Lorbrena Yields “Unprecedented” Progression-Free Survival for ALK-Positive Lung Cancer

With five years of follow-up, first-line lorlatinib reduced the risk of disease progression or death as well as progression of brain metastasis.

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Lorbrena (lorlatinib) as initial treatment delayed disease progression at five years in more than half of people with ALK-positive metastatic non-small-cell lung cancer (NSCLC), according to study results presented Friday at the American Society of Clinical Oncology Annual Meeting (ASCO 2024) in Chicago. This is the longest progression-free survival ever reported for advanced NSCLC, according to the researchers.

In the second follow-up analysis after the trial’s primary endpoint was met, 60% of people in the Lorbrena group were still alive without disease progression, compared with 8% of those who were treated with an older ALK inhibitor, reflecting an 81% reduction in the risk of disease progression or death. Overall survival—the gold standard for clinical benefit—was not reported.

“ALK-positive advanced NSCLC is typically aggressive and often impacts younger people in the prime of their lives,” said principal investigator Benjamin Solomon, MBBS, PhD, of Peter MacCallum Cancer Centre, in a Pfizer news release. “This updated analysis shows that Lorbrena helped patients live longer without disease progression, with the majority of patients experiencing sustained benefit for over five years, including nearly all patients having protection from progression of disease in the brain.”

NSCLC, which accounts for more than 80% of all lung cancer, is often detected at a late stage and has a high mortality rate. Genetic testing can show whether lung tumors carry driver mutations, such as ALK, EGFR or ROS1 alterations, that can be treated with specific targeted therapies. Around 3% to 5% of people with NSCLC have ALK-positive tumors, which are more common among women, younger people and nonsmokers. About a third of people with this kind of lung cancer develop brain metastasis within a few years after diagnosis.

“Although ALK-positive advanced NSCLC accounts for only approximately 5% of all NSCLC cases, this translates to 72,000 people who are diagnosed worldwide each year,” according to Kenneth Culver, MD, director of research and clinical affairs for ALK Positive, a nonprofit patient support

and advocacy group.

Lorbrena is next-generation oral tyrosine kinase inhibitor (TKI) that interferes with anaplastic lymphoma kinase, a protein that plays a role in cell growth. It was designed to inhibit tumor mutations that drive drug resistance and to penetrate the blood-brain barrier to treat brain metastasis. Previously approved drugs in this class include Xalkori (crizotinib), Zykadia (ceritinib), Alecensa (alectinib) and Alunbrig (brigatinib); the experimental drug ensartinib is awaiting approval. Lorbrena was granted accelerated approval in November 2018 for people with ALK-positive metastatic NSCLC who were previously treated with older targeted medications; it received regular full approval in March 2021 for patients with or without prior systemic therapy.

The first-line indication for Lobrena was based on results from the Phase III CROWN trial (NCT03052608), which enrolled 296 patients with previously untreated Stage IIIb or IV ALK-positive NSCLC. About 60% were women, nearly half were white, 44% were Asian and the median age was approximately 59 years. About a quarter had central nervous system metastasis at baseline. The participants were randomly assigned to receive Lorbrena alone once daily or Xalkori monotherapy twice daily.

The trial's primary endpoint was progression-free survival (PFS), or how long patients remain alive without their disease worsening. Overall survival was a secondary endpoint. The study also looked at responses in people whose lung cancer had spread to the brain.

In 2020, the researchers reported the main study results in The New England Journal of Medicine showing that 78% of Lorbrena recipients were still alive without disease progression at one year, compared with 39% in the Xalkori group. Among those with measurable brain metastasis, 82% and 23%, respectively, had an intracranial response.

Treatment with Lorbrena is generally safe, but side effects are common. According to the product label, the most common adverse events include swelling (edema), peripheral neuropathy, weight gain, cognitive and mood effects, fatigue, shortness of breath, joint pain, diarrhea, elevated blood lipids and cough. The label includes warnings about serious liver toxicity, central nervous system effects, heart problems, lung inflammation and more. In the initial analysis of the CROWN trial, patients who used Lorbrena were more likely than Xalkori recipients to experience severe adverse events (72% versus 56%), but about the same proportion discontinued treatment for this reason (7% and 9%).

The study met its primary endpoint, so formal analysis of progression-free survival ended as planned. But because many participants were still doing well, follow-up continued in an unplanned analysis. In 2022, the researchers reported extended results in The Lancet Respiratory Medicine. At three years, progression-free survival was 64% in the Lorbrena group versus 19% in the Xalkori group. The median PFS time was 9.3 months in the Xalkori group but was not reached in the Lorbrena group because a majority of patients were still responding. Progression of brain metastasis was delayed—and people who did not have cancer in the brain at baseline were less likely to develop it—in the Lorbrena group. Adverse event and discontinuation rates stayed about

the same in both groups, and there were no new safety signals.

Given that median progression-free survival was not yet reached after three years, post hoc follow-up continued. After five years, half of the study participants were still receiving Lorbrena, while just 5% were still taking Xalkori. In the five-year analysis reported at the ASCO meeting and in the Journal of Clinical Oncology, 60% of patients in the Lorbrena group were still alive without disease progression versus 8% in the Xalkori group. However, the PFS rate was lower for Lorbrena recipients with brain metastasis compared to those without (53% and 63%). The median PFS time was 9.1 months in the Xalkori group but still has not been reached in the Lorbrena group.

Lorbrena recipients had an 81% lower risk of disease progression or death and a 94% lower rate of disease progression in the brain. Among people without brain metastasis at baseline, just four out of 114 patients in the Lorbrena group developed brain progression within the first 16 months of treatment, compared with 39 out of 109 in the Xalkori group. What's more, new ALK mutations that could confer drug resistance were not detected in circulating tumor DNA collected at the end of Lorbrena treatment.

Again, the safety of both drugs was consistent with previous findings. At five years, 77% of Lorbrena recipients and 57% of Xalkori recipients experienced severe adverse events, and treatment-related events led to permanent discontinuation in 5% and 6%, respectively.

"After five years of follow-up, median PFS has yet to be reached in the lorlatinib group, corresponding to the longest PFS ever reported with any single-agent molecular targeted treatment in advanced NSCLC and across all metastatic solid tumors," the researchers concluded. "These results coupled with prolonged intracranial efficacy and absence of new safety signals represent an unprecedented outcome for patients with advanced ALK-positive NSCLC and set a new benchmark for targeted therapies in cancer."

Overall survival rates were not reported in either of the two post hoc analyses. In the initial analysis, 23 patients (15%) in the Lorbrena group and 28 (19%) in the Xalkori group had died, a difference that was not statistically significant. The researchers will continue to follow the study participants until the median PFS time is reached in the Lorbrena group and to evaluate whether patients who receive Lorbrena ultimately live longer.

Many experts—and the media—lauded the findings, but others weren't as enthused. Vinay Prasad, MD, MPH, of the University of California San Francisco, and Timothée Olivier, MD, of Geneva University Hospital, noted that the CROWN trial had a "suboptimal" control group. Xalkori was the first ALK inhibitor, approved more than a decade ago. They suggested that the control arm of the CROWN trial should have been the newer ALK inhibitor Alecensa, which is more effective than Xalkori and is considered a standard of care. Xalkori has largely been supplanted in the United States, but it is still used in other countries.

However, David Spigel, MD, of the Sarah Cannon Research Institute, said that the Lorbrena results are "the best we've ever seen" for an ALK TKI inhibitor in the first-line setting. Drugs in this class

have different safety profiles—including more cholesterol and cognitive side effects with Lorbrena—which could affect treatment decisions in specific cases. While cautioning against comparing results across studies, he said that Alecensa and Alunbrig have not shown durable progression-free survival of this magnitude.

“We have not seen anything close to this,” Spigel told reporters at an ASCO media briefing. While some clinicians prefer to save highly effective therapies like Lorbrena for subsequent treatment after older drugs fail, Spigel argued for the opposite approach. “Patients don’t always make it to the next line of therapy,” he said. “I want to give the best drug I can give up front.”

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