Brigatinib approval yields additional treatment options for crizotinib-resistant, ALK-positive NSCLC patients

The accelerated approval by the United States Food and Drug Administration (FDA) of the anaplastic lymphoma kinase (ALK) inhibitor brigatinib, marked the fourth approved drug in this class.[1] The most recent approval expands the available treatment options for patients with metastatic ALK-positive non–small-cell lung cancer (NSCLC) whose disease is no longer responding to the first-line ALK inhibitor crizotinib. The FDA based its decision on the results of the phase 2 ALTA trial, in which a significant proportion of patients experienced tumor shrinkage.[2]

The pivotal trial was a noncomparative, 2-arm, open-label, multicenter study that was carried out during June 2014-September 2015 at 71 centers across 18 countries. Eligible patients were 18 years or older, with locally advanced or metastatic ALK-positive NSCLC, disease progression while taking crizotinib, at least 1 measurable lesion, adequate organ and hematologic function, and Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 (range, 0-5, where 0 means the patient is fully active, and 2, ambulatory and capable of all self-care but not able to carry out any work activities).

Patients were excluded from the trial if they had received previous ALK inhibitor therapy, other than crizotinib, or had received crizotinib within 3 days of the first dose of brigatinib, or they had received chemotherapy, radiation therapy, or investigational drugs within 14 days or monoclonal antibody therapy within 30 days of the first dose of the study drug. Anyone with a history or the presence of pulmonary interstitial disease or drug-related pneumonitis or symptomatic central nervous system (CNS) metastases that were neurologically unstable or required an increasing dose of corticosteroids was also ineligible.

A total of 222 patients were randomized to receive one of two brigatinib doses, either 90 mg daily or 180 mg daily after a 7-day lead-in at 90 mg (the latter to help mitigate pulmonary adverse events observed in previous studies). Randomization was stratified according to baseline brain metastases (present or absent) and best investigator-assessed response to crizotinib (complete response [CR] or partial response [PR] vs other or unknown)

Chest and abdomen imaging by computed-tomography (CT) or magnetic resonance imaging (MRI) with contrast were performed to assess disease at screening and every 8 weeks through cycle 15, and then every 12 weeks until disease progression. Contrast-enhanced brain MRI was carried out at screening and repeated after baseline for the 68% of patients who had CNS metastases at the time of enrollment.

The primary endpoint was confirmed investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST, version

What's new, what's important

Approval of the ALK inhibitor, brigatinib, expanded the treatment options for patients with metastatic ALK-positive NSCLC who no longer respond to the first-line ALK inhibitor, crizotinib.

The approval was based on findings in the noncomparative phase 2 ALTA trial, in which a significant proportion of patients experienced tumor shrinkage. In all, 222 patients were randomized to receive either 90 mg daily or 180 mg daily, following a 7-day lead-in at 90 mg to mitigate previously observed pulmonary adverse events. ORRs were 48% and 53% for the 90-mg and 180-mg doses, respectively. Responses occurred quickly and were durable in both arms; median DoR was 13.8 months for both doses. Especially notable were the intracranial response rates in patients with brain metastases (42% and 67%, respectively) because of the poor ability of crizotinib to penetrate the blood-brain barrier. Secondary outcomes also favored the 180-mg dose (PFS, 9.2 and 12.9 months, respectively; estimated 1-year OS, 71% and 80%; with 1 confirmed CR in the 90-mg arm and 4 CRs in the 180-mg arm.)

The most common AEs were nausea, diarrhea, fatigue, cough and headache, and visual disturbances. Pneumonia and interstitial lung disease/pneumonitis were noted as the most serious AEs. The drug carries warnings about hypertension, bradycardia, creatine phosphokinase and pancreatic enzyme elevation, and hyperglycemia. Patients should be monitored for respiratory symptoms, blood pressure and heart rate, new visual symptoms, and muscle pain. Patients of reproductive potential should be advised of the risks and necessary precautions.

— Jame Abraham, MD, FACP (abrahaj5@ccf.org)

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Mechanism of action: brigatinib

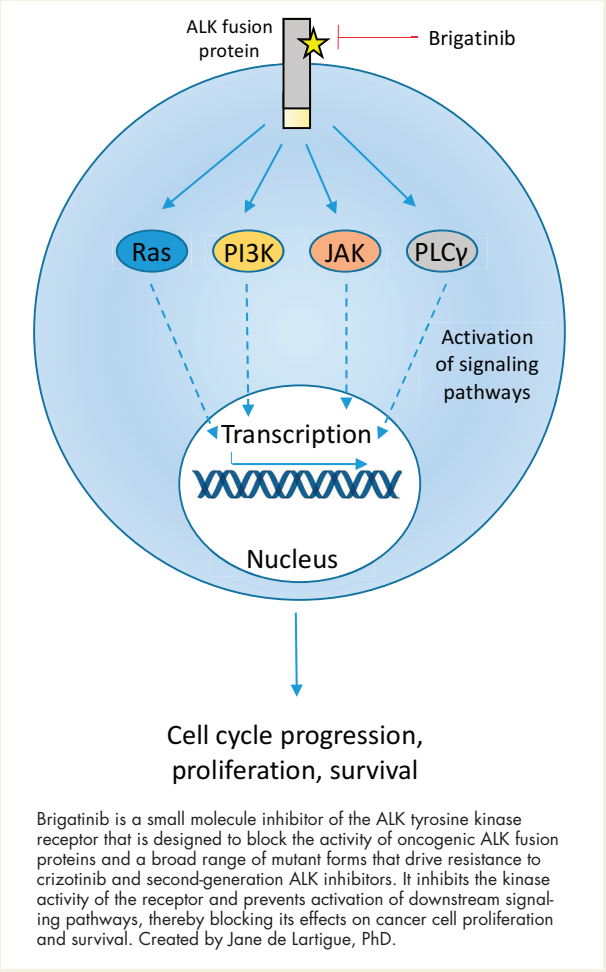
Next-generation ALK inhibitor blocks broadest range of resistance mechanisms to date. The anaplastic lymphoma kinase (ALK) protein is a receptor tyrosine kinase of the insulin receptor family. Although oncogenic forms of the ALK protein were first observed in patients with anaplastic large-cell lymphoma, their potential as an anticancer drug target was not fully recognized until the identification of the EML4-ALK fusion protein in patients with non–small-cell lung cancer (NSCLC).

Oncogenic ALK fusion proteins are formed when a chromosomal translocation leads to part of the *ALK* gene breaking off and fusing to another gene, resulting in inappropriate activation of ALK's kinase activity, which promotes cancer cell proliferation and survival. Although ALK-positive disease is found in only 3%-7% of patients with NSCLC, the number of cases of ALK-positive disease is estimated to exceed 8,000 a year in the United States because of the prevalence of NSCLC.

A first-generation ALK inhibitor, crizotinib, was rapidly taken from bench to bedside following discovery of ALK fusions in NSCLC and has demonstrated clear clinical benefit. However, the majority of patients treated with crizotinib ultimately relapse owing to the development of resistance by their tumors. A number of mechanisms of resistance have been identified, including the development of mutations in the ALK protein that render crizotinib incapable of binding.

Second-generation ALK inhibitors, including ceritinib and alectinib, have been developed that have activity against several of the resistance-conferring ALK mutant forms, but their efficacy is also limited by the development of resistance by other means and, therefore, researchers have been working to generate drugs that can potently inhibit all known resistance mutations and seeking ways to combat other common mechanisms of resistance.

This is where brigatinib fits in, as a potent inhibitor of multiple tyrosine kinases, including ALK, ROS1, IGF1R, and FLT3 but, more importantly, the broadest inhibition of ALK resistance mutations to date, including the G1202R and L1196M mutations, as well as EGFR point mutations and deletions, ROS1 mutants, and FLT3 mutants



Brigatinib is a small molecule inhibitor of the ALK tyrosine kinase receptor that is designed to block the activity of oncogenic ALK fusion proteins and a broad range of mutant forms that drive resistance to crizotinib and second-generation ALK inhibitors. It inhibits the kinase activity of the receptor and prevents activation of downstream signaling pathways, thereby blocking its effects on cancer cell proliferation and survival. Created by Jane de Lartigue, PhD.

1.1), and secondary endpoints included CNS response, duration of response (DoR), progression-free and overall survival (PFS and OS, respectively). ORRs for the 90-mg and 180-mg doses were 48% and 53%, respectively. Responses occurred quickly and were durable in both arms; after a median follow-up of 8 months, median DoR was 13.8 months for both doses. Among the patients with brain metastases, the intracranial response rates for the two doses were 42% and 67%, respectively, notable because of the poor ability of crizotinib to penetrate the blood-brain barrier.

Other secondary outcomes also favored the 180-mg dose. Investigator-assessed PFS for the 90-mg and 180-mg doses were 9.2 months and 12.9 months, respectively, and estimated 1-year OS was 71% and 80%, respectively, the latter representing a nonstatistically significant 43% reduction in the risk of death with the 180 mg dose. There were 4 confirmed CRs in the 180-mg arm and 1 in the 90-mg arm.

The safety of brigatinib was evaluated in 219 patients who received at least 1 dose of brigatinib. Treatment was discontinued in 8% of patients in the 180-mg arm and 3% in the 90-mg arm because of adverse events (AEs). The most common AEs were nausea, diarrhea, fatigue, cough, and headache, and visual disturbances also occurred. The most common serious AEs were pneumonia and interstitial lung disease/pneumonitis.

The prescribing information details warnings and precautions about these and other potential toxicities, including hypertension, bradycardia, creatine phosphokinase (CPK) and pancreatic enzyme elevation, and hyperglyce-

mia.[3] Patients should be monitored for new or worsening respiratory symptoms, especially during the first week of initiating brigatinib treatment; blood pressure should be controlled before treatment initiation and monitored after 2 weeks and at least monthly thereafter; heart rate and blood pressure should be monitored frequently; patients should be advised to report any visual symptoms, or any unexplained muscle pain, tenderness or weakness; CPK, lipase, and amylase levels should be monitored during treatment, and fasting glucose tested before starting treatment and periodically thereafter.

Brigatinib should be withheld in any patient with new or worsening respiratory symptoms, for grade 3 hypertension despite optimal antihypertensive therapy, for symptomatic bradycardia, for patients with new or worsening visual symptoms of grade 2 or above, for grade 3 or 4 CPK or pancreatic enzyme elevation, or if adequate hyperglycemia control cannot be achieved. Treatment should be permanently discontinued for grade 3 or 4 or recurrent interstitial lung disease/pneumonitis, grade 4 or recurrent grade 3 hypertension, life-threatening bradycardia, and grade 4 visual disturbance.

Based on its mechanism of action, brigatinib can cause fetal harm and patients of reproductive potential should be advised of the risks and necessary precautions. Brigatinib is marketed as Alunbrig by Ariad Pharmaceuticals Inc.

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