Next-Generation Targeted Therapy Improves Lung Cancer Survival

Two types of treatment targeting different genetic mutations show promising results in clinical studies.

June 15, 2017 By Liz Highleyman

Two second-generation therapies for non–small cell lung cancer with specific genetic mutations slowed disease progression and increased survival in people with advanced disease, researchers reported at the American Society of Clinical Oncology (ASCO) annual meeting last week in Chicago.

Dacomitinib, an experimental EGFR inhibitor, delayed disease progression or death by five and a half months compared with an older drug in the same class. Another study showed that the ALK inhibitor Alecensa (alectinib) more than doubled progression-free survival.

Non–small cell lung cancer, which accounts for more than 80 percent of all lung cancers, is often detected late and has a high mortality rate. It is the leading cause of cancer-related death for both men and women, according to the U.S. Centers for Disease Control and Prevention.

Lung cancer is difficult to treat, but targeted therapies and immunotherapy have improved outcomes. Targeted therapy works against cancer with specific genetic characteristics. This type of treatment is often better tolerated than traditional chemotherapy, which kills not only cancer cells but also rapidly dividing healthy cells throughout the body.

EGFR Inhibitors

Tony Mok, MD, of the Chinese University of Hong Kong presented results from the first head-to-head Phase III trial comparing two EGFR (epidermal growth factor receptor) tyrosine kinase inhibitors for initial treatment of advanced non–small cell lung cancer. These drugs target cancer with overactive EGFR proteins, which promote tumor growth.

Iressa (gefitinib), one of the earliest EGFR inhibitors, is part of the current standard of care for people with newly diagnosed EGFR-positive lung cancer. Dacomitinib is an experimental second-generation inhibitor that irreversibly binds to three related tyrosine kinases (EGFR, HER2 and HER4).

The ARCHER 1050 study included 452 people in seven countries with advanced (stage IIIB or IV) lung cancer who were starting treatment for the first time. A majority were women, three quarters were Asian and the median age was about 62 years. Two thirds had never smoked, which is the main risk factor for lung cancer.

An earlier study showed that dacomitinib works best for people whose tumors have EGFR-activating mutations, so that group was selected for this trial. About 10 percent of people in the United States with non–small cell lung cancer have these mutations; this figure rises to 35 percent in East Asian countries. Women and nonsmokers are also more likely to have the desired EGFR mutations.

Study participants were randomly assigned to receive dacomitinib (45 milligrams) or Iressa (250 mg), both taken by mouth once daily.

After two years of follow-up, the progression-free survival rate—meaning that patients were still alive with no worsening of disease—was 31 percent in the dacomitinib group, compared with 10 percent in the Iressa group. People who received dacomitinib had a 41 percent lower likelihood of cancer progression or death during this time.

The median duration of progression-free survival was 14.7 and 9.2 months, respectively, a gain of 5.5 months for people taking dacomitinib. Mok noted that 14.7 months is among the longest durations seen in this type of lung cancer trial. Overall survival duration could not yet be determined because a majority of patients were still alive.

The objective response rate—meaning complete or partial tumor shrinkage—was similar in the two groups: 75 percent for dacomitinib and 72 percent for Iressa. However, the dacomitinib group had a significantly longer duration of response, 14.8 versus 8.3 months, respectively.

While dacomitinib was more effective than Iressa, it also came with more side effects. Overall, severe adverse events were more common in the dacomitinib group than in the Iressa group, including diarrhea (8 percent versus 1 percent), nail infections (8 percent versus 1 percent) and dermatitis (14 percent versus 0 percent). But severe elevated liver enzymes were seen more often in the Iressa group (1 percent versus 9 percent). Ten percent of dacomitinib recipients and 7 percent of Iressa recipients stopped therapy due to treatment-related adverse events, while 66 percent and 8 percent, respectively, reduced their doses.

“We changed the treatment paradigm for EGFR-positive lung cancer a few years ago, when targeted therapy replaced chemotherapy,” Mok said. “This study shows that dacomitinib may be an even more effective treatment for these patients. However, patients should be aware of the need to deal with potential side effects when making treatment decisions.”

ALK Inhibitors

Another study at ASCO compared two drugs with a different target: a mutation in the anaplastic lymphoma kinase (ALK) gene. About 5 percent of non–small cell lung cancer is ALK positive, making it susceptible to this type of treatment.

Alice Shaw, MD, of Massachusetts General Hospital Cancer Center in Boston, presented findings from a head-to-head comparison of Xalkori (crizotinib), the first ALK tyrosine kinase inhibitor and part of the current standard of care, and the newer drug Alecensa, which is currently approved by the U.S. Food and Drug Administration as second-line treatment for lung cancer that progresses while on Xalkori.

The Phase III ALEX study enrolled 303 patients with advanced or metastatic (spread beyond the lungs) lung cancer who were being treated for the first time. Just over half were women, around 45 percent were Asian and the median age was about 56 years. Again, two thirds were nonsmokers. About 40 percent had cancer metastasis in their brain.

Participants were randomly assigned to receive Alecensa (600 mg) or Xalkori (250 mg), both taken by mouth twice daily. Treatment continued until patients experienced disease progression or unacceptable side effects.

In this study, 41 percent of patients taking Alecensa experienced disease progression or death, compared with 61 percent of those taking Xalkori—a 50 percent reduction. The median duration of progression-free survival was 25.7 months and 10.4 months, respectively.

“Nobody imagined it would be possible to delay advanced lung cancer progression by this much,” Shaw said. “Most targeted therapies for lung cancer are associated with a median progression-free survival of roughly 12 months.”

The objective response rate was 83 percent in the Alecensa group and 76 percent in the Xalkori group. Four people taking Alecensa and one person taking Xalkori had complete responses. Six percent and 16 percent, respectively, had stable disease.

Just 9 percent of Alecensa recipients had cancer progression in their central nervous system after a year, compared with 41 percent of those taking Xalkori, showing that Alecensa is better at getting through the blood-brain barrier. About twice as many people taking Alecensa experienced improved central nervous system disease (59 percent versus 26 percent).

Unlike the EFGR inhibitor trial, higher effectiveness did not come with worse side effects in the ALK inhibitor study; in fact, the newer drug was generally better tolerated.

Forty-one percent in the Alecensa group and 50 percent in the Xalkori group had severe adverse events. A similar proportion stopped treatment due to adverse events in both groups (11 percent and 13 percent, respectively). The most common severe side effect was elevated liver enzymes.

Based on these findings, Alecensa should be considered the new standard of care for people with previously untreated advanced ALK-positive non–small cell lung cancer, the researchers concluded.

“The fact that this second-generation targeted treatment halted advanced lung cancer growth for more than two years while preventing brain metastases is a remarkable result in this difficult disease,” John Heymach, MD, of the University of Texas MD Anderson Cancer Center, said in an ASCO press statement. “Thanks to this advance, we are on the road to helping these patients live longer and better.”

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