FDA Approves Chemo-Free Combo for Advanced Lung Cancer

Rybrevant plus Lazcluze is now approved as first-line treatment for people with advanced or metastatic non-small-cell lung cancer with EGFR mutations.

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On August 29, the Food and Drug Administration (FDA) approved Rybrevant (amivantamab) plus Lazcluze (lazertinib) as a chemotherapy-free initial regimen for people with locally advanced or metastatic non-small cell lung cancer (NSCLC) with specific mutations.

The new combination is indicated for the treatment of NSCLC tumors with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations. EGFR is a protein that plays a role in cell growth and blood vessel development. Around 15% of Western patients and up to 50% of Asian patients with adenocarcinoma type NSCLC have EGFR mutations. The five-year survival rate for people with advanced EGFR-mutated NSCLC treated with current standard-of-care tyrosine kinase inhibitor (TKI) monotherapy is less than 20%.

“This approval is a crucial development for patients with EGFR-mutated NSCLC, who have faced significant unmet needs for far too long,” Jill Feldman, cofounder of the EGFR Resisters patient advocacy group, said in a Johnson & Johnson news release. “Having witnessed firsthand the remarkable evolution in lung cancer treatment, this profoundly important milestone brings a novel therapeutic approach to patients and their families.”

Rybrevant is a bispecific monoclonal antibody that targets both EGFR and MET receptors. It was granted accelerated approved in 2021 a single agent for advanced NSCLC with EGFR exon 20 insertion mutations that has progressed despite platinum-based chemotherapy and received the nod earlier this year for first-line treatment in combination with chemotherapy. Lazcluze is an oral EGFR TKI that is able to reach the brain.

Approval of the combination regimen was supported by the Phase III MARIPOSA trial (NCT04487080). This international study included 1,074 previously untreated people with locally advanced or metastatic NSCLC with exon 19 deletions or exon 21 L858R substitutions. They were randomly assigned to receive Rybrevant plus Lazcluze, Lazcluze alone or the standard-of-care EGFR TKI Tagrisso (osimertinib). Rybrevant was administered by IV infusion once weekly for four

weeks then every two weeks. Lazcluze and Tagrisso are both once-daily pills.

As described at last year's European Society of Medical Oncology Congress and in The New England Journal of Medicine, patients who received Rybrevant plus Lazcluze showed a significant improvement in progression-free survival (PFS), with a 30% reduction in the likelihood of disease progression or death. The median PFS time was 23.7 months in the combination group, 18.5 months in the Lazcluze monotherapy group and 16.6 months in the Tagrisso group.

The overall response rate was similar in the Rybrevant plus Lazcluze and Tagrisso groups (about 85%), but the median duration of response was longer with the combination regimen (25.8 versus 16.8 months). Overall survival data are not yet mature, but so far appear to favor the combination. Longer-term follow-up data will be presented at the World Congress on Lung Cancer next month.

[Update: The late-breaking data (presented September 8) showed that at three years, 61% of people treated with Rybrevant plus Lazcluze were still alive, compared with 53% of those treated with Tagrisso. The median overall survival time was 37.3 months in the latter group but could not yet be calculated in the former group. The combination also demonstrated a trend toward improved central nervous system disease control. More people taking Rybrevant plus Lazcluze were still on that treatment at three years and had not needed to switch to a subsequent regimen.

"Even more encouraging is the marked improvement in the hazard ratio and the ongoing separation of survival curves, showing an 8% improvement at three years for Rybrevant plus Lazcluze compared to [Tagrisso]. This supports the long-term benefit of the combination as a first-line treatment option in this setting," said presenter Shirish Gadgeel, MD, or Henry Ford Cancer Institute.]

Treatment was generally safe, but side effects were common. EGFR drugs can cause skin rash, nail problems, mouth sores (stomatitis) and eye problems. Some Rybrevant recipients experienced infusion reactions. People taking Rybrevant plus Lazcluze had an elevated risk for blood clots (venous thromboembolic events), and prophylactic anticoagulants should be used for the first four months of treatment. More people taking Rybrevant plus Lazcluze stopped treatment due to adverse events compared with the Tagrisso group (10% versus 3%).

"Patients will now have the option of a potential new first-line standard of care with significant clinical benefits over osimertinib," said MARIPOSA investigator Alexander Spira, MD, PhD, of Virginia Cancer Specialists Research Institute. "This first-line therapy uses a targeted approach aiming to achieve the best possible patient outcomes while reserving chemotherapy for later stages of treatment when resistance becomes more complex."

Rybrevant is currently administered via IV infusion, but a subcutaneous injection formulation is awaiting FDA review. As reported at this year's American Society for Clinical Oncology Annual Meeting and in the Journal of Clinical Oncology, the Phase 3 PALOMA-3 study showed that not only did the injectable version lead to a reduction in infusion reactions, it was also associated with

longer progression-free and overall survival.

Johnson & Johnson's J&J withMe offers patient support, resources and help to access and pay for Rybrevant and Lazcluze, regardless of insurance type. See RybrevantwithMe.com or call 833-JNJ-wMe1 (833-565-9631).

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