Lung cancer is one of the most frequently diagnosed cancers, as well as the leading cause of cancer-related mortality in the United States. According to the American Cancer Society, more than 159,000 Americans will die from lung cancer in 2014, representing approximately 27% of all cancer deaths. Non–small-cell lung cancer (NSCLC), the most common form of lung cancer, accounts for 85% to 90% of all cases. NSCLC comprises a number of histologies, including adenocarcinoma, squamous-cell carcinoma, nonsquamous carcinoma, large-cell carcinoma, sarcomatoid carcinoma, and adenosquamous carcinoma.

A recent analysis of claims data from an oncology registry associated with a large US commercial health plan has demonstrated the substantial cost burden associated with NSCLC. This study, which was published in 2013, assessed the total cost of treatment for more than 300 patients with advanced NSCLC who were continuously enrolled in the plan from diagnosis until death. The average total healthcare costs ranged from approximately $19,000 to $167,000 for first-line NSCLC management, and from approximately $35,000 to $135,000 for second-line management. In this analysis, systemic therapy represented 20% to 55% of first-line total costs, and 22% to 68% of second-line total costs.

Traditionally, patients with metastatic NSCLC have been managed with combinations of cytotoxic agents. Although the use of platinum-based doublets has improved the median overall survival for patients with advanced NSCLC from 4 to 5 months to 8 to 10 months (in treatment-naïve patients), these chemotherapy combinations are limited by significant toxicities, including myelosuppression, nausea and vomiting, and severe fatigue.

As knowledge of tumor-cell biology in lung cancer evolves, small molecules that target specific genetic mutations offer the opportunity to manage patients with NSCLC using a personalized approach. In NSCLC, multiple driver oncogenes have been identified, including EGFR, ALK, and KRAS. Among North American patients with advanced NSCLC, approximately 10% express mutations in EGFR, approximately 23% express mutations in KRAS, and up to 13% express activating mutations or translocations of ALK.

Identifying EGFR and ALK mutations can help to decide whether a given patient with NSCLC can benefit from today’s targeted therapies, including erlotinib and afatinib (EGFR inhibitors) or crizotinib (an ALK inhibitor).

Granted an accelerated approval by the US Food and Drug Administration (FDA) in 2011, crizotinib was the first treatment available for patients with metastatic NSCLC whose tumors are ALK-positive. An open-label, active-controlled, multinational, randomized clinical trial demonstrated prolonged progression-free survival with crizotinib compared with chemotherapy in ALK-positive, metastatic NSCLC. Vision disorders, nausea, diarrhea, vomiting, constipation, edema, elevated transaminases, and fatigue were the most common adverse reactions observed among recipients of crizotinib in this trial. To overcome the documented resistance to crizotinib, researchers continue to investigate medications that target ALK mutations. Novel kinase inhibitors currently being investigated in clinical trials for patients with ALK mutation NSCLC include alectinib, ganetespib, and AP26113.

Ceritinib: New Treatment Option for ALK-Positive NSCLC

On April 29, 2014, the FDA approved ceritinib (Zykadia; Novartis Pharmaceuticals), a kinase inhibitor, for the treatment of patients with metastatic ALK-positive NSCLC who are intolerant of, or whose disease progressed during therapy with, crizotinib. This approval was granted under the FDA’s accelerated process based on unpublished clinical trial data demonstrating significant tumor response rate and duration of response. Improvements in survival or disease-related symptoms have not been demonstrated.

The approval of ceritinib was based on the results of a multicenter, single-arm, open-label clinical trial that enrolled 163 patients with ALK-positive metastatic NSCLC that had progressed with crizotinib or who were intolerant of that drug. Ceritinib was administered at a dose of 750 mg once daily.

“Zykadia represents an important treatment option for ALK-positive NSCLC patients who relapse after starting initial therapy with crizotinib,” noted lead investigator Alice T. Shaw, MD, PhD, of Massachusetts Gen-

Zykadia (Ceritinib) Approved for Patients with Crizotinib-Resistant ALK-Positive Non–Small-Cell Lung Cancer

By Lisa A. Raedler, PhD, RPh, Medical Writer
Table 1: Response Rate and Duration of Response with Crizotinib in Patients with ALK-Positive NSCLC

<table>
<thead>
<tr>
<th>Efficacy end point</th>
<th>Investigator assessment (N = 163)</th>
<th>BIRC assessment (N = 163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, %</td>
<td>54.6 (95% CI, 47-62)</td>
<td>43.6 (95% CI, 36-52)</td>
</tr>
<tr>
<td>Complete response, %</td>
<td>1.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Partial response, %</td>
<td>53.4</td>
<td>41.1</td>
</tr>
<tr>
<td>Duration of response, median months</td>
<td>7.4 (95% CI, 5.4-10.1)</td>
<td>7.1 (95% CI, 5.6-not estimable)</td>
</tr>
</tbody>
</table>

BIRC indicates Blinded Independent Review Committee; CI, confidence interval.

Source: Zykadia (ceritinib) capsules prescribing information; April 2014.

**Mechanism of Action**

In vitro and in vivo assays demonstrate that ceritinib, a kinase inhibitor, hinders the proliferation of ALK-dependent cancer cells by blocking the autophosphorylation of ALK, as well as ALK-mediated phosphorylation of STAT3, a downstream signaling protein. Ceritinib also targets insulin-like growth factor 1 receptor, insulin receptor, and ROS1.

**Dosing and Administration**

Ceritinib should be administered at a dose of 750 mg orally once daily until disease progression or until unacceptable toxicity. It should be taken on an empty stomach, but not within 2 hours of a meal. If a dose of ceritinib is missed, it should be administered only if the next dose is not due within 12 hours.

**Single-Arm Phase 2 Trial**

The multicenter, single-arm, open-label trial of ceritinib enrolled 163 patients with the ALK-mutation NSCLC whose disease progressed while receiving crizotinib or those who were intolerant of crizotinib. Objective response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors version 1.0 was the primary end point of this study. This parameter was evaluated by the investigators and by a central Blinded Independent Review Committee.

Most patients with ALK-positive NSCLC were female (54%), Caucasian (66%), aged <65 years (87%), and never or former smokers (97%). The majority (87%) had an Eastern Cooperative Oncology Group performance status of 0 or 1.

Overall, 91% of patients had progressed with previous treatment of crizotinib, 84% had received ≥2 previous therapies, and 93% had adenocarcinoma histology. Common sites of extrathoracic metastases included the brain (60%), liver (42%), and bone (42%). Retrospective verification of ALK positivity was performed by review of local test results for 99% of patients.

The phase 2 study demonstrated that ceritinib is active in patients with ALK-positive NSCLC, with an ORR of 54.6% by investigator assessment and a median duration of response of 7.4 months. All participants received ceritinib at an initial dose of 750 mg daily. The median duration of exposure to ceritinib was 6 months. The findings of the Blinded Independent Review Committee were similar to those of the investigators. Table 1 lists the findings on ORR and duration of response from this study.

**Safety and Adverse Events**

The safety of ceritinib was established based on data from 255 patients with ALK-positive disease in the phase 2 study—246 patients with NSCLC and 9 patients with other cancer types. A total of 59% of the patients receiving ceritinib required dose reductions as a result of adverse reactions. The adverse reactions that led to dose reductions or interruptions were reported in ≥10% of patients and included increased alanine aminotransferase (ALT; 29%), nausea (20%), increased aspartate aminotransferase (AST; 16%), diarrhea (16%), and vomiting (16%).

Serious adverse drug reactions that were reported in ≥2% of patients receiving ceritinib included convulsion, pneumonia, interstitial lung disease/pneumonitis, dyspnea, dehydration, hyperglycemia, and nausea. Of the patients receiving ceritinib, 5% had fatal adverse reactions, including pneumonia, respiratory failure, interstitial lung disease/pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade, and 1 case of sepsis.

Overall, 10% of patients receiving ceritinib discontinued therapy as a result of adverse reactions. Pneumonia, interstitial lung disease/pneumonitis, and decreased appetite were the most common adverse drug reactions that led to discontinuation in ≥1% of patients. Of note, ceritinib should be discontinued in patients who do not tolerate 300 mg daily dosing.

Table 2 lists the common adverse reactions and Table 3 lists the laboratory abnormalities reported in patients treated with ceritinib.

Additional adverse reactions occurring in ≥2% of the patients receiving ceritinib include neuropathy (17%), manifested as paresthesia, muscular weakness, gait disturbance, peripheral neuropathy, hypoesthesia, periph-
eral sensory neuropathy, dysesthesia, neuralgia, peripheral motor neuropathy, hypotonia, or polyneuropathy; vision disorder (9%), including vision impairment, blurred vision, photopsia, accommodation disorder, presbyopia, or reduced visual acuity; prolonged QT interval (4%); and bradycardia (3%).

Ceritinib has no contraindications.

**Warnings and Precautions**

**Severe/persistent gastrointestinal toxicity.** Of the 255 patients receiving ceritinib in the phase 2 study, 96% had diarrhea, nausea, vomiting, or abdominal pain; severe cases were reported in 14% of the patients. Dose modification was required in 38% of patients as a result of diarrhea, nausea, vomiting, or abdominal pain. Patients should be managed using standards of care, as needed. Based on the severity of the adverse drug reaction, ceritinib should be withheld and then resumed with a 150-mg dose reduction.

**Hepatotoxicity.** Of the 255 patients in the phase 2 study, 27% had elevations in ALT that were greater than 5 times the upper limit of normal. Permanent discontinuation resulting from elevated transaminases and jaundice was required in 1 (0.4%) patient. Patients should undergo laboratory tests, including ALT, AST, and total bilirubin, once monthly and as clinically indicated. More frequent testing is warranted in patients who develop transaminase elevations. Ceritinib should be withheld, dose reduced, or should be permanently discontinued based on the severity of the hepatotoxicity reaction.

**Interstitial lung disease/pneumonitis.** Severe, life-threatening, or fatal interstitial lung disease/pneumonitis has occurred in patients receiving ceritinib. Pneumonitis was reported in 4% of the 255 patients in the phase 2 study. In all, 3% of patients had grade 3 or 4 disease, and 1 patient died. Ceritinib was discontinued in 1% of patients because of interstitial lung disease/pneumonitis. If symptoms indicative of interstitial lung disease/pneumonitis are observed, exclude other potential causes. If interstitial lung disease/pneumonitis is deemed to be treatment-related, discontinue ceritinib therapy permanently.

**QT interval prolongation.** In the phase 2 study and across the development program of ceritinib, 3% of patients had corrected QT (QTc) interval increase from a baseline of >60 msec. Across the development program of ceritinib, 1 patient using doses ranging from 50 mg to 750 mg had a QTc of >500 msec.

Ceritinib should be avoided in patients with congenital long QT syndrome. Patients with congestive heart failure, bradyarrhythmias, or electrolyte abnormalities, and those taking medications known to prolong the QTc interval should undergo periodic electrocardiograms (ECGs) and electrolyte monitoring.

Ceritinib should be withheld in patients who develop a QTc interval of >500 msec on at least 2 separate ECGs. Ceritinib can be resumed with a 150-mg dose reduction if the QTc interval is <481 msec or on recovery to baseline if the QTc interval is ≥481 msec. Ceritinib should be permanently discontinued in patients who develop QTc interval prolongation in combination with torsades de pointes, polymorphic ventricular tachycardia, or signs or symptoms of serious arrhythmia.

**Hyperglycemia.** Grade 3 or 4 hyperglycemia based on...
laboratory values occurred in 13% of patients in the phase 2 study of ceritinib. The risk for grade 3 or 4 hyperglycemia in patients with diabetes or glucose intolerance was increased 6-fold. There was a 2-fold increase in the risk for grade 3 or 4 hyperglycemia in patients taking corticosteroids. Serum glucose levels should be monitored, and antihyperglycemic medications should be used as indicated. Ceritinib should be withheld until hyperglycemia is controlled and then resumed with a 150-mg dose reduction. If adequate hyperglycemic control cannot be achieved, ceritinib should be discontinued.\footnote{13}

**Bradycardia.** Sinus bradycardia was observed as a new finding in 1% of patients and was reported as an adverse drug reaction in 3% of patients in the phase 2 study of ceritinib.\footnote{13} Ceritinib should be avoided in patients taking other agents known to cause bradycardia (eg, beta-blockers, nondihydropyridine calcium channel blockers, clonidine, and digoxin) if possible. Heart rate and blood pressure should be monitored regularly.\footnote{13} If symptomatic bradycardia is not life-threatening, ceritinib should be withheld until recovery or until the heart rate is $\geq 60$ beats per minute (bpm). Concomitant medication use should be evaluated, and ceritinib dose should be adjusted. If bradycardia is associated with a medication known to cause bradycardia or hypotension, ceritinib can be withheld until recovery or to a heart rate of $\geq 60$ bpm. If the concomitant medication can be adjusted or discontinued, ceritinib can be restarted at a 150-mg dose reduction on recovery to asymptomatic bradycardia or to a heart rate of $\geq 60$ bpm, with frequent monitoring. Ceritinib should be discontinued if life-threatening bradycardia is observed and no concomitant medication use is identified.\footnote{13}

**Embryofetal toxicity.** Based on its mechanism of action, ceritinib may cause fetal harm when administered to a pregnant woman.\footnote{13}

### Specific Populations

**Pregnancy.** Ceritinib has a pregnancy Category D. Women of reproductive potential should be made aware of the potential hazard to a fetus, as well as the need to use effective contraception during treatment with ceritinib and for at least 2 weeks after the completion of therapy.\footnote{13}

**Nursing mothers.** Whether ceritinib or its metabolites are excreted in human milk is not known. Nursing mothers who take ceritinib should discontinue breastfeeding.\footnote{13}

**Pediatric use.** The safety and effectiveness of ceritinib have not been established in pediatric patients.\footnote{13}

**Geriatric use.** Clinical studies of ceritinib did not include sufficient numbers of patients aged $\geq 65$ years to assess its effect on older patients. Of the 255 patients in the phase 2 study, 40 (16%) were aged $\geq 65$ years.\footnote{13}

**Hepatic impairment.** Because ceritinib is eliminated primarily in the liver, patients with hepatic impairment may have increased exposure. Based on a pharmacokinetic-analysis, dose adjustment is not recommended for patients with mild hepatic impairment. A recommended dose has not been determined for patients with moderate-to-severe hepatic impairment.\footnote{13}

### Conclusion

NSCLC remains the main cause of death from cancer in the United States for men and women. The disease is still diagnosed mainly at advanced stages; therefore, prognosis is poor, and long-term survival is rare. Ceritinib, the second oral kinase inhibitor approved for the initial treatment of ALK-positive metastatic NSCLC, has demonstrated efficacy with manageable side effects. Ceritinib joins crizotinib as the second FDA-approved agent for this subset of patients with NSCLC, offering an effective alternative to cytotoxic therapy. Ceritinib may confer clinical value in other cancers in which ALK mutations are present. Clinical studies are evaluating ceritinib in pediatric malignancies and other tumors characterized by genetic abnormalities of ALK.\footnote{15}

### References


