The data described below is based primarily on 343 patients with ALK-positive metastatic NSCLC who received XALKORI 250 mg 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 ROST-positve metastatic NSCLC from a single-arm study (Study 3). The most common adverse reactions (≥25%) of XALKORI 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

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, intolerability 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/m² in combination with cisplatin 75 mg/m² (n=91) or carboplatin at a dose calculated to produce an area under the concentration-time curve (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. At the time of the planned interim analysis, the interim investigator determined that the chemotherapy arm was meeting its primary end point of progression-free survival.

Serious adverse events were reported in 58 patients (34%) 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 6.4% 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 8.2%. 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XALKORI (N=171)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged Bradycardia</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td>Vision disorder</td>
<td>71</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Vomiting</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Dysphagia</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Esophagitis</td>
<td>6</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Dizziness</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Dysequisia</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>22</td>
</tr>
</tbody>
</table>

### General Disorders and Administration Site Conditions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XALKORI (N=171)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Edema</td>
<td>49</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Illusions and Infestations Upper respiratory infection</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Investigations Increased weight</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders Pain in extremity</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System Disorders Dizziness</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dysequisia</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>22</td>
</tr>
</tbody>
</table>

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

Additional adverse reactions occurring at an overall incidence between 1% and 6% in patients treated with XALKORI included nausea (66%), decreased appetite (30%), fatigue (29%), neurophathy (21%), gastrointestinal disturbances (20%), dyspnea (19%), hypogonadism (10%), renal cyst (5%), ILD (1%;ILD, pneumonitis), syncope (1%), and decreased blood testosterone (1%; hypogonadism).

### 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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XALKORI (N=172)</th>
<th>Chemotherapy (Pemetrexed or Docetaxel) (N=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong> Dizziness</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dysequisia</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>3</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong> Vision disorder</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong> Electrocardiogram QT prolonged Bradycardia</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pemetrexed or Docetaxel</td>
<td>5</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong> Vomiting</td>
<td>47</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Dysphagia</td>
<td>8</td>
</tr>
<tr>
<td>**Infections and Infestations Upper respiratory infection</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong> Pulmonary embolism</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong> Edema</td>
<td>31</td>
<td>0</td>
</tr>
</tbody>
</table>

*Adverse reactions were graded using NCI CTCAE version 4.0. Includes cases reported within the clustered terms:
- Dizziness (Balance disorder, Dizziness, Postural dizziness)
- Vision Disorder (Diplopia, Photophobia, Photopsia, Reduced visual acuity, Blurred vision, Vitreous floaters, Visual impairment)
- Bradycardia (Bradycardia, Sinus bradycardia)
- Upper respiratory infection (Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Upper respiratory tract infection)
- Pulmonary embolism (Pulmonary artery thrombosis, Pulmonary embolism)
- Edema (Face edema, Generalized edema, Local swelling, Localized edema, Edema, Periorbital 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%), dysesthesis, gait disturbance, hypotension, motor 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).
250 mg orally once daily [see Clinical Pharmacology (12.3)]. After discontinuation of a strong CYP3A risk to a fetus.

Based on its mechanism of action, XALKORI can cause fetal harm when administered to a pregnant woman [see Nonclinical Toxicology (13.1)].

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 Nonclinical Toxicology (13.1)].

Pediatric Use
The safety and efficacy of XALKORI in pediatric patients has not been established.

Animal 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.

8.5 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.

8.6 Hepatic Impairment
Crizotinib concentrations increased in patients with pre-existing moderate (any AST and total bilirubin >1.5 times ULN and <3 times ULN) or severe (any AST and total bilirubin >3 times ULN) hepatic impairment [see Clinical Pharmacology (12.3)]. Reduce XALKORI dose in patients with moderate or severe hepatic impairment [see Dosage and Administration (2.2)]. No dose adjustment is recommended in patients with pre-existing mild hepatic impairment.

8.7 Renal Impairment
Increased exposure to crizotinib occurred in patients with pre-existing severe renal impairment (CLcr <30 mL/min) not requiring dialysis. Administer XALKORI at a dose of 250 mg taken orally once daily in patients with severe renal impairment not requiring dialysis [see Dosage and Administration (2,2) and Clinical Pharmacology (12.3)]. No dose adjustment is recommended in patients with mild to moderate renal impairment.

10 OVERDOSAGE
There have been no known cases of XALKORI overdose. There is no antidote for XALKORI.

11 DESCRIPTION
XALKORI (crizotinib) is an oral receptor tyrosine kinase inhibitor. The molecular formula for crizotinib is C21H22Cl2FN5O. The molecular weight is 450.34 daltons. Crizotinib is described chemically as 3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1H-pyrazol-4-yl]pyridin-2-amine.

The chemical structure of crizotinib is shown below:

[Chemical structure of crizotinib]

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 1.63.

Table 6. Laboratory Abnormalities with Grade 3 or 4 Incidence of >2% in XALKORI-Treated Patients in Study 2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>XALKORI Grade 3-4 (%)</th>
<th>XALKORI Grade 3-4 (%)</th>
<th>Chemotherapy Grade 3-4 (%)</th>
<th>Chemotherapy Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49</td>
<td>12</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>51</td>
<td>9</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT elevation</td>
<td>76</td>
<td>17</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>AST elevation</td>
<td>61</td>
<td>9</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>18</td>
<td>4</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>28</td>
<td>5</td>
<td>25</td>
<td>6</td>
</tr>
</tbody>
</table>

Additional laboratory test abnormalities 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%).
12 CLINICAL PHARMACOLOGY

12.1 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 fusions. 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.

12.2 Pharmacokinetics

Cardiac electrophysiology

In an ECG substudy conducted in 52 patients with ALK-positive NSCLC who received crizotinib 250 mg twice daily for the maximum 28-day period, QTc (corrected by the Fridericia method) change from baseline was 12.3 ms (2-sided 90% upper CI: 19.5 ms). An exposure-QT analysis suggested a crizotinib plasma concentration-dependent increase in QTc [see Warnings and Precautions (5.3)].

12.3 Pharmacokinetics

Absorption

Following a single oral dose, crizotinib was absorbed with median time to achieve peak concentration of 4 to 6 hours. Following multiple dosing, steady state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8. Steady-state systemic exposure [observed minimum concentration (Cmin) and AUC] appeared to increase in a greater than dose-proportional manner over the dose range of 200-300 mg twice daily.

The mean absolute bioavailability of crizotinib was 43% (range: 32% to 66%) following a single 250 mg oral dose.

A high-fat meal reduced crizotinib AUC from time zero to infinity (AUCinf) and maximum observed plasma concentration (Cmax) by approximately 14%. XALKORI can be administered with or without food [see Dosage and Administration (2.2)].

Distribution

The geometric mean volume of distribution (Vd) of crizotinib was 1772 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.

Elimination

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

Metabolism

Crizotinib is predominantly metabolized by CYP3A4/5. The primary metabolic pathways in humans were oxidation of the piperidine ring to crizotinib lactam and -dealkylation, with subsequent Phase 2 conjugation of polypeptides (OATP) B1 or OATP1B3, or the renal uptake transport proteins organic anion transporting polypeptide (OATP) B1 or OATP1B3, or the renal uptake transport proteins organic anion transporter (OAT) 1 or OAT3 in vitro at clinically relevant concentrations.

Other transporters: Crizotinib inhibited P-gp in vitro at clinically relevant concentrations. Therefore, crizotinib has the potential to increase plasma concentrations of coadministered drugs that are substrates of P-gp.

Crizotinib inhibited the hepatic uptake transporter, organic anion transporter (OAT) 1, and renal uptake transporter, OAT3, in vitro at clinically relevant concentrations. Therefore, crizotinib has the potential to increase plasma concentrations of coadministered drugs that are substrates of OAT1 or OAT2.

Crizotinib did not inhibit the human hepatic uptake transport proteins, organic anion transporting polypeptides (OATP) B1 or OATP1B3, or the renal uptake transport proteins organic anion transporter (OAT) 1 or OAT3 in vitro at clinically relevant concentrations.

Other transporters: Crizotinib did not inhibit the hepatic efflux bile salt export pump transporter (BSEP) in vitro at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with crizotinib have not been conducted.

Crizotinib was genotoxic in in vitro micronucleus assay in Chinese Hamster Ovary cells, in an in vitro human lymphocyte chromosomal aberration, 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 pachydicty and 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.

14 CLINICAL STUDIES

14.1 ALK-Positive Metastatic NSCLC

Previously Untreated ALK-Positive Metastatic NSCLC - Study 1

The efficacy and safety 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. The major safety outcome measure was overall survival (OS). Patients 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/m2 with cisplatin 75 mg/m2 or carboplatin AUC of 5 or 6 mg/min/L 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 an adjuvant or neoadjuvant therapy. Of those randomized to chemotherapy, 70% received XALKORI after IRD documented progression.

Study 1 demonstrated a statistically significant improvement in PFS in the patients treated with XALKORI. The OS analysis conducted at the time of the PFS analysis did not suggest a difference in survival between arms. 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

<table>
<thead>
<tr>
<th></th>
<th>XALKORI (N=172)</th>
<th>Chemotherapy (N=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-Free Survival (Based on IRR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Events (%)</td>
<td>100 (58%)</td>
<td>137 (80%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>89 (52%)</td>
<td>132 (77%)</td>
</tr>
<tr>
<td>Death</td>
<td>11 (6%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>10.9 (8.3, 13.9)</td>
<td>7.0 (6.8, 8.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.45 (0.35, 0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Events (%)</td>
<td>44 (26%)</td>
<td>46 (27%)</td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.82 (0.54, 1.26)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Tumor Responses (Based on IRR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective Response Rate % (95% CI)</td>
<td>74% (67, 81)</td>
<td>45% (37, 53)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>3 (1.7%)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>125 (73%)</td>
<td>75 (44%)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.34 (0.23, 0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Duration of Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>11.3 (8.1, 13.8)</td>
<td>5.3 (4.1, 5.8)</td>
</tr>
</tbody>
</table>

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

* Based on the Cox proportional hazards stratified analysis. 
* Based on the stratified log-rank test. 
* Based on the stratified Cochran-Mantel-Haenszel test.

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

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, baseline ECOG performance status of 0, 1, or 2, adequate organ function, and measurable disease. The efficacy outcome measures were ORR and DOR. The efficacy outcome measures were ORR and DOR according to RECIST version 1.1 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 ≥15% of a minimum of 50 evaluated nuclei contained a ROS1 gene rearrangement. For assessment by RT-PCR, the median PFS was 4.2 months. For docetaxel, the median PFS was 2.6 months. 

Based on the stratified log-rank test. 
* Based on the stratified Cochran-Mantel-Haenszel test.

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

### Table 8. Previously Treated ALK-Positive Metastatic NSCLC - Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>XALKORI (N=173)</th>
<th>Chemotherapy (N=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-Free Survival (Based on IRR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Events (%)</td>
<td>100 (58%)</td>
<td>127 (73%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>84 (49%)</td>
<td>119 (68%)</td>
</tr>
<tr>
<td>Death</td>
<td>16 (9%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>7.7 (6.0, 8.8)</td>
<td>3.0 (2.6, 4.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.49 (0.37, 0.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Events (%)</td>
<td>116 (67%)</td>
<td>126 (72%)</td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>21.7 (18.9,30.5)</td>
<td>21.9 (16.8,26.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.85 (0.66, 1.10)</td>
<td>0.229</td>
</tr>
<tr>
<td><strong>Tumor Responses (Based on IRR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective Response Rate % (95% CI)</td>
<td>65% (58, 72)</td>
<td>20% (14, 26)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>1 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>112 (65%)</td>
<td>34 (20%)</td>
</tr>
<tr>
<td><strong>Duration of Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, Months (95% CI)</td>
<td>7.4 (6.1, 9.7)</td>
<td>5.6 (3.4, 8.3)</td>
</tr>
</tbody>
</table>

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

* For pemetrexed, the median PFS was 4.2 months. For docetaxel, the median PFS was 2.6 months. 
* Based on the Cox proportional hazards stratified analysis. 
* Based on the stratified log-rank test. 
* Based on the stratified Cochran-Mantel-Haenszel test.

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

14.2 ROS1-Positive Metastatic NSCLC

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, adequate organ function, and measurable disease. The efficacy outcome measures were ORR and DOR according to RECIST version 1.1 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 ≥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 - Efficacy Results*

<table>
<thead>
<tr>
<th>Efficacy Parameters</th>
<th>IRR (N=50)</th>
<th>Investigator-Assessed (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate (95% CI)</td>
<td>66% (51, 79)</td>
<td>72% (58, 84)</td>
</tr>
<tr>
<td>Complete Response, n</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Partial Response, n</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Duration of Response</td>
<td>Median, Months (95% CI)</td>
<td>NR (14.5, NR)</td>
</tr>
</tbody>
</table>

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

16 HOW SUPPLIED/STORAGE AND HANDLING

- 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: NDC 0069-8140-20

- 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: NDC 0069-8141-20

Store at room temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

16 Drug Interactions

Inform patients to avoid grapefruit or grapefruit juice while taking XALKORI. Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions (7)].

16 Dosing and Administration

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.

16 Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.6) and Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with XALKORI and for at least 45 days after the final dose [see Use in Specific Populations (8.3)].

16 Females and Males of Reproductive Potential

Advise females and males of reproductive potential of the potential for reduced fertility from XALKORI [see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)].

Advise male patients with female partners of reproductive potential to use condoms during treatment with XALKORI and for at least 90 days after the final dose [see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)].

16 Lactation

Advise females not to breastfeed during treatment with XALKORI and for 45 days after the final dose [see Use in Specific Populations (8.3)].

16 Infertility

Advise females and males of reproductive potential of the potential for reduced fertility from XALKORI [see Use in Specific Populations (8.3)].

This product’s labeling may have been updated. For full prescribing information, please visit www.XALKORI.com.
What is the most important information I should know about XALKORI?

XALKORI may cause serious side effects, including:

- **Liver problems.** XALKORI may cause life-threatening liver injury that may lead to death. Your healthcare provider should do blood tests at least every month to check your liver during treatment with XALKORI. Tell your healthcare provider right away if you get any of the following new or worsening symptoms:
  - yellowing of your skin or the white part of your eyes
  - decreased appetite
  - severe tiredness
  - pain on the right side of your stomach
  - dark or brown (tea color) urine
  - nausea or vomiting
  - bleed or bruise more easily than normal
  - itching

- **Lung problems (pneumonitis).** XALKORI may cause life-threatening lung problems that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening symptoms, including:
  - trouble breathing or shortness of breath
  - cough with or without mucus
  - fever

- **Heart problems.** XALKORI may cause very slow, very fast, or abnormal heartbeats. Your healthcare provider may check your heart during treatment with XALKORI. Tell your healthcare provider right away if you feel dizzy or faint or have abnormal heartbeats. Tell your healthcare provider if you take any heart or blood pressure medicines.

- **Vision problems.** Vision problems are common with XALKORI. These problems usually happen within 1 week of starting treatment with XALKORI. Vision problems with XALKORI can be severe and may cause partial or complete loss of vision in one or both eyes. Your healthcare provider may stop XALKORI and refer you to an eye healthcare provider if you develop severe vision problems during treatment with XALKORI. Tell your healthcare provider right away if you have any loss of vision or any change in vision, including:
  - double vision
  - light hurting your eyes
  - seeing flashes of light
  - new or increased floaters
  - blurry vision

- **See “What are possible side effects of XALKORI?” for more information about side effects.**

What is XALKORI?

XALKORI is a prescription medicine that is used to treat people with non-small cell lung cancer (NSCLC) that has spread to other parts of the body and is caused by a defect in either a gene called ALK (anaplastic lymphoma kinase) or a gene called ROS1. It is not known if XALKORI is safe and effective in children.

What should I tell my healthcare provider before taking XALKORI?

**Before you take XALKORI, tell your healthcare provider if you:**

- have heart problems, including a condition called long QT syndrome
- have liver or kidney problems
- have vision or eye problems
- have any other medical conditions
- are pregnant, or plan to become pregnant. XALKORI can harm your unborn baby.
  - **Females** who are able to become pregnant should use effective birth control during treatment with XALKORI and for at least 45 days after the final dose of XALKORI.
  - **Males** who have female partners who can become pregnant should use condoms during treatment with XALKORI and for at least 90 days after the final dose of XALKORI.
  - Talk to your healthcare provider about birth control methods that may be right for you.
  - If you or your partner becomes pregnant, tell your healthcare provider right away.
- are breastfeeding or plan to breastfeed. It is not known if XALKORI passes into your breast milk. Do not breastfeed during treatment with XALKORI and for 45 days after the final dose. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements.

How should I take XALKORI?

- Take XALKORI exactly as your healthcare provider tells you.
- Swallow XALKORI capsules whole.
- You may take XALKORI with or without food.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with XALKORI if you have certain side effects. Do not change your dose or stop taking XALKORI unless your healthcare provider tells you.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose (within 6 hours), just take your next dose at your regular time.
- If you vomit after taking a dose of XALKORI, do not take an extra dose, just take your next dose at your regular time.
What should I avoid while taking XALKORI?

- You should not drink grapefruit juice or eat grapefruit during your treatment with XALKORI. It may increase the amount of XALKORI in your blood to a harmful level.
- XALKORI can cause changes in your vision, dizziness, and tiredness. If you have these symptoms avoid driving a car, using machinery, or doing anything that needs you to be alert.

What are the possible side effects of XALKORI?

XALKORI may cause serious side effects, including:

- See “What is the most important information I should know about XALKORI?”

The most common side effects of XALKORI include:

- vision problems. See “What is the most important information I should know about XALKORI?”
- nausea
- diarrhea
- vomiting
- swelling of your hands, feet, face, and eyes
- constipation
- increased liver function blood test results. See “What is the most important information I should know about XALKORI?”
- tiredness
- decreased appetite
- upper respiratory infection
- dizziness
- feeling of numbness or tingling in the extremities

XALKORI may cause decreased fertility in females and males. In females, this could affect your ability to become pregnant. In males, this could affect your ability to father a child. Talk to your healthcare provider if you have concerns about fertility.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of XALKORI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XALKORI?

- Store XALKORI at room temperature between 68°F to 77°F (20°C to 25°C).

Keep XALKORI and all medicines out of the reach of children.

General information about XALKORI

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XALKORI for a condition for which it was not prescribed. Do not give XALKORI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about XALKORI that is written for health professionals.

What are the ingredients in XALKORI?

Active ingredient: crizotinib

Inactive ingredients: colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, and magnesium stearate.

Pink opaque capsule shell contains: gelatin, titanium dioxide, and red iron oxide.

White opaque capsule shell contains: gelatin and titanium dioxide.

Printing ink contains: shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

Distributed by

Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

LAB-0441-8.0

For more information, go to www.XALKORI.com.

This Patient Information has been approved by the U.S. Food and Drug Administration.