NSCLC: New EGFR Inhibitor Shows Robust Activity in Treatment-Resistant Disease

BY MARK FUERST

A third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) shows promise as a treatment for patients with advanced, EGFR-mutant, non-small-cell lung cancer (NSCLC) that is resistant to standard EGFR inhibitors, according to the results of a study presented at the American Society of Clinical Oncology Annual Meeting (***Abstract 8009***).

In the study, which was featured in an ASCO pre-meeting news briefing for the media, the drug, AZD9291, induced an overall response rate of 64 percent without dose-limiting toxicities in patients with an acquired EGFR T790M resistance mutation.

"There is currently no standard treatment for patients with lung cancer who experience disease progression after initial therapy with an EGFR kinase inhibitor," said the lead author, Pasi A. Jänne, MD, PhD, Director of the Lowe Center for Thoracic Oncology at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School. "Although it is still a bit early, our study suggests that AZD9291 may offer an effective new therapy option for these patients, without the skin side effects we typically see with existing EGFR inhibitors."

He explained that in patients with NSCLC, EGFR mutations are found in about 10 to 15 percent of Caucasian patients and about 40 percent of Asian patients, and that although many of them initially respond well to the approved EGFR inhibitors erlotinib and afatinib, all generally ultimately become resistant within about 10 to 14 months.

AZD9291 earlier this year received the FDA's Breakthrough Therapy designation for the treatment of patients with metastatic, EGFR T790M mutation-positive NSCLC whose NSCLC has progressed during treatment with an FDA-approved EGFR tyrosine kinase inhibitor.

There are no approved treatments for patients with T790M-positive NSCLC, Jänne noted. The only therapy that is somewhat effective in patients with the T790M mutation is a combination of afatinib and cetuximab, but the toxicity is very high. AZD9291, a third-generation, mutant-selective inhibitor of EGFR, was shown to have an effect in preclinical tumor models with both EGFR-TKI-sensitizing and T790M resistance mutations.

Phase I Study Results

In the Phase I, open-label, multicenter AURA study Jänne presented, oral AZD9291 was given once daily to Asian and Western patients with advanced NSCLC with documented radiological progression while on prior therapy with an EGFR-TKI. The primary endpoints were safety and tolerability in EGFR-TKI-refractory patients. The secondary endpoints were the maximum tolerated dose, pharmacokinetics, and preliminary efficacy. The 199 enrolled patients with EGFR-mutant NSCLC received treatment with AZD9291 at five doses, from 20 to 240 mg. The median age of patients was 60; two-thirds were Asians, and one-third were Caucasians.

Responses by Response Evaluation Criteria in Solid Tumors (RECIST) were seen at all dose levels, including in patients with brain metastases. In the 177 evaluable patients treated with the drug, the overall response rate (ORR) was 51 percent. In 89 patients with confirmed T790M resistance mutations, the ORR was 64 percent and the disease control rate was 96 percent. In 43 patients without the T790M mutations, the ORR was 23 percent.

The responses were still ongoing in nearly all patients at data cut-off, he said. Median duration of response had not been reached at the time of the analysis, with the longest duration of response more than eight months.

The most common adverse events, mostly Grade 1, were diarrhea occurring in 30 percent of patients; rash in 24 percent; and nausea in 17 percent. "The rash was mostly mild in nature and diarrhea was also mild," Jänne noted, explaining that since AZD9291 is an irreversible inhibitor of EGFR and T790M mutations, with a reduced affinity for wild-type EGFR, the rate of skin rash was therefore considerably lower than with earlier EGFR inhibitors.

Grade 3/4 adverse events occurred in 16 percent of patients, with six patients (3%) requiring a dose reduction. Over the course of the trial, seven patients (4%) had to discontinue treatment because of adverse events. There were five reports of interstitial lung disease, most of which occurred with a 160 mg dose of the drug. All five patients then responded well to treatment and recovered fully, with no fatal events, he noted.

PASI A. JÄNNE, MD, PHD: "The promising results from this Phase I trial warrant further investigation of the activity of AZD9291 in this setting, and additional clinical development is ongoing."

In conclusion, Jänne said, "There is no currently approved therapy for patients with T790M-positive NSCLC whose disease progresses on EGFR-TKI treatment. AZD9291 has shown very promising results with an ORR of 64 percent in patients with EGFR-mutant NSCLC and T790M-acquired resistance to EGFR-TKIs. AZD9291 has exhibited no dose-limiting toxicities, and a non-tolerated dose was not defined. The promising results from this Phase I trial warrant further

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Orphan Drug Status to Selinexor for DLBCL

The U.S. Food and Drug Administration has granted Orphan Drug status to Selinexor (KPT-330), an oral selective inhibitor of nuclear export (SINE) compound, for the treatment of patients with diffuse large B-cell lymphoma (DLBCL). Orphan drug status had previously been granted to the drug for the treatment of patients with acute myeloid leukemia (***http://bit.ly/1kddAGl***).

The Orphan Drug designation—to encourage development of drugs in the diagnosis, prevention, or treatment of a medical condition affecting fewer than 200,000 people in the U.S.—grants a product market exclusivity for a seven-year period if the sponsor complies with certain FDA specifications, as well as tax credits and prescription drug user fee waivers. The designation does not, though, shorten the duration of the regulatory review and approval process.

Approximately 21,000 patients will be diagnosed with DLBCL in the United States in 2014, according to American Cancer Society estimates.

Phase I clinical trials for Selinexor, which is marketed by Karyopharm Therapeutics, are ongoing and continuing to enroll patients.

AZD9291

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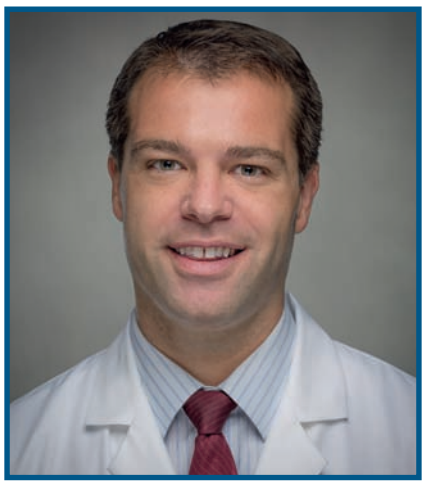
Longer follow-up will determine whether the therapy prolongs overall survival. Given that these data show that AZD9291 is working more effectively for patients with the T790M mutation, future studies of this drug will be limited to this subgroup of patients, he said.

A separate open-label Phase II study, he noted, has now been initiated to explore the 80 mg dose of AZD9291 specifically in patients with T790M-positive metastatic NSCLC that has progressed after treatment with a prior EGFR inhibitor.



BENJAMIN C. CREELAN, MD: "The study addresses a widespread, unmet need to treat resistant disease. Nothing has emerged to fix that."

'New Understanding of Cancer Biology'

ASCO President Peter P. Yu, MD, Director of Cancer Research at the Palo Alto Medical Foundation, who co-moderated the presscast news briefing with ASCO 2013-2014 President Clifford A. Hudis, MD, said: "Drug resistance has been the bane of chemotherapy treatment of cancers for decades. Efforts to understand drug resistance—how it is acquired and how to overcome that—have been very difficult to break through. However, here we have a molecularly targeted therapy that brings the new science understanding of cancer biology to bear, which has identified a mutation that drives this form of lung cancer.

"The reduced skin toxicity seen with AZD9291 heralds greater precision in targeting cancer mutations and sparing healthy tissues, which retain normal germ line EGFR status. As the newer treatments fine tune and hone their targets, we are seeing less toxicity. In this study, two of the major limiting toxicities of the first-generation drugs, diarrhea and rash, were seen less frequently and were milder."

Asked his opinion for this article, Benjamin C. Creelan, MD, a medical oncologist at Moffitt Cancer Center, called the results "a notable breakthrough—The study addresses a widespread, unmet need to treat resistant disease. Nothing has emerged to fix that," he said. "This drug will probably improve the quality of life of patients, sparing them the customary rash and diarrhea. It's exciting to see a newer, more effective drug that targets inhibition and has less toxicity. Still, we don't know about the durability yet."

Creelan said AZD9291 is important because it selectively targets EGFR in tumors and appears to cause fewer skin toxicities than approved EGFR TKIs do. Existing drugs block both the mutant EGFR in the tumor and the normal EGFR in the skin (and other organs), which often leads to debilitating skin rash or acne. In contrast, AZD9291 acts mostly on the mutant EGFR in a tumor.

"More than half of resistant patients progress because of the gatekeeper mutation T790M," he continued. "The third-generation inhibitors have been specifically designed to overcome the T790M mutation. This allows for an improved benefit-to-toxicity ratio. Theoretically, we can ramp up the dose some because we are not worried about off-target side effects."

He noted that the adverse events from second-generation EGFR inhibitors are manageable for most patients, but definitely affect quality of life—"Patients on EGFR inhibitors frequently struggle to control skin toxicity. This is not just a cosmetic problem. The rash can be severe. Other side effects include alopecia, inflammation of the nail beds, and pustules that become infected."

Creelan said that if a NSCLC patient does not respond to a first-generation EGFR inhibitor, he would consider quickly switching to a third-generation inhibitor. He noted that if AZD9291 receives FDA approval for patients who are refractory or intolerant to other EGFR inhibitors, the FDA may require proof of the T790 mutation before allowing the treatment—"I suspect this will not be part of the label, but if it is, this would require a tissue biopsy and introduce an additional hurdle."

Currently, a tissue biopsy may take weeks to schedule and several more weeks to acquire the information. Blood-based tests using circulating DNA have not been established for community practice as yet, he noted.

Looking at the analysis of the study, Creelan said that it could be that a substantial proportion of patients derived benefit from the drug even though there were no objective RECIST responses: "Stable disease could shrink by 30 percent. In fact, for first-line treatment with Tarceva [erlotinib], the ORR is 60 to 70 percent," he said.

Other resistance mechanisms are presumably at work. In 20 percent of NSCLC patients who acquire resistance, MET is amplified. Other resistance pathways may include cellular membranes, receptors, and downstream activation of MEK or KRAS.

Although the responses appear to be durable, the duration of only eight months is still short, not only for response but more importantly, for adverse events. "Some adverse events can take months to develop," he said, noting that the presence of interstitial lung disease is "not surprising since this is common in Tarceva and Iressa [gefinib]."

Another adverse event to watch for is hyperglycemia, which has been noted in other third-generation EGFR inhibitors, he added.

Creelan said he foresees taking the same therapeutic approach to other mutant proteins, such as B-RAF for melanoma, which has similar toxicity: "Perhaps we can develop a drug that is more selective to the mutant in melanoma as well," he said.

"Here we have a molecularly targeted therapy that brings the new science understanding of cancer biology to bear, which has identified a mutation that drives this form of lung cancer."