CRIZOTINIB (XALKORI): IN THE TREATMENT OF ALK-FUSION NON SMALL CELL LUNG CANCER (NSCLC)

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ABSTRACT

The number of new cases of ALK-fusion NSCLC is about 9,000 per year in the U.S. and about 45,000 worldwide. Lung cancer is the leading cause of cancer-related mortality in the United States. NSCLC is any type of epithelial lung cancer other than small cell lung cancer (SCLC). The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, but there are several other types that occur less frequently, and all types can occur in unusual histologic variants. About 7% of NSCLC have EML4-ALK translocations; these may benefit from ALK inhibitors which are in clinical trials.[2] Although NSCLCs are associated with cigarette smoke, adenocarcinomas may be found in patients who have never smoked. On November 20, 2013, the U.S. Food and Drug Administration granted regular approval for crizotinib (Xalkori, Pfizer, Inc.) capsules 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. As a class, NSCLCs are relatively insensitive to chemotherapy and radiation therapy compared with SCLC. Patients with advanced metastatic disease may achieve improved survival and palliation of symptoms with chemotherapy, targeted agents, and other supportive measures. Crizotinib was previously granted accelerated approval in August, 2011 based on durable, objective response rates (ORR) of 50% and 61% in two single-arms, open-label studies. Crizotinib is used to treat certain types of non-small cell lung cancer that has spread to nearby tissues or to other parts of the body.

Keywords: non-small cell lung cancer (NSCLC), types, ALK-NSCLC, diagnosis, CRIZOTINIB, treatment, drug interactions, chemotherapy.
INTRODUCTION
Metastatic non-small cell lung cancer (NSCLC) is the most common type of lung cancer. It usually grows and spreads more slowly than small cell lung cancer. Stage IV non-small cell lung cancer includes cancers that have spread to areas beyond the chest, like the brain. Stage IV cancer also includes people who have a fluid collection around the lung (called a malignant pleural effusion) caused by the cancer. Stage IV non-small cell lung cancer cannot be cured, but treatment can reduce pain, ease breathing, and extend and improve quality of life. More than 90 percent of non-small cell lung cancers are caused by smoking tobacco. People who are exposed to second-hand smoke, air pollution, asbestos and arsenic in drinking water are more likely to develop non-small cell lung cancer. Knowing the clinical stage of lung cancer helps an oncologist create a treatment plan. The brain, the bones, and the area around the lungs (the pleural space) are common places for cancer to spread in people with non-small cell lung cancer. Cancer that has spread to the brain or bones is called metastatic lung cancer, not brain cancer or bone cancer. In some cases, certain areas of spread require particular treatment directed toward the metastases. NSCLC arises from the epithelial cells of the lung of the central bronchi to terminal alveoli. The histological type of NSCLC correlates with site of origin, reflecting the variation in respiratory tract epithelium of the bronchi to alveoli.\(^1\) Squamous cell carcinoma usually starts near a central bronchus. Adenocarcinoma and bronchioloalveolar carcinoma usually originate in peripheral lung tissue. Adenocarcinomas grow in the outer parts of the lung. Squamous cell carcinomas grow on or near the bronchial tubes. Large cell carcinomas grow anywhere in the lung and are more likely to metastasize.\(^1\)

Lung cancer in never-smokers is almost universally NSCLC, with a sizeable majority being adenocarcinoma. On relatively rare occasions, malignant lung tumors are found to contain components of both SCLC and NSCLC. In these cases, the tumors should be classified as combined small cell lung carcinoma (c-SCLC), and are (usually) treated like "pure" SCLC.\(^2\) Biomarkers are substances that are produced by cancer cells or by other cells within the body. Recently, scientists have begun to understand that cancers, including advanced-stage non-small cell lung cancer (NSCLC), can respond differently to treatment based on certain biological characteristics or "biomarkers". Tissues from tumour can be used to determine if cancer has any specific biomarkers, including one that is called epidermal growth factor receptor (EGFR).\(^3\)
Malignant pleural effusion: a pleural effusion is a collection of fluid in the chest that is located in the pleural space, a pocket between the lung and the tissues of the chest wall. This space is normally empty, although it can accumulate fluid in people with advanced lung cancer. The fluid pushes against the lung, compressing it and preventing the lung from fully expanding when breathing. Thus, the most common symptom of a pleural effusion is shortness of breath. In most people with advanced lung cancer, the pleural effusion is caused by the cancer. This is called a malignant pleural effusion. Treatment of the pleural effusion is usually recommended for people who develop shortness of breath. Shortness of breath often worsens as more fluid accumulates.  

Figure 1: Pie chart showing incidences of non-small cell lung cancers as compared to carcinoma shown at right, with fractions of smokers versus non-smokers shown for each type.  

Non-small cell lung cancer is divided into five stages: 

- **Stage 0** - the cancer has not spread beyond the inner lining of the lung.  
- **Stage I** - the cancer is small and haven’t spread to the lymph nodes.  
- **Stage II** - the cancer has spread to some lymph nodes near the original tumor.  
- **Stage III** - the cancer has spread to nearby tissue or to far away lymph nodes.  
- **Stage IV** - the cancer has spread to other organs of the body, such as the other lung, brain, or liver.
1. **Lung adenocarcinoma:** (40% of lung cancers)
Adenocarcinoma of the lung is currently the most common type of lung cancer in "never smokers" (lifelong non-smokers). Adenocarcinomas account for approximately 40% of lung cancers. Historically, adenocarcinoma was more often seen peripherally in the lungs than small cell lung cancer and squamous cell lung cancer, both of which tended to be more often centrally located. Interestingly, however, recent studies suggest that the "ratio of centrally-to-peripherally occurring" lesions may be converging toward unity for both adenocarcinoma and squamous cell carcinoma.  

The following variants of adenocarcinoma are recognized in the WHO/IASLC classification:

- Well-differentiated fetal adenocarcinoma.
- Mucinous (colloid) adenocarcinoma.
- Mucinous cystadenocarcinoma.
- Signet ring adenocarcinoma.
- Clear cell adenocarcinoma.

2. **Squamous cell lung carcinoma:** (25% of lung cancers)
Squamous cell carcinoma (SCC) of the lung is more common in men than in women. It is closely correlated with a history of tobacco smoking, more so than most other types of lung cancer. It most often arises centrally in larger bronchi, and while it often metastasizes to loco-regional lymph nodes (particularly the hilar nodes) early in its course, it generally...
disseminates outside the thorax somewhat later than other major types of lung cancer. Large
tumors may undergo central necrosis, resulting in cavitation.9

Photograph 1: of a squamous-cell carcinoma. Tumour is on the left, obstructing the bronchus
(lung). Beyond the tumour, the bronchus is inflamed and contains mucus.

A squamous cell carcinoma is often preceded for years by squamous
cell metaplasia or dysplasia in the respiratory epithelium of the bronchi, which later
transforms to carcinoma in situ. In carcinoma in situ, atypical cells may be identified
by cytologic smear test of sputum, bronchoalveolar lavage or samples from end bronchial.
However, squamous-cell carcinoma in situ is asymptomatic and undetectable on X-ray
radiographs. Eventually, it becomes symptomatic, usually when the tumor mass begins to
obstruct the lumen of a major bronchus, often producing distal atelectasis and infection.
Simultaneously, the lesion invades into the surrounding pulmonary substance. On
histopathology, these tumors range from well differentiated, showing keratin pearls and cell
junctions, to anaplastic, with only minimal residual squamous cell features.

Currently, four variants (papillary, small cell, clear cell, and basaloid) of squamous cell
carcinoma of the lung are recognized.9 Of these variants, there is some evidence that the
basaloid and poorly differentiated small-cell variants may have worse prognoses than
"conventional" squamous cell carcinomas. The papillary variant occurs more frequently as a
primarily superficial, endobronchial lesion, with a modestly better prognosis Recently, four
mRNA expression subtypes (primitive, basal, secretory, and classical) were identified and
validated within squamous cell carcinoma. The primitive subtype correlates with worse
patient survival. These subtypes, defined by intrinsic expression differences, provide a
possible foundation for improved patient prognosis and research into individualized
therapies.
Large-cell lung carcinoma: (10% of lung cancers)

Large cell lung carcinoma (LCLC) is a heterogeneous group of undifferentiated malignant neoplasms originating from transformed epithelial cells in the lung. LCLC's have typically comprised between around 10% of all NSCLC in the past, although newer diagnostic techniques seem to be reducing the incidence of diagnosis of "classic" LCLC in favor of more poorly differentiated squamous cell carcinomas and adenocarcinomas. LCLC is, in effect, a "diagnosis of exclusion", in that the tumor cells lack light microscopic characteristics that would classify the neoplasm as a small-cell carcinoma, squamous-cell carcinoma, adenocarcinoma, or other more specific histologic type of lung cancer. LCLC is differentiated from small cell lung carcinoma (SCLC) primarily by the larger size of the anaplastic cells, a higher cytoplasmic-to-nuclear size ratio, and a lack of "salt-and-pepper" chromatin.\(^\text{10}\)

More than one kind of treatment is often used, depending on the stage of the cancer, the individual's overall health, age, response to chemotherapy, and other factors such as the likely side effects of the treatment.

In addition to the general category of large cell carcinoma, several uncommon variants are recognized in the WHO/IASLC classification,\(^\text{10}\) including the following

- LCNEC.
- Basaloid carcinoma.
- Lymphoepithelioma-like carcinoma.
- Clear cell carcinoma.
- Large cell carcinoma with rhabdoid phenotype.

Basaloid carcinoma is also recognized as a variant of squamous cell carcinoma, and rarely, adenocarcinomas may have a basaloid pattern; however, in tumors without either of these features, they are regarded as a variant of large cell carcinoma.

SYMPTOMS:\(^\text{11}\)

1. Symptoms due to the presence of a tumor in the lungs such as
   - Persistent cough.
   - Coughing up blood (hemoptysis).
   - Shortness of breath.
   - Hoarseness.
   - Pain the chest, back, shoulder or arms.
   - Repeated episodes of pneumonia or bronchitis.
• Wheezing.

2. Symptoms due to spread of the tumor to other regions of the body, for example
• Pain in the back, hips, or ribs if the tumor has spread to bone.
• Difficulty swallowing due to a tumor being near or invading the esophagus.
• Headaches, vision changes, weakness, or seizures if a tumor spreads to the brain.
• Jaundice (a yellowing of the skin) from tumor that has spread to the liver.

3. Symptoms related to metastatic cancer in general
• Fatigue
• Unintentional weight loss
• Loss of appetite

ALK FUSION ONCOGENE POSITIVE - NON-SMALL CELL LUNG CANCER (NSCLC)

Anaplastic lymphoma kinase (ALK) gene abnormalities – A fusion (combination) of the ALK gene with another gene such as EML can drive the growth of some non-small cell lung cancers. Crizotinib (Xalkori) is a targeted medicine that blocks the cancer stimulus caused by this ALK abnormality. Crizotinib is more effective than standard chemotherapy in patients with lung cancer containing this abnormality, and thus crizotinib is generally recommended as the initial therapy instead of standard chemotherapy in this situation.¹²

A group of patients with non-small cell lung cancer (NSCLC) have tumors that contain an inversion in chromosome 2 that juxtaposes the 5' end of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the 3' end of the anaplastic lymphoma kinase (ALK) gene, resulting in the novel fusion oncogene EML4-ALK. This fusion oncogene rearrangement is transforming both in vitro and in vivo and defines a distinct clinicopathologic subset of NSCLC.¹³

Tumors that contain the EML4-ALK fusion oncogene or its variants are associated with specific clinical features, including never or light smoking history, younger age, and adenocarcinoma with signet ring or acinar histology. ALK gene arrangements are largely mutually exclusive with EGFR or KRAS mutations. Screening for this fusion gene in NSCLC is important, as "ALK-positive" tumors (tumors harboring a rearranged ALK gene/fusion protein) are highly sensitive to therapy with ALK-targeted inhibitors.¹⁴
Cancer cell lines harboring the EML4-ALK translocation are effectively inhibited by small molecule inhibitors that target the ALK tyrosine kinase (TK). In vivo, treatment of EML4-ALK transgenic mice with ALK inhibitors results in tumor regression, supporting the notion that ALK-driven lung cancers are "addicted" to the fusion oncogene.

Patients with ALK fusion oncogene-positive lung cancer are relatively younger at onset than those without this abnormality. The two studies that were used to support the approval of crizotinib included 255 patients whose tumors contained an ALK fusion oncogene; in this database, the median age was 52 years (range 21 to 82 years). The estimated median age for other patients with lung cancer is approximately 66 years. The ALK fusion oncogene in patients with NSCLC is strongly associated with a history of never or light smoking (<10 packet years).

In the crizotinib study database of 255 patients, never smokers and former smokers comprised 70 and 28 percent of cases, respectively. The vast majority of lung tumors that harbor the ALK fusion oncogene are adenocarcinomas. In the 255 patients with the ALK fusion oncogene included in the crizotinib database, 97 percent were adenocarcinoma. ALK rearrangement has been reported in squamous cell carcinoma but is rare.

**TESTS:** Tests that may be performed to diagnose lung cancer or see if it has spread include:

1. Bone scan
2. Chest x-ray
3. Complete blood count (CBC)
4. CT scan of the chest
5. MRI of the chest
6. Positron emission tomography (PET) scan
7. Sputum test to look for cancer cells
8. Thoracentesis (sampling of fluid build-up around the lung)

In some cases, the health care provider may need to remove a piece of tissue from your lungs for examination under a microscope. This is called a biopsy. There are several ways to do this:

9. Bronchoscopy combined with biopsy
10. CT-scan-directed needle biopsy
11. Endoscopic esophageal ultrasound (EUS) with biopsy
12. Mediastinoscopy with biopsy
13. Open lung biopsy
14. Pleural biopsy
If the biopsy shows that you do have lung cancer, more imaging tests will be done to determine the stage of the cancer. Stage means how big the tumor is and how far it has spread.

DIAGNOSIS
Anaplastic lymphoma kinase (ALK) gene rearrangements or the resulting fusion proteins may be detected in tumor specimens using fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and reverse transcription polymerase chain reaction of cDNA (RT-PCR).

1. FISH: The gold standard assay for diagnosing ALK-positive NSCLC is FISH. The commercial break-apart probes include two differently colored (red and green) probes that flank the highly conserved translocation breakpoint within ALK. In non-rearranged cells, the overlying red and green probes result in a yellow (fused) signal; in the setting of an ALK rearrangement, these probes are separated and splitting of the red and green signals is observed. Atypical patterns of rearrangement have also been identified, and these are also responsive to ALK inhibition with crizotinib. ALK gene amplification alone is not predictive of crizotinib response and does not carry the same significance as rearrangement.

2. IHC: Multiple monoclonal antibodies have been developed to use for the IHC detection of the ALK fusion oncogene, and IHC using these antibodies is highly sensitive and specific. Thus, IHC can potentially be used to screen for and identify the presence of ALK positivity. In the United States, FISH is the only approved test to diagnose ALK-positive NSCLC, and thus FISH should be used to confirm the IHC results.

3. RT-PCR: RT-PCR of cDNA is another commonly used screening strategy for detecting ALK gene rearrangements in NSCLC. A number of multiplex assays have been developed to simultaneously capture all possible in-frame fusions between EML4 and ALK in which the kinase domain of ALK would be preserved. While different breakpoints in EML4 or ALK may be detected, novel ALK fusion partners will not. Furthermore, this method is frequently limited by the quality of the RNA that can be isolated from archival tissue.
Molecular Features: The identification of mutations in lung cancer has led to the development of molecularly targeted therapy to improve the survival of subsets of patients with metastatic disease. In particular, subsets of adenocarcinoma now can be defined by specific mutations in genes encoding components of the epidermal growth factor receptor (EGFR) and downstream mitogen-activated protein kinases (MAPK) and phosphatidylinositol 3-kinases (PI3K) signaling pathways. These mutations may define mechanisms of drug sensitivity and primary or acquired resistance to kinase inhibitors. Other genetic abnormalities of potential relevance to treatment decisions include translocations involving the anaplastic lymphoma kinase (ALK)-tyrosine kinase receptor, which are sensitive to ALK inhibitors, and amplification of MET (mesenchymal epithelial transition factor), which encodes the hepatocyte growth factor receptor. MET amplification has been associated with secondary resistance to EGFR tyrosine kinase inhibitors.

TREATMENT
There are many different types of treatment for non-small cell lung cancer. Treatment depends on the stage of the cancer.

Table 1: Standard Treatment Options for NSCLC

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<thead>
<tr>
<th>Stage (TNM Staging Criteria)</th>
<th>Standard Treatment Options</th>
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<tr>
<td>Occult NSCLC</td>
<td>Surgery</td>
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<td>Stage 0 NSCLC</td>
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<td>Endobronchial therapies</td>
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<td>Stages IA and IB NSCLC</td>
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<td>Stages IIA and IIB NSCLC</td>
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<td>Neoadjuvant chemotherapy</td>
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<td>Adjuvant chemotherapy</td>
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<td>Radiation therapy</td>
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<td>Stage IIIA NSCLC</td>
<td>Resected or resectable disease</td>
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<td>Surgery</td>
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<td>Adjuvant therapy</td>
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<td>Unresectable disease</td>
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<td>Stage (TNM Staging Criteria)</td>
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<td>Superior sulcus tumors</td>
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<td>Radiation therapy and surgery</td>
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<td>Concurrent chemotherapy with radiation therapy and surgery</td>
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<td>Surgery alone (for selected patients)</td>
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<td>Tumors that invade the chest wall</td>
<td>Surgery</td>
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<td>Surgery and radiation therapy</td>
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<td>Radiation therapy alone</td>
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<td>Chemotherapy combined with radiation therapy and/or surgery</td>
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<td>Stage IIIB NSCLC</td>
<td>Sequential or concurrent chemotherapy and radiation therapy</td>
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<td>Chemotherapy followed by surgery (for selected patients)</td>
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<td>Radiation therapy alone</td>
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<td>Stage IV NSCLC</td>
<td>Cytotoxic combination chemotherapy (first line)</td>
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<td>Combination chemotherapy with bevacizumab or cetuximab</td>
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<td>EGFR tyrosine kinase inhibitors (first line)</td>
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<td>EML4-ALK inhibitors in patients with EML-ALK translocations</td>
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<td>Maintenance therapy following first-line chemotherapy</td>
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<td>Endobronchial laser therapy and/or brachytherapy (for obstructing lesions)</td>
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<td>External-beam radiation therapy (primarily for palliation of local symptomatic tumor growth)</td>
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<td>Recurrent NSCLC</td>
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<td>Chemotherapy or kinase inhibitors alone</td>
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<td>EGFR inhibitors in patients with/without EGFR mutations</td>
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<td>EML4-ALK inhibitors in patients with EML-ALK translocations</td>
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Stage (TNM Staging Criteria) | Standard Treatment Options
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Surgical resection of isolated cerebral metastasis (for highly selected patients) | Laser therapy or interstitial radiation therapy (for endobronchial lesions)
Stereotactic radiation surgery (for highly selected patients)

CHEMOTHERAPY

When no specific abnormality is identified, chemotherapy is generally recommended to treat stage IV non-small cell lung cancer. Chemotherapy can often slow or stop the growth of tumors at least temporarily.

The presence of the ALK fusion oncogene conferred sensitivity to crizotinib, a specific inhibitor of the anaplastic lymphoma kinase (ALK) tyrosine kinase, in phase II and III studies. Although the trials with crizotinib contained only a limited number of elderly patients, this approach is preferred for the initial treatment of these patients.\(^{22}\) For elderly or poor performance status patients whose tumors contain the ALK fusion oncogene, we recommend initial therapy with crizotinib rather than chemotherapy (Grade 1B).

Chemotherapy is given to slow or stop the growth of cancer cells. It is not given every day but instead is given in cycles. A cycle of chemotherapy (about 21 days) refers to the time it takes to give the treatment and then allow the body to recover from the side effects of the medicines. Most treatments involve a combination (regimen) of two chemotherapy drugs. The most commonly used regimens include either cisplatin (Platinol) or carboplatin (Paraplatin); this is combined with one of several other drugs (such as pemetrexed [Alimta], paclitaxel [Taxol], docetaxel [Taxotere], gemcitabine [Gemzar], vinorelbine [Navelbine]).\(^{23}\) Most of the drugs are given into a vein (intravenous, IV) once every three weeks. In some cases, recommend combining these chemotherapy drugs with bevacizumab (Avastin), a medicine that blocks a protein called vascular endothelial growth factor (VEGF).

Four to six cycles of chemotherapy are usually recommended, depending upon your response to treatment. If you’re initial chemotherapy treatment does not work, or if you initially respond and then have progressive disease, your doctor may recommend treatment with other chemotherapy medications or a targeted agent such as erlotinib.\(^{24}\)
SIDE EFFECTS: the most serious side effect of chemotherapy is a temporary drop in your blood count. This can increase your risk of developing an infection. Blood counts typically fall 7 to 14 days after the chemotherapy is given. During this time, you should call your doctor or nurse immediately if you develop chills or have a fever (temperature higher than 100.4°F or 38°C). A number of other side effects are possible and these include: 24

- Temporary hair loss
- Numbness in the fingers and toes (called neuropathy)
- Nausea and vomiting
- Skin rash

CRIZOTINIB
Crizotinib (trade name Xalkori, Capsules, Oral, Pfizer), is an anti-cancer drug acting as an ALK (anaplastic lymphoma kinase) and ROS1 (receptor tyrosine kinase c-ros oncogene 1) inhibitor, approved for treatment of some non-small cell lung carcinoma (NSCLC) in the US and some other countries, and undergoing clinical trials testing its safety and efficacy in anaplastic large cell lymphoma, neuroblastoma, and other advanced solid tumours in both adults and children. It is a multitargeted small molecule tyrosine kinase inhibitor, which was originally developed as an inhibitor of mesenchymal epithelial transition growth factor (c-MET); it is also a potent inhibitor of anaplastic lymphoma kinase (ALK) phosphorylation and signal transduction. This inhibition is associated with G1-S phase cell cycle arrest and induction of apoptosis in ALK-positive cells in vitro and in vivo. 25

Efficacy: Crizotinib induces rapid tumour regression and objective responses in the majority of patients whose tumours contain the ALK gene rearrangement. These responses result in a significant prolongation in progression-free survival compared to single agent chemotherapy in previously treated patients.

The activity of crizotinib in ALK rearrangement positive NSCLC is illustrated by the results of an international phase III trial in which 347 patients with the ALK rearrangement were randomly assigned to crizotinib (250 mg twice daily) or single agent chemotherapy with either pemetrexed or docetaxel. All patients had received one prior chemotherapy regimen with a platinum regimen. Patients who were assigned to chemotherapy were allowed to cross over and receive treatment with crizotinib when they developed progressive disease. 26

Key efficacy results included the following: 27
1. At a median follow-up of 12 months, progression-free survival, the primary endpoint of the trial was significantly increased with crizotinib compared with chemotherapy (median 7.7 versus 3.0 months, hazard ratio [HR] for progression 0.49, 95% CI 0.37-0.64).

2. The objective response rate based upon independent radiologic review was also significantly increased (65 versus 20 percent). Responses were achieved more rapidly than with chemotherapy (median time to response 6.3 versus 12.6 weeks) and were of longer duration (32 versus 24 weeks).

3. There was no significant difference in overall survival (median 20.3 versus 22.8 months, HR for death 1.02). The absence of an overall survival benefit presumably reflects subsequent treatment since 64 percent of chemotherapy-treated patients had crossed over to crizotinib after progressing on chemotherapy.

**DRUG DESCRIPTION**

XALKORI (crizotinib) is an oral receptor tyrosine kinase inhibitor. The molecular formula for crizotinib is C_{21}H_{22}Cl_{2}F_{2}N_{5}O. The molecular weight is 450.34 Daltons and half life is about 46 hours. Crizotinib is described chemically as (R)-3-[1-[(2, 6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1H-pyrazol-4-yl] pyridin-2-amine.\(^{27}\)

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 1.65.

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

Xalkori is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. This indication is based on response rate.\(^{27}\)
DOSAGE AND ADMINISTRATION: HOW SUPPLIED\textsuperscript{28}

- Dosage Forms And Strengths

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

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

- Storage And Handling

1.250 mg capsules: Hard gelatine 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.

2.200 mg capsules; Hard gelatine 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).

The recommended dose and schedule of Xalkori is 250 mg taken orally twice daily. Xalkori may be taken with or without food. Swallow capsules whole. If a dose of Xalkori is missed, make up that dose unless the next dose is due within 6 hours.

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then reduce the dose of Xalkori to 200 mg taken orally twice daily. If further dose reduction is necessary, then reduce the dosage to 250 mg taken orally once daily.

MECHANISM OF ACTION

Crizotinib has an amino pyridine structure, and functions as a protein kinase inhibitor by competitive binding within the ATP-binding pocket of target kinases. About 4% of patients with non-small cell lung carcinoma have a chromosomal rearrangement that generates a fusion gene between EML4 (‘echinoderm microtubule-associated protein-like 4’) and ALK (‘anaplastic lymphoma kinase’), which results in constitutive kinase activity that contributes to carcinogenesis and seems to drive the malignant phenotype. The kinase activity of the
fusion protein is inhibited by crizotinib. Patients with this gene fusion are typically younger non-smokers who do not have mutations in either the epidermal growth factor receptor gene (EGFR) or in the K-Ras gene.\textsuperscript{28}

Crizotinib inhibits the c-Met/Hepatocyte growth factor receptor (HGFR) tyrosine kinase, which is involved in the oncogenesis of a number of other histological forms of malignant neoplasms. Crizotinib is currently thought to exert its effects through modulation of the growth, migration, and invasion of malignant cells. Other studies suggest that crizotinib might also act via inhibition of angiogenesis in malignant tumours.\textsuperscript{28}

ALK mutations are thought to be important in driving the malignant phenotype in about 15\% of cases of neuroblastoma, a rare form of peripheral nervous system cancer that occurs almost exclusively in very young children.

**PHARMACOKINETICS**

**Absorption**

Single oral dose of crizotinib was absorbed with median time to achieve peak concentration of 4-6 hours. Crizotinib 250 mg twice daily, steady state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8. The mean absolute bioavailability of crizotinib was 43\% (range: 32\% to 66\%). A high-fat meal reduced crizotinib AUC and Cmax by approximately 14\%. Xalkori can be administered with or without food.\textsuperscript{29}

**Distribution**

Binding of crizotinib to human plasma proteins in vitro is 91\% and is independent of drug concentration. In vitro studies, crizotinib is a substrate for P-glycoprotein. The blood-to-plasma concentration ratio is approximately 1. The geometric mean volume of distribution (Vss) of crizotinib was 1,772 L following i.v. administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma.\textsuperscript{29}

**Metabolism**

In vitro studies, 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. In vitro studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP3A.\textsuperscript{29}
Elimination
A single dose of crizotinib, the mean apparent plasma terminal half-life of crizotinib was 42 hours in patients. A single 250 mg radiolabel crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in faeces and urine, respectively. Unchanged crizotinib represented approximately 53% and 2.3% of the administered dose in faeces and urine, respectively. The mean apparent clearance (CL/F) of crizotinib was lower at steady state (60 L/hr) after 250 mg twice daily.\textsuperscript{29}

CLINICAL TRIALS
On August 26, 2011, the U.S. Food and Drug Administration approved crizotinib (Xalkori) to treat certain late-stage (locally advanced or metastatic) non-small cell lung cancers that express the abnormal anaplastic lymphoma kinase (ALK) gene. Approval required a companion molecular test for the EML4-ALK fusion.\textsuperscript{30}

The trial demonstrated significantly prolonged progression-free survival (PFS) for crizotinib treatment compared to chemotherapy [HR=0.49, (95% CI: 0.37, 0.64), p<0.0001]. Median PFS was 7.7 and 3.0 months on the crizotinib and chemotherapy arms, respectively. The ORR was significantly higher for the crizotinib arm (65% vs. 20%) with median response durations of 7.4 and 5.6 months in the crizotinib and chemotherapy arms, respectively. No difference in overall survival was noted between the two arms [HR= 1.02 (95% CI: 0.68, 1.54)] in a planned interim analysis.\textsuperscript{30}

Additionally, a phase 2 trial, PROFILE 1005, studies patients meeting similar criteria who have received more than one line of prior chemotherapy. A phase 3 trial, PROFILE 1007, compares crizotinib to standard second line chemotherapy (pemetrexed or taxotere) in the treatment of ALK-positive NSCLC.

Crizotinib is also being tested in clinical trials of advanced disseminated anaplastic large-cell lymphoma and neuroblastoma.

SIDE EFFECTS
Common adverse reactions in clinical trials with crizotinib, occurring at an incidence of 25% or higher.\textsuperscript{31}
1. diarrhoea
2. constipation
3. stomach pain
4. sores in the mouth
5. change in ability to taste food
6. heartburn
7. headache
8. numbness, burning, or tingling in the hands or feet
9. difficulty falling asleep or staying asleep

Some side effects can be serious
- Shortness of breath
- cough
- fever
- swelling of the arms, hands, feet, ankles, or lower legs
- chest pain
- slow heartbeat
- rash
- weakness
- excessive tiredness
- pain in the right upper part of the stomach
- nausea
- vomiting
- yellowing of the skin or eyes
- dark urine
- itching
- unusual bleeding or bruising
- double vision
- blurred vision
- sensitivity to light
- seeing sudden flashes of light
- seeing new or increased floaters (spots in vision)

**DRUG INTERACTIONS:** These are

1. Drugs That May Increase Crizotinib Plasma Concentrations: Strong CYP3A inhibitors eg, Atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir,
ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole. Avoid grapefruit or grapefruit juice which may also increase plasma concentrations of crizotinib.

2. Drugs That May Decrease Crizotinib Plasma Concentrations: Strong CYP3A inducers eg, carbamazepine, phenobarbital, phenytoin, rifabutin, and rifampin.

3. Drugs Whose Plasma Concentrations May Be Altered By Crizotinib: Crizotinib inhibits CYP3A both In vitro and in vivo. Dose reduction may be needed for coadministered drugs that are predominantly metabolized by CYP3A. Avoid coadministration of crizotinib with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus.

PRECAUTIONS

1. Hepatotoxicity: Drug-induced hepatotoxicity with fatal outcome has occurred during xalkori treatment in less than 1% of patients in clinical trials. Concurrent elevations in ALT greater than 3 times the upper limit of normal and total bilirubin greater than 2 times the upper limit of normal, with normal alkaline phosphatase, occurred in less than 1% of patients in clinical trials. Monitor with liver function tests including ALT and total bilirubin 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.

2. Pneumonitis: Xalkori has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 255 (1.6%) patients across Studies A and B. All of these cases occurred within 2 months after the initiation of treatment. Monitor patients for pulmonary symptoms indicative of pneumonitis. Exclude other causes of pneumonitis, and permanently discontinue Xalkori in patients diagnosed with treatment-related pneumonitis.

3. Bradycardia: Bradycardia with a heart rate < 50 beats per minute occurred in 10% of 890 patients and 14% of 114 patients treated with Xalkori in Studies A and B, respectively. 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 Grade 2 and 3
symptomatic bradycardia hold Xalkori, re-evaluate the use of concomitant medications, and adjust the dose of Xalkori. Permanently discontinue for Grade 4 bradycardia due to Xalkori. In cases of Grade 4 bradycardia associated with concomitant medications known to cause bradycardia or hypotension.33

4. ALK Testing: Detection of ALK-positive NSCLC using an FDA-approved test, indicated for this use, is necessary for selection of patients for treatment with Xalkori. Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results.

5. Pregnancy: Pregnancy Category D: Xalkori can cause fetal harm when administered to a pregnant woman based on its mechanism of action. In nonclinical studies in rats, crizotinib was embryotoxic and fetotoxic at exposures similar to and above those observed in humans at the recommended clinical dose of 250 mg twice daily. Postimplantation loss was increased at doses ≥ 50 mg/kg/day (approximately 1.2 times the AUC at the recommended human dose) in rats. Advise women of childbearing potential to avoid becoming pregnant while receiving xalkori.

6. 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.

7. 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 10 times the AUC in adult patients at the recommended human dose).

8. 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 in patients with hepatic impairment.
9. Renal Impairment: Complex renal cysts occurred in 2 (1%) patients treated with xalkori. No starting dose adjustment is needed for patients with mild (creatinine clearance [CLcr] 60 to 89 mL/min) and moderate (CLcr 30 to 59 mL/min) renal impairment, as steady-state trough concentrations in these two groups were similar to those in patients with normal renal function (CLcr ≥ 90 mL/min) in Study B. Increased exposure to crizotinib occurred in patients with severe renal impairment (CLcr < 30 mL/min) not requiring dialysis. Administer Xalkori at a starting dose of 250 mg taken orally once daily in patients with severe renal impairment not requiring dialysis.

10. QT Interval Prolongation

QTc prolongation has been observed. 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, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval. Permanently discontinue Xalkori in patients who develop Grade 4 QTc prolongation. Withhold Xalkori in patients who develop Grade 3 QTc prolongation until recovery to less than or equal to Grade 1, then resume Xalkori at 200 mg twice daily. In case of recurrence of Grade 3 QTc prolongation, withhold Xalkori until recovery to less than or equal to Grade 1, then resume Xalkori at 250 mg once daily. Permanently discontinue Xalkori if Grade 3 QTc prolongation recurs.

Nonclinical Toxicology

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

2. Fertility: Crizotinib is considered to have the potential to impair reproductive function and fertility in humans based on findings in repeat-dose toxicity studies in the rat. Findings observed in the male reproductive tract included testicular pachytene spermatocyte degeneration in rats given greater than or equal to 50 mg/kg/day for 28 days (greater than 3 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 on a mg/m² basis) for 3 days.
CHEMOTHERAPY VERSUS TARGETED THERAPY

Advanced non-small cell lung cancer (NSCLC) associated with the anaplastic lymphoma kinase (ALK) fusion oncogene is highly sensitive to the ALK TK inhibitor crizotinib. Treatment with crizotinib, an ALK TK inhibitor, should be limited to patients whose tumors contain this abnormality as demonstrated by FISH.\textsuperscript{34}

Crizotinib is preferred as the initial therapy for patients whose tumor contains this genetic abnormality in countries where it is approved for this indication. In other countries, its use may be restricted to those who have progressed following chemotherapy. Thus patients should have tumor tissue assessed for the presence of ALK rearrangement, as well as for other driver mutations (especially in the epidermal growth factor receptor [EGFR]).

If systemic treatment is required before the results of genotype testing are available, systemic chemotherapy rather than targeted therapy is indicated. When the results of genotype testing become available, the treatment plan should be reassessed. There are no clinical trials that directly address the optimal timing of crizotinib in patients who have already started on chemotherapy.

If an ALK fusion oncogene is identified after the initiation of treatment, we suggest continuing chemotherapy for four cycles if therapy is tolerated and there is no evidence of disease progression. There are no data directly comparing continuation using maintenance chemotherapy versus a switch to crizotinib after completion of this initial chemotherapy. The author’s preference is to switch to crizotinib, rather than to use maintenance chemotherapy, because there are some patients who will deteriorate due to disease progression and thus miss the opportunity to be treated with crizotinib.\textsuperscript{34}

For patients who continue treatment with chemotherapy, crizotinib is indicated when there is evidence of disease progression. Factors that should be discussed with the patient in defining a treatment plan include the quality of the initial response to chemotherapy and the potential side effects of maintenance therapy.

Brain metastases: Surgery and/or radiation therapy are the primary treatment modalities for patients with brain metastases from NSCLC, including those with the EML4–ALK fusion oncogene. There are only limited data on the activity of crizotinib on brain metastases in this setting.
Isolated brain metastases (a central nervous system (CNS) relapse without evidence of extracranial progression) may be a particular problem for patients treated with crizotinib. In this setting, continuation of treatment with crizotinib after treatment of the CNS relapse with surgery and/or radiation therapy may be associated with a significant period of control of extracranial disease.

TOXICITY
Treatment with crizotinib is generally well tolerated. The key toxicities observed in the phase II database included:

1. Visual disturbances, which were seen in 60 to 65 percent of cases, are primarily associated with the transition from light to dark. Uncommon visual manifestations include photophobia, decreased visual acuity, blurred vision, vitreous floaters, and diplopia. These events generally started within two weeks of drug administration. Consider ophthalmological evaluation, particularly if patients experience photopsia or experience new or increased vitreous floaters. Severe or worsening vitreous floaters and/or photopsia could also be signs of a retinal hole or pending retinal detachment. Advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder.

2. Less severe side effects included gastrointestinal symptoms, which were seen in 25 percent or more of patients and included nausea, vomiting, diarrhea, and constipation. Edema and fatigue each occurred in 20 to 40 percent of cases, but were severe in 2 percent or less of cases.

3. Abnormal liver function tests were observed with elevations of ALT and AST in 71 percent and 61 percent of cases, respectively. These elevations of ALT and AST were grade 3 or 4 and required interruption of treatment and/or dose reduction in 7 and 3 percent of cases respectively.

4. Severe, life-threatening, or fatal treatment-related pneumonitis occurred in four cases (1.6 percent). The development of pneumonitis due to crizotinib should result in discontinuation of treatment with this agent.

5. Sinus bradycardia is relatively frequent in patients treated with crizotinib and may be severe in some cases. However, patients with sinus bradycardia were asymptomatic, and the
bradycardia was not explained by other comorbidity or medications. Caution should be used in the concomitant administration of beta blockers in patients treated with crizotinib.

6. QTc interval prolongation has been observed with crizotinib, and crizotinib should be avoided in patients with congenital long QT syndrome.

7. Crizotinib is metabolized by cytochrome P450 CYP3A4. Thus caution should be used when it is given with CYP3A4 inhibitors, and care is required when crizotinib is coadministered with other agents that are predominantly metabolized by this system.

8. Rapid, significant depression of serum testosterone levels has been observed in men treated with crizotinib. In a series of 32 patients treated with crizotinib, the mean serum testosterone levels was below the lower limit of normal in 27 of 32 men (84 percent) compared with 6 of 19 (32 percent) among those not receiving crizotinib. Levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) were also low.

9. Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 5.2%, 0.4%, and 11.4% of patients, respectively.

10. Neuropathy as defined in and attributed to study drug by the investigator was reported in 34 (13%) patients. While most events were Grade 1, Grade 2 motor neuropathy and Grade 3 peripheral neuropathy were reported in 1 patient each.

**ONGOING TRIALS**

In two ongoing phase III trials, patients with ALK-positive lung cancer who have not received prior systemic therapy for advanced disease are being randomly assigned to either crizotinib or chemotherapy with pemetrexed plus a platinum compound (either cisplatin or carboplatin). Patients assigned to chemotherapy can crossover to crizotinib when progressive disease is documented. The primary endpoint in both trials is progression-free survival.35

1. For patients with advanced or metastatic non-small cell lung cancer whose tumors contain a characteristic ALK fusion oncogene, we recommend initial treatment with crizotinib rather than chemotherapy (Grade 1B). For patients in areas where crizotinib is not available for first line therapy, enrollment in the phase III protocol may be an alternative.
A. Crizotinib should not be used in patients without ALK rearrangement. In accordance with the FDA label, ALK-positivity must be demonstrated by FISH using the FDA-approved test (Vysis Probes).

B. Chemotherapy is an appropriate option as second-line therapy for patients who have progressed while on treatment with crizotinib. An alternative option is a trial with a second generation ALK inhibitor. Preliminary efficacy data with two second generation ALK inhibitors (LDK378 and AP26113) suggest that these drugs induce responses in the majority of patients who have previously relapsed on crizotinib.

C. Crizotinib is indicated as second-line therapy when progressive disease occurs for patients whose tumor contains the ALK fusion oncogene and initially was treated with chemotherapy.

2. In some cases, chemotherapy is required before the results of molecular testing are available. If the tumor is found to contain the ALK fusion oncogene and patients have an ongoing objective response or stable disease after completing their initial doublet chemotherapy, the authors prefer to switch to crizotinib although both crizotinib and single-agent maintenance chemotherapy are options. Factors that should be discussed with the patient in defining a treatment plan include the quality of the initial response to chemotherapy and the potential side effects of maintenance therapy.35

3. In addition to blocking ALK and ROS1, crizotinib is also a potent MET inhibitor and there is case-report level evidence that strong responses can occur in MET-amplified NSCLC patients. Several centers in the US have a clinical trial of crizotinib open for MET-amplified patients. The ROS1 tyrosine kinase is highly sensitive to crizotinib in preclinical models, due to a high degree of homology between the ALK and ROS tyrosine kinase domains. There is case report level evidence of patients with ROS1 positive NSCLC responding to crizotinib. The dose expansion cohort of the crizotinib phase I trial was expanded to include patients with ROS1; in a preliminary report of 14 patients treated on this trial, 8 (57 percent) had an objective response following treatment with crizotinib, with the vast majority of patients having some degree of clinical benefit.

ROS1 translocation: ROS1 is a receptor tyrosine kinase of the insulin receptor family that acts as a driver oncogene in 1 to 2 percent of NSCLC via a genetic translocation between ROS1 and the partners CD74, SLC24A2. Histologic and clinical features that are associated
with ROS1 translocations include adenocarcinoma histology, younger patients, and never-smokers. ROS1 translocations are identified by a FISH break-apart assay similar to that used for ALK translocations.

CONCLUSION

More than 90 percent of non-small cell lung cancers are caused by smoking tobacco. People who are exposed to second-hand smoke, air pollution, asbestos and arsenic in drinking water are more likely to develop non-small cell lung cancer. Crizotinib is more effective than standard chemotherapy in patients with lung cancer containing this abnormality, and thus crizotinib is generally recommended as the initial therapy instead of standard chemotherapy in this situation. The presence of the ALK fusion oncogene conferred sensitivity to crizotinib, a specific inhibitor of the anaplastic lymphoma kinase (ALK) tyrosine kinase, in phase II and III studies. Crizotinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

REFERENCES

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