Guideline Highlights

CAP/IASLC/AMP

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

This booklet does not reflect all the recommendations contained within the full guideline. The selected excerpts should not be used to replace the full guideline for clinical decision making.

Abbreviations: ALK, anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; CAP, College of American Pathologists; EGFR, epidermal growth factor receptor; IASLC, International Association for the Study of Lung Cancer.

XALKORI® (crizotinib) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

Please see Important Safety Information on pages 8-10 and full Prescribing Information at the end of this document.

For more information, please visit www.XALKORIhcp.com.
Who should be tested?

Clinical characteristics should not determine which patients are tested

ALK molecular testing should be used to select patients for ALK-targeted tyrosine kinase inhibitor therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics (eg, age, sex, ethnicity, smoking history) (1.1b: Recommendation).

Histology may determine which patients should be tested

In the setting of lung cancer resection specimens, EGFR and ALK testing

- Is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component, regardless of histologic grade (1.2: Recommendation)
- Is not recommended for fully excised lung cancer specimens that lack any adenocarcinoma component, such as pure squamous cell carcinomas, pure small cell carcinomas, or large cell carcinomas lacking any immunohistochemistry (IHC) evidence of adenocarcinoma differentiation (1.2: Recommendation)

In the setting of more limited lung cancer specimens (biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous or small cell histology but clinical criteria (eg, young age, lack of smoking history) may be useful in selecting a subset of these samples for testing (1.3: Recommendation).

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For more information, please visit www.XALKORIhcp.com.
When should patients be tested?

Disease stage at diagnosis should be taken into account

ALK rearrangement testing should be ordered at the time of diagnosis for patients presenting with advanced-stage disease (stage IV according to the 7th edition TNM staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower-stage disease but were not previously tested (2.1b: Suggestion).

For these patients, timely diagnosis is critical and molecular testing should be initiated as soon as a diagnosis of adenocarcinoma is established (2.1b: Suggestion).

Reflex testing, a testing policy that does not require a separate clinician order for each case, is appropriate if agreed on by the lung cancer care team and may help to ensure expedited and consistent routing of specimens for molecular testing (2.1b: Suggestion).

ALK testing of tumors at diagnosis from patients presenting with stage I, II, or III disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team (2.2b: Expert consensus opinion).

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; TNM, tumor node metastasis.

XALKORI® (crizotinib) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.
What samples should be provided for ALK testing?

Sufficient tissue of adequate quality is necessary for testing

To determine EGFR and ALK status for initial treatment selection, primary tumors or metastatic lesions are equally suitable for testing (1.4: Recommendation).

Tissue should be prioritized for EGFR and ALK testing (2.3: Recommendation).

It is critical to retain sufficient material for molecular analysis and to be judicious in the use of sections for IHC studies, histochemical stains, or deeper levels that may not be essential to establish a histopathologic diagnosis (2.3: Recommendation).

A pathologist should be involved in the selection of sections for ALK FISH testing by assessing tumor architecture, cytology, and specimen quality (9.3: Expert consensus opinion).

Specimen requirements for ALK FISH are generally similar to those for EGFR mutation testing: formalin fixation is acceptable, specimens should have enough cancer cells to analyze clearly, and DNA-damaging fixatives or acidic decalcifying agents should be avoided, as should specimens with abundant necrosis. Unlike EGFR mutation testing, however, FISH testing can be problematic when performed on alcohol-fixed samples (9.3: Expert consensus opinion).

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How long should the testing process take?

Results should be available within 2 weeks

EGFR and ALK results should be available within 2 weeks (10 working days) of receiving the specimen in the testing laboratory (3.1: Expert consensus opinion).

A TAT goal of 1 week (5 working days) should be established for EGFR and ALK testing, up to a maximum TAT of 2 weeks (10 working days). This TAT refers to the period from the receipt of suitable material by the molecular pathology laboratory where the testing is performed to the reporting of the final results to the clinical care team, and is not related to the period of time between when a patient undergoes a diagnostic procedure and when a specimen is submitted to the laboratory for testing (3.1: Expert consensus opinion).

Laboratories with average TATs beyond 2 weeks need to make available a more rapid test—either in-house or through a reference laboratory—in instances of clinical urgency (3.2: Expert consensus opinion).

Laboratory departments should establish processes to ensure that specimens that have a final histopathologic diagnosis are sent to outside molecular pathology laboratories within 3 working days of receiving requests and to intramural molecular pathology laboratories within 24 hours (3.3: Expert consensus opinion).

Abbreviations: FISH, fluorescence in situ hybridization; TAT, turnaround time.

XALKORI® (crizotinib) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.
Molecular testing is important to determine who may benefit from a biomarker-driven therapy

➤ **ALK** rearrangement, a therapeutic target in NSCLC, can contribute to cell proliferation and tumor survival$^{2-5}$

--- **EGFR** and **ALK** are associated with approved therapies$^{6-8}$

➤ As an ALK inhibitor, XALKORI has been shown to block important growth and survival pathways in tumors, which may lead to regression or stabilization of tumors$^{9}$

**XALKORI® (crizotinib) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.**

**SELECTED SAFETY INFORMATION**

**Hepatotoxicity:** Drug-induced hepatotoxicity with fatal outcome occurred in 0.2% of patients treated with XALKORI across clinical trials (n=1225). Transaminase elevations generally occurred within the first 2 months of treatment. Monitor with liver function tests including ALT 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 or 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.
There is no “one type” of patient who has ALK-positive NSCLC

➤ In XALKORI studies, the ALK fusion gene was identified across ages, genders, and ethnicities
   — It was identified predominantly in patients with adenocarcinoma but was found in other histologic types
   — It was identified more frequently in never-smokers but was also seen in former and current smokers

APPROXIMATELY

3%-5%

OF PATIENTS WITH NSCLC HAVE AN ALK-POSITIVE TUMOR

➤ Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK positivity in tumor specimens as detected by an FDA-approved test

*Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.

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For more information, please visit www.XALKORIhcp.com.
IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Drug-induced hepatotoxicity with fatal outcome occurred in 0.2% of patients treated with XALKORI across clinical trials (n=1225). Transaminase elevations generally occurred within the first 2 months of treatment. Monitor with liver function tests including ALT 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 or 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.

Interstitial Lung Disease (Pneumonitis): Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with XALKORI. Across clinical trials (n=1225), 2.5% of XALKORI-treated patients had any grade ILD, 0.9% had Grade 3/4, and 0.5% had fatal cases. These cases generally occurred within 2 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 in patients treated with XALKORI. Across clinical trials (n=1225), QTc prolongation (all grades) was observed in 2.7% of patients and QTc >500 ms on at least 2 separate electrocardiograms (ECGs) occurred in 1.4% of patients. Avoid use of XALKORI in patients with congenital long QT syndrome. Consider periodic monitoring with 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 in patients receiving XALKORI. Across clinical trials, bradycardia with a heart rate <50 beats per minute (bpm) occurred in 11% of patients treated with XALKORI (n=1174). Avoid using XALKORI in combination with other agents known to cause bradycardia to the extent possible. Monitor heart

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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. Otherwise, temporarily suspend and resume or dose-reduce XALKORI as indicated.

**Embryofetal Toxicity:** XALKORI can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid pregnancy while receiving XALKORI. If the patient or patient’s partner becomes pregnant while taking this drug, apprise the patient of potential hazard to the fetus.

**Adverse Reactions:** Safety was evaluated in a phase 3 study in patients with ALK-positive metastatic NSCLC randomized to XALKORI (n=172) or chemotherapy (n=171). Serious adverse reactions were reported in 37.2% patients treated with XALKORI and 23.4% 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 occurred in 9 (5%) patients, consisting of acute respiratory distress syndrome, arrhythmia, dyspnea, ILD, pneumonia, pneumonitis, pulmonary embolism, respiratory failure, and sepsis. Common adverse reactions (all grades) occurring in ≥25% and more commonly (≥5%) in patients treated with XALKORI vs chemotherapy were vision disorder (60% vs 9%), diarrhea (60% vs 19%), nausea (55% vs 37%), vomiting (47% vs 18%), constipation (42% vs 23%), edema (31% vs 16%), upper respiratory infection (26% vs 13%), and dysgeusia (26% vs 9%). Grade 3/4 events occurring at a higher incidence with XALKORI vs chemotherapy and at >2% incidence were syncope (3% vs 0%), QT prolongation (3% vs 0%), and pulmonary embolism (5% vs 2%). In patients treated with XALKORI vs chemotherapy, the following occurred: elevation of ALT (any grade [76% vs 38%] or Grade 3/4 [17% vs 4%]); elevation of AST (any grade [61% vs 33%] or Grade 3/4 [9% vs 0%]); neutropenia (any grade [49% vs 28%] or Grade 3/4 [12% vs 12%]); lymphopenia (any grade [51% vs 60%] or Grade 3/4 [9% vs 25%]). In patients treated with XALKORI vs chemotherapy, renal cysts occurred (4% vs 1%). Decreased appetite (27%), fatigue (27%), and neuropathy (19%) also occurred in patients taking XALKORI.

*Please see full Prescribing Information at the end of this document.*
IMPORTANT SAFETY INFORMATION (CONT’D)

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.

Nursing Mothers: Given the potential for serious adverse reactions in nursing infants, consider whether to discontinue nursing or discontinue XALKORI.

Hepatic Impairment: XALKORI has not been studied in patients with hepatic impairment. As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Use caution in patients with hepatic impairment.

Renal Impairment: 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. No starting dose adjustment is needed for patients with mild and moderate renal impairment.

Please see full Prescribing Information at the end of this document.

For more information, please visit www.XALKORIhcp.com.
The discovery and clinical relevance of **EGFR** and **ALK** have impacted how NSCLC is diagnosed and treated

Evidence-based guideline recommendations for the molecular testing of lung cancers are available from CAP/IASLC/AMP

These guideline recommendations may aid in the implementation and standardization of molecular testing in your institution.

- Clinical characteristics should not determine which patients are tested for **EGFR** and **ALK**
- Disease stage at diagnosis should be taken into account to determine when a patient’s sample is tested
- Sufficient tissue of adequate quality is necessary for molecular testing
- Molecular test results should be available within 2 weeks

See inside for more detailed recommendations from the CAP/IASLC/AMP Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors.

Please see Important Safety Information on pages 8-10 and full Prescribing Information at the end of this document.

References:
Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Summary of Recommendations

SECTION I. WHEN SHOULD MOLECULAR TESTING OF LUNG CANCERS BE PERFORMED?

QUESTION 1. WHICH PATIENTS SHOULD BE TESTED FOR EGFR MUTATIONS AND ALK REARRANGEMENTS?

1.1a: Recommendation: EGFR molecular testing should be used to select patients for EGFR-targeted TKI therapy, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

1.1b: Recommendation: ALK molecular testing should be used to select patients for ALK-targeted TKI, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

1.2: Recommendation: In the setting of lung cancer resection specimens, EGFR and ALK testing is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component, regardless of histologic grade.

In the setting of fully excised lung cancer specimens, EGFR and ALK testing is not recommended in lung cancers that lack any adenocarcinoma component, such as “pure” squamous cell carcinomas, “pure” small cell carcinomas, or large cell carcinomas lacking any immunohistochemistry (IHC) evidence of adenocarcinoma differentiation.

1.3: Recommendation: In the setting of more limited lung cancer specimens (biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous or small cell histology but clinical criteria (eg, young age, lack of smoking history) may be useful in selecting a subset of these samples for testing.

1.4: Recommendation: To determine EGFR and ALK status for initial treatment selection, primary tumors or metastatic lesions are equally suitable for testing.

1.5: Expert consensus opinion: For patients with multiple, apparently separate, primary lung adenocarcinomas, each tumor may be tested but testing of multiple different areas within a single tumor is not necessary.

QUESTION 2. WHEN SHOULD A PATIENT SPECIMEN BE TESTED FOR EGFR MUTATION OR ALK REARRANGEMENT?

2.1a: Recommendation: EGFR mutation testing should be ordered at the time of diagnosis for patients presenting with advanced-stage disease (stage IV according to the 7th edition TNM staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower-stage disease but were not previously tested.

2.1b: Suggestion: ALK rearrangement testing should be ordered at the time of diagnosis for patients presenting with advanced-stage disease (stage IV according to the 7th edition TNM staging system) who are suitable for therapy or at time of recurrence or progression in patients who originally presented with lower-stage disease but were not previously tested.

2.2a: Expert consensus opinion: EGFR testing of tumors at diagnosis from patients presenting with stage I, II, or III disease is encouraged but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.
2.2b Expert consensus opinion: ALK testing of tumors at diagnosis from patients presenting with stage I, II, or III disease is encouraged, but the decision to do so should be made locally by each laboratory, in collaboration with its oncology team.

2.3: Recommendation: Tissue should be prioritized for EGFR and ALK testing.

**QUESTION 3. HOW RAPIDLY SHOULD TEST RESULTS BE AVAILABLE?**

3.1: Expert consensus opinion: EGFR and ALK results should be available within 2 weeks (10 working days) of receiving the specimen in the testing laboratory.

3.2: Expert consensus opinion: Laboratories with average turnaround times beyond 2 weeks need to make available a more rapid test—either in-house or through a reference laboratory—in instances of clinical urgency.

3.3: Expert consensus opinion: Laboratory departments should establish processes to ensure that specimens that have a final histopathologic diagnosis are sent to outside molecular pathology laboratories within 3 working days of receiving requests and to intramural molecular pathology laboratories within 24 hours.

**SECTION II. HOW SHOULD EGFR TESTING BE PERFORMED?**

**QUESTION 4. HOW SHOULD SPECIMENS BE PROCESSED FOR EGFR MUTATION TESTING?**

4.1: Expert consensus opinion: Pathologists should use formalin-fixed, paraffin-embedded (FFPE) specimens or fresh, frozen, or alcohol-fixed specimens for PCR-based EGFR mutation tests. Other tissue treatments (e.g., acidic or heavy metal fixatives, or decalcifying solutions) should be avoided in specimens destined for EGFR testing.

4.2: Expert consensus opinion: Cytologic samples are also suitable for EGFR and ALK testing, with cell blocks being preferred over smear preparations.

**QUESTION 5. WHAT ARE THE SPECIMEN REQUIREMENTS FOR EGFR TESTING?**

5.1: Expert consensus opinion: Pathologists should determine the adequacy of specimens for EGFR testing by assessing cancer cell content and DNA quantity and quality.

5.2: Expert consensus opinion: Each laboratory should establish the minimum proportion and number of cancer cells needed for mutation detection during validation.

5.3: Expert consensus opinion: A pathologist should assess the tumor content of each specimen and either perform, or guide a trained technologist to perform, microdissection for tumor cell enrichment as needed.

**QUESTION 6. HOW SHOULD EGFR TESTING BE PERFORMED?**

6.1: Recommendation: Laboratories may use any validated EGFR testing method with sufficient performance characteristics.

6.2: Expert consensus opinion: Laboratories should use EGFR test methods that are able to detect mutations in specimens with at least 50% cancer cell content, although laboratories are strongly encouraged to use (or have available at an external reference laboratory) more sensitive tests that are able to detect mutations in specimens with as little as 10% cancer cells.
6.3: Expert consensus opinion: Clinical EGFR mutation testing should be able to detect all individual mutations that have been reported with a frequency of at least 1% of EGFR-mutated lung adenocarcinomas.

6.4: Recommendation: Immunohistochemistry for total EGFR is not recommended for selection of EGFR TKI therapy.

6.5: Recommendation: EGFR copy number analysis (ie, FISH or CISH) is not recommended for selection of EGFR TKI therapy.

**QUESTION 7. WHAT IS THE ROLE OF KRAS ANALYSIS IN SELECTING PATIENTS FOR TARGETED THERAPY WITH EGFR TKIs?**

7.1: Recommendation: KRAS mutation testing is not recommended as a sole determinant of EGFR TKI therapy.

**QUESTION 8. WHAT ADDITIONAL TESTING CONSIDERATIONS ARE IMPORTANT IN THE SETTING OF SECONDARY OR ACQUIRED EGFR TKI RESISTANCE?**

8.1: Recommendation: If a laboratory performs testing on specimens from patients with acquired resistance to EGFR kinase inhibitors, such tests should be able to detect the secondary EGFR T790M mutation in as few as 5% of cells.

**SECTION III. HOW SHOULD ALK TESTING BE PERFORMED?**

**QUESTION 9. WHAT METHODS SHOULD BE USED FOR ALK TESTING?**

9.1: Recommendation: Laboratories should use an ALK FISH assay using dual-labeled break-apart probes for selecting patients for ALK TKI therapy; ALK immunohistochemistry, if carefully validated, may be considered as a screening methodology to select specimens for ALK FISH testing.

9.2: Recommendation: RT-PCR is not recommended as an alternative to FISH for selecting patients for ALK inhibitor therapy.

9.3: Expert consensus opinion: A pathologist should be involved in the selection of sections for ALK FISH testing, by assessing tumor architecture, cytology, and specimen quality.

9.4: Expert consensus opinion: A pathologist should participate in the interpretation of ALK FISH slides, either by performing the analysis directly or by reviewing the interpretations of cytogeneticists or technologists with specialized training in solid tumor FISH analysis.

9.5: Expert consensus opinion: Testing for secondary mutations in ALK associated with acquired resistance to ALK inhibitors is not currently required for clinical management.

**SECTION IV: SHOULD OTHER GENES BE ROUTINELY TESTED IN LUNG ADENOCARCINOMA?**

**QUESTION 10. ARE OTHER MOLECULAR MARKERS SUITABLE FOR TESTING IN LUNG CANCER?**

10.1a: Recommendation: Testing for EGFR should be prioritized over other molecular markers in lung adenocarcinoma.

10.1b: Suggestion: After EGFR testing, testing for ALK should be prioritized over other proposed molecular markers in lung adenocarcinoma, for which published evidence is insufficient to support testing guideline development at the present time.
SECTION V: HOW SHOULD MOLECULAR TESTING OF LUNG ADENOCARCINOMAS BE IMPLEMENTED AND OPERATIONALIZED?

QUESTION 11. MUST ALL ADENOCARCINOMAS BE TESTED FOR BOTH EGFR AND ALK?

11.1: Expert consensus opinion: Laboratories may implement testing algorithms to enhance the efficiency of molecular testing of lung adenocarcinomas, provided the overall turnaround time requirements are met.

QUESTION 12. HOW SHOULD EGFR AND ALK RESULTS BE REPORTED?

12.1: Expert consensus opinion: EGFR mutation testing reports and ALK FISH reports should include a results and interpretation section readily understandable by oncologists and by nonspecialist pathologists.

QUESTION 13. HOW SHOULD EGFR AND ALK TESTING BE VALIDATED?

13.1: Expert consensus opinion: EGFR and ALK testing validation should follow the same guidelines as for other molecular diagnostics and FISH tests.

QUESTION 14. HOW SHOULD QUALITY ASSURANCE BE MAINTAINED?

14.1: Expert consensus opinion: Laboratories should follow similar quality control and quality assurance policies and procedures for EGFR and ALK testing in lung cancers as for other clinical laboratory assays. In particular, laboratories performing EGFR and ALK testing for TKI therapy should enroll in proficiency testing, if available.

Content is adapted from Table 3 of the Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors, with permission from the College of American Pathologists.

Abbreviations: ALK, anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; CAP, College of American Pathologists; CISH, chromogenic in situ hybridization; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; IASLC, International Association for the Study of Lung Cancer; KRAS, Kirsten rat sarcoma; PCR, polymerase chain reaction; RT-PCR, reverse transcription-polymerase chain reaction; TKI, tyrosine kinase inhibitor; TNM, tumor node metastasis.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XALKORI® safely and effectively. See full prescribing information for XALKORI.
XALKORI® (crizotinib) Capsules, oral
Initial U.S. Approval: 2011

1 INDICATIONS AND USAGE
XALKORI is a kinase inhibitor indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. (1)

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients for the treatment of metastatic NSCLC with XALKORI based on the presence of ALK positivity in tumor specimens [see Indications and Usage (1) and Clinical Studies (14)]. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.

2.2 Recommended Dosing
The recommended dose of XALKORI in patients with severe renal impairment (creatinine clearance <30 mL/min) not requiring dialysis is 250 mg orally, once daily. 

2.3 Dose Modification
If contributing concomitant medication is adjusted, resume at reduced dose upon recovery to baseline or to a heart rate of 60 bpm or above. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.

2.4 Overdose
No specific treatments are available for XALKORI overdosage. Monitor cardiac rhythm and vital signs. Bradycardiaa (symptomatic, may be severe and medically significant, medical intervention indicated) Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.

Table 1. XALKORI Dose Modification – Hematologic Toxicities*

<table>
<thead>
<tr>
<th>CTCAE Grade</th>
<th>XALKORI Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>Withhold until recovery to Grade 2 or less, then resume at the same dose schedule</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Withhold until recovery to Grade 2 or less, then resume at next lower dose</td>
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</tbody>
</table>

*Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

Table 2. XALKORI Dose Modification – Non-Hematologic Toxicities

<table>
<thead>
<tr>
<th>Criteria</th>
<th>XALKORI Dosing</th>
</tr>
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<tbody>
<tr>
<td>ALT or AST elevation greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 1.5 times ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Total bilirubin greater than 3 times ULN with concurrent total bilirubin elevation greater than 1.5 times ULN (in the absence of cholestasis or hemolysis)</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Any Grade drug-related interstitial lung disease/pneumonitis</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>QTc greater than 500 ms on at least 2 separate ECGs</td>
<td>Withhold 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>
</tbody>
</table>

Adverse Events (≥25%)

- Hematologic toxicity: Fatality hematotoxicity occurred in 0.2% of patients. Monitor with periodic liver testing. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Occurred in 2% of patients. Permanently discontinue in patients with ILD/pneumonitis. (5.2)
- QT Interval Prolongation: Occurred in 2.7% of patients. Monitor with electrocardiograms and electrolytes in patients who have a history of or predisposition for QTc prolongation, or who are taking medications that prolong QT. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (5.3)
- Bradycardia: XALKORI can cause bradycardia. Monitor heart rate and blood pressure regularly. Temporarily suspend, dose reduce, or permanently discontinue XALKORI. (5.4)
- Embryofetal Toxicity: XALKORI can cause fetal harm when administered to a pregnant woman. (5.5, 8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2014
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)]
- Intestinal 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)]

6.1 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.

Safety evaluation of XALKORI is based on more than 1200 patients with ALK-positive metastatic NSCLC who received XALKORI as monotherapy at a starting oral dose of 250 mg twice daily continuously.

The most common adverse reactions (≥25%) of XALKORI are vision disorder, nausea, diarrhea, vomiting, constipation, edema, elevated transaminases, and fatigue.

ALK-positive metastatic NSCLC—Study

The data in Table 3 are derived from 343 patients with ALK-positive metastatic NSCLC enrolled in a randomized, multicenter, active-controlled, open-label trial (Study 1). 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/m² (n=89) or docetaxel 75 mg/m² (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 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 547 patients who were randomized to study treatment, 343 received at least one dose of study treatment, the median age was 50 years; 84% of patients in the XALKORI arm and 87% of patients in the chemotherapy arm were younger than 65 years.

A total of 57% of patients on XALKORI and 55% of chemotherapy-treated patients were female. Forty-six percent (46%) of XALKORI-treated and 45% of chemotherapy-treated patients were from Asia. Serious adverse reactions reported in 24 patients (7.2%) treated with XALKORI and 40 patients (23.4%) 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 interstitial lung disease (ILD; 2.9%). Fatal adverse reactions in XALKORI-treated patients in Study 1 occurred in 9 (5%) patients, consisting of: acute respiratory distress syndrome, arrhythmia, dyspnea, pneumonia, pneumonitis, pulmonary embolism, ILD, respiratory failure, and sepsis.

Bradycardia occurred in 16% of XALKORI-treated patients. The most frequent adverse reactions that led to dose reduction in the patients treated with XALKORI were alanine aminotransferase (ALT) elevation (7.6%) including some patients with concurrent aspartate aminotransferase (AST) elevation, ALT prolongation (2.9%), and neutropenia (2.3%). Discontinuation of therapy in XALKORI-treated patients for adverse reactions was 17.0%.

The most frequent adverse reactions that led to discontinuation in XALKORI-treated patients were ILD (1.7%), ALT and AST elevation (1.2%), dyspnea (1.2%), and pulmonary embolism (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=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>Nervous System Disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision disorder</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QT prolonged</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>47</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>55</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>42</td>
<td>2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>31</td>
<td>0</td>
</tr>
</tbody>
</table>

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>Bradycardia (life-threatening consequences, urgent intervention indicated)</td>
<td>Permanently discontinue if no contributing concomitant medication is identified</td>
</tr>
</tbody>
</table>

* Heart rate less than 60 beats per minute (bpm).
* Permanently discontinue for recurrence.

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

3 DOSAGE FORMS AND STRENGTHS

- 250 mg capsules
- 200 mg capsules
- 500 mg capsules
- 250 mg tablets

3.2 Interstitial Lung Disease (Pneumonitis)

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with XALKORI. Across clinical trials (n=1225), 31 XALKORI-treated patients (2.5%) had any grade ILD. 11 patients (0.9%) had Grade 3 or 4, and 6 patients (0.5%) had fatal cases. These cases generally occurred within 2 months after the initiation of treatment.

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 (2.3) and Adverse Reactions (6.2)).

5.3 QT Interval Prolongation

QTc prolongation can occur in patients treated with XALKORI. Across clinical trials (n=1225), QTc prolongation (all grades) was observed in 94 (2.7%) patients and QTc greater than 500 ms on at least 2 separate ECGs occurred in 17 (1.4%) patients.

Avoid use of XALKORI in patients with congenital long QT syndrome. Consider periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, bodyweight abnormalities, or who are taking medications that are known to prolong the QT interval. Permanently discontinue XALKORI in patients who develop QTc greater than 60 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Withhold XALKORI if 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 equivalent.

5.4 Bradycardia

Symptomatic bradycardia can occur in patients receiving XALKORI. Across clinical trials, bradycardia with a heart rate less than 60 beats per minute occurred in 11% of 1174 patients treated with XALKORI. In Study 1, Grade 3 syncope occurred in 2.9% of XALKORI-treated patients and in none of the chemotherapy-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 (6.2)).

5.5 Embryofetal Toxicity

XALKORI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. In nonclinical studies in rats, crozotinib was embryotoxic and fetotoxic at exposures similar to those observed in humans at the recommended clinical dose of 250 mg twice daily. There are no adequate and well-controlled studies in pregnant women using XALKORI. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus [see Use in Specific Populations (8.1)].
Additional adverse reactions occurring at an overall incidence between 1% and 30% in patients treated with XALKORI included decreased appetite (27%), fatigue (27%), neuropraxia (19%); dysesthesia, gait disturbance, hypoesthesia, muscular weakness, naevus, peripheral neuropraxia, parasthesia, peripheral sensory neuropathy, polyneuropathy, burning sensation in skin), rash (9%), ILD (4%), acute respiratory distress syndrome, IUD, pneumonitis), renal cyst (4%), and hepatic failure (1%).

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Crizotinib Any Grade</th>
<th>Crizotinib Grade 3/4</th>
<th>Chemotherapy Any Grade</th>
<th>Chemotherapy Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemotology</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>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category [see Warnings and Precautions (5.5)]

XALKORI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies of XALKORI in pregnant women. In nonclinical studies in rats, crizotinib was embryotoxic and fetotoxic at exposures similar to those of human dose. Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

8.4 Pediatric Use

The safety and efficacy of XALKORI in pediatric patients has not been established. Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 5.4 times the AUC in adult patients at the recommended human dose). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

8.6 Hepatic Impairment

XALKORI has not been studied in patients with hepatic impairment. As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Clinical studies excluded patients with AST or ALT greater than 2.5 x ULN, or greater than 5 x ULN, if due to liver metastases. Patients with total bilirubin greater than 1.5 x ULN were also excluded. Therefore, use caution with patients in hepatic impairment [see Clinical Pharmacology (12.3)].

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 C_{26}H_{28}N_O. The molecular weight is 450.4 Daltons. Crizotinib is described chemically as (R)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(pipеридин-4-yl)-1H-pyrrozol-4-yl]pyridin-2-amine.

The chemical structure of crizotinib is shown below:

![Chemical Structure of Crizotinib](image)

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

XALKORI capsules are supplied as printed hard-shell capsules containing 250 mg or 200 mg of crizotinib together with colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate, and hard gelatin capsule shells as inactive ingredients. The white 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 potassic carmine, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGF), 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 kinases can contribute to increased cell proliferation and survival in tumors expressing these proteins. Crizotinib inhibits ALK, ROS1, and c-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing xenografts that expressed EML4- or NPM-ALK fusion proteins or c-Met.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The QT interval prolongation potential of crizotinib was assessed in all patients who received XALKORI 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady state to evaluate the effect of crizotinib on QT intervals. Sixteen of 1167 patients (1.4%) were found to have QTc (corrected QT by the Fridericia method) greater than or equal to 500 msec and 51 of 1350 patients (4.4%) had an increase from baseline QTc greater than or equal to 60 msec by automated machine-read evaluation of ECG. A pharmacokinetic/pharmacodynamic analysis suggested a concentration-dependent increase in QTc [see Warnings and Precautions (5.3)].

Advise women of childbearing potential to avoid becoming pregnant while receiving XALKORI. Women of childbearing potential who are receiving this drug, or partners of women of childbearing potential receiving this drug, should use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. If this drug is used during pregnancy, or if the patient or their partner becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and efficacy of XALKORI in pediatric patients has not been established. Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 5.4 times the AUC in adult patients at the recommended human dose). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

8.5 Geriatric Use

Of XALKORI treated patients in Study 1, 27 (16%) were 65 years or older, in Study 2, 152 (16%) were 65 years or older, and in Study 3, 15 (13%) were 65 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

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 C_{26}H_{28}N_O. The molecular weight is 450.4 Daltons. Crizotinib is described chemically as (R)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(pipеридин-4-yl)-1H-pyrrozol-4-yl]pyridin-2-amine.

The chemical structure of crizotinib is shown below:
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 crizotinib 250 mg twice daily, steady state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8. Steady-state systemic exposure (Cmax and AUClast) increased to 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 AUC00 and 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 (Vss) of crizotinib was 1,772 L following intravenous administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma.

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

Metabolism
Crizotinib is predominantly metabolized by CYP3A4/5. The primary metabolic pathways in humans were oxidation of the piperidine ring to crizotinib lactam and O-dealkylation, with subsequent Phase 2 conjugation of O-dealkylated metabolites.

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

Following the administration of a single 250 mg radiolabeled crizotinib dose to healthy subjects, 62% and 22% of the administered dose recovered in feces and urine, respectively. Unchanged crizotinib represented approximately 53% and 2.3% of the administered dose in feces and urine, respectively.

The mean apparent clearance (CL/F) of crizotinib was lower at steady state (60 L/h) after steady-state crizotinib exposure has not been evaluated [see Drug Interactions (7.1)].

XALKORI has been studied in patients with severe renal impairment.

An in vitro study suggests that clinical drug-drug interactions as a result of crizotinib-mediated inhibition of the metabolism of substrates for CYP3A1, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 are unlikely to occur.

Crizotinib is an inhibitor of CYP2B6 in vitro.

An in vitro study suggests that clinical drug-drug interactions as a result of crizotinib-mediated inhibition of the metabolism of substrates for CYP1A2, CYP2B6, CYP2C9, CYP3A4, and CYP2D6 are unlikely to occur. UGT substrates: In vitro studies suggest that clinical drug-drug interactions as a result of crizotinib-mediated inhibition of the metabolism of drugs that are substrates for UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 are unlikely to occur.

Substrates of transporters: Crizotinib inhibited P-glycoprotein (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 cation transporter 1 (OCT1), and renal uptake transporter, organic cation transporter 2 (OCT2), in vitro at clinically relevant concentrations.

Therefore, crizotinib has the potential to increase plasma concentrations of coadministered drugs that are substrates of OCT1 or OCT2.

Crizotinib did not inhibit the human hepatic uptake transport proteins OATP1B1 or OATP1B3, or the renal uptake transport proteins OAT1 or OAT3 in vitro at clinically relevant concentrations.

Effect on other transport proteins: Crizotinib did not inhibit the hepatic efflux bile salt export pump transporter (BSEP) in vitro at clinically relevant concentrations.

Specific Populations

Hepatic Impairment: As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. However, XALKORI has not been studied in patients with hepatic impairment. Clinical studies excluded patients with ALT or AST greater than 2.5 x ULN or greater than 5 x ULM for due to liver metastases. Patients with total bilirubin greater than 1.5 x ULM were also excluded [see Use in Specific Populations (8.6)]. The population pharmacokinetic analysis using the data from Studies 1, 2 and 3 suggested that baseline total bilirubin (0.1 to 2.1 mg/dL) or AST levels (7 to 124 U/L) did not have a clinically relevant effect on the exposure of crizotinib.

Renal impairment: The pharmacokinetics of crizotinib were evaluated using a population pharmacokinetic model in patients with mild (CLcr 90-60 mL/min, N=433) and moderate (CLcr 30-59 mL/min, N=137) renal impairment enrolled in Studies 1, 2, and 3. Mild or moderate renal impairment has no clinically relevant effect on the exposure of crizotinib.

A study was conducted in 7 patients with severe renal impairment (CLcr <30 mL/min) who did not require dialysis and 8 patients with normal renal function (CLcr >90 mL/min). All patients received a single 250 mg oral dose of XALKORI. The mean AUC24 for crizotinib increased by 79% and the mean Cmax increased by 34% in patients with severe renal impairment compared to those with normal renal function. Similar changes in AUC24 and Cmax were observed for the active metabolite of crizotinib [see Dosage and Administration (2.2) and Use in Specific Populations (8.7)].

Ethnicity: No clinically relevant difference in the exposure of crizotinib between Asian patients (N=523) and non-Asian patients (N=691).

Age: Age has no effect on the exposure of crizotinib based on the population pharmacokinetic analysis from Studies 1, 2, and 3.

Body weight and gender: No clinically relevant effect of body weight or gender on the exposure of crizotinib based on the population pharmacokinetic analysis from Studies 1, 2, and 3.

13 NONCLINICAL TOXICOLOGY

13.1 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 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 pachytcine spermatocyte degeneration in rats given greater than or equal to 50 mg/kg/day for 28 days (greater than 1.7 times the AUC at the recommended human dose). 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 daily dose) of crizotinib.

14 CLINICAL STUDIES

ALK-Positive metastatic NSCLC-Study 1

The efficacy and safety of XALKORI as monotherapy for the treatment of 347 patients with metastatic ALK-positive NSCLC, previously treated with one platinum-based chemotherapy regimen, was demonstrated in a randomized, multicenter, open-label, active-controlled study (Study 1). The major efficacy outcome was progression-free survival (PFS) as assessed by independent radiology review [IRR]. Additional efficacy outcomes included objective response rate (ORR) as assessed by IRR and overall survival (OS).

Patients were randomized to receive XALKORI 250 mg orally twice daily (n=173) or chemotherapy (n=174). Chemotherapy consisted of pemetrexed 500 mg/m² (if pemetrexed naïve, n=99) or docetaxel 75 mg/m² (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. A total of 112 (64%) patients randomized to the chemotherapy arm subsequently received XALKORI after disease progression.

The demographic characteristics of the overall study population were 56% female, median age of 50 years, baseline ECOG performance status 0 (39%) or 1 (52%), 52% White and 45% Asian, 4% current smokers, 33% past-smokers, and 63% never smokers. The disease characteristics were metastatic disease in at least 95% of patients and at least 93% of patients’ tumors were classified as adenocarcinoma histology.

Study 1 demonstrated a statistically significant improvement in PFS in the patients treated with XALKORI. Table 5 and Figure 1 summarize the efficacy results.

Table 5. ALK-Positive Metastatic NSCLC - Efficacy Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XALKORI (n=173)</th>
<th>Chemotherapy (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (IRR)</td>
<td>Median, Months (95% CI) 7.7 (6.0, 8.8) 4.0 (3.6, 4.3)</td>
<td>7.7 (6.0, 8.8) 4.0 (3.6, 4.3)</td>
</tr>
<tr>
<td>PFS (HR)</td>
<td>0.49 (NR, NR)</td>
<td>0.49 (NR, NR)</td>
</tr>
</tbody>
</table>
Single-arm studies in ALK-positive metastatic NSCLC—Studies 2 and 3

The safety and anti-tumor activity of single-agent XALKORI in the treatment of metastatic ALK-positive NSCLC was demonstrated in two multinational, single-arm studies (Studies 2 and 3). The major outcome in both studies was investigator-assessed ORR according to RECIST. Patients in both studies received 250 mg of XALKORI orally twice daily.

In Study 2 (n=934) the demographic characteristics were 57% female, median age of 52 years, baseline ECOG performance status of 0/1 (82%) or 2/3 (18%), 52% White and 44% Asian, 4% current smokers, 30% past-smokers, and 66% never smokers. The disease characteristics were 92% metastatic; 94% of the cancers were classified as adenocarcinoma histology. Of the 934 ALK-positive metastatic NSCLC patients who received XALKORI in Study 2, 765 were ALK-positive as identified by Vysis ALK Break-Apart FISH Probe Kit and evaluable for response; 95% of the cancers were classified as adenocarcinoma histology, and 13% had a median duration of treatment of 32 weeks. Based on investigator assessments, there were 8 complete and 357 partial responses for an ORR of 48% (95% CI: 0.44, 0.51) and the median DR was 11.0 months.

In Study 3 (n=119) the demographic characteristics were 50% female, median age of 51 years, baseline ECOG performance status of 0 (35%) or 1 (53%), 62% White and 29% Asian, less than 1% current smokers, 27% past-smokers, and 72% never smokers. The disease characteristics were 96% metastatic, 98% of the cancers were classified as adenocarcinoma histology, and 13% had no prior systemic therapy for metastatic disease. In Study 3, 119 patients with metastatic ALK-positive NSCLC were treated with XALKORI with a median duration of treatment of 32 weeks. Based on investigator assessments, the ORR was 61% (95% CI: 0.52, 0.70) and the median DR was 11.1 months.

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

See FDA-approved patient labeling (Patient Information).

• Inform patients of the symptoms of hepatotoxicity, and that they should be reported immediately [see Warnings and Precautions (5.1)].
• Advise patients to immediately report any new or worsening pulmonary symptoms [see Warnings and Precautions (5.2)].
• Inform patients that symptoms of bradycardia including diziness, lightheadedness, and syncope can occur while taking XALKORI. Advise patients to report these symptoms and to inform their physician about the use of any heart or blood pressure medications [see Warnings and Precautions (5.4)].
• Inform patients that nausea, diarrhea, vomiting, and constipation are the most commonly reported gastrointestinal adverse events occurring in patients who received XALKORI. Nausea and vomiting began most commonly during the first few days of treatment [see Adverse Reactions (6)].
• Inform patients that visual changes such as perceived flashes of light, blurry vision, light sensitivity, and floaters are commonly reported adverse events and may occur while driving or operating machinery. The onset of visual disorders most commonly occurs during the first week of treatment [see Adverse Reactions (6)].
• Inform patients to avoid grapefruit or grapefruit juice while taking XALKORI. Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions (7)].
• Advise patients to take XALKORI with or without food and swallow XALKORI capsules whole.
• If a patient misses a dose, advise the patient to take it as soon as remembered unless it is less than 6 hours until the next dose, in which case, advise the patient not to take the missed dose. If a patient vomits after taking a dose of XALKORI, advise the patient not to take an extra dose, but to take the next dose at the regular time.
• Inform patients of childbearing potential to use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. Advise patients to inform their doctor if they or their partners are pregnant or think they may be pregnant. Also advise patients not to breastfeed while taking XALKORI [see Use in Specific Populations (8.1 and 8.3)].

This product’s label may have been updated. For full prescribing information, please visit www.XALKORI.com.

LAB-0440-11.0

PATIENT INFORMATION

XALKORI® (zal-KOR-ee)
(crizotinib)
Capsules

Read this patient information leaflet before you start taking XALKORI and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your condition or treatment.

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 or fatal liver injury. Your doctor should do blood tests at least every month to check your liver while you are taking XALKORI. Tell your doctor right away if you get any of the following:
• your skin or the whites of your eyes turn yellow
• you feel tired
• your urine turns dark or brown (tea color)
• you have nausea or vomiting
• you have a decreased appetite
• you have pain on the right side of your stomach
• you bleed or bruise more easily than normal
• you have itching

Lung problems (pneumonitis). XALKORI may cause life-threatening or fatal swelling (inflammation) of the lungs during treatment. Symptoms may be similar to those symptoms from lung cancer. Tell your doctor right away if you have any new or worsening symptoms, including:
• trouble breathing or shortness of breath
• cough with or without mucous
• fever

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

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 a gene called ALK (anaplastic lymphoma kinase).

It is not known if XALKORI is safe and effective in children.

What should I tell my doctor before taking XALKORI?

Before you take XALKORI, tell your doctor if you:
• have heart problems, including a condition called long QT syndrome
• have liver or kidney problems
• have any other medical conditions
• are pregnant, or plan to become pregnant. XALKORI may harm your unborn baby.
• Women who are able to become pregnant and men who take XALKORI should use birth control during treatment and for 3 months after stopping XALKORI.
• Talk to your doctor about the birth control methods that may be right for you.
• If you or your partner becomes pregnant, tell your doctor right away.
• are breastfeeding or plan to breastfeed. It is not known if XALKORI passes into your breast milk. You and your doctor should decide if you will take XALKORI or breastfeed. You should not do both.

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

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

How should I take XALKORI?
• Take XALKORI exactly as your doctor tells you.
• Swallow XALKORI capsules whole.
• You may take XALKORI with or without food.
• Do not change your dose or stop XALKORI unless your doctor 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.
• Call your doctor right away if you take too much XALKORI.
• Your doctor will check your blood and heart while you are taking XALKORI.

What should I avoid while taking XALKORI?
• You should not drink grapefruit juice or eat grapefruit during your treatment with XALKORI. It may make the amount of XALKORI in your blood increase 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. These problems usually happen within 1 week of starting XALKORI. Tell your doctor right away if you have any change in vision, such as double vision, flashes of light, blurred vision, light hurting your eyes, new or increased floaters.
• nausea
• diarrhea
• vomiting
• constipation
• swelling of your hands and feet
• feeling tired

Tell your doctor 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 doctor 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 it to other people, even if they have the same symptoms you have. It may harm them.

This leaflet provides the most important information about XALKORI. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for more information about XALKORI that is written for health professionals.

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

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

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