Lazcluze™ (lazertinib) – New drug approval, Rybrevant® (amivantamab) – New indication

- On August 20, 2024, J&J announced the FDA approval of Lazcluze (lazertinib), in combination with Rybrevant® (amivantamab), for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test.

- Lazcluze is a brain-penetrant EGFR tyrosine kinase inhibitor that targets both the T790M mutation and activating EGFR mutations while sparing wild-type EGFR.

- In addition to the new drug approval, this new indication was added to the drug label for Rybrevant. Rybrevant is also approved for:

    - In combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test
    - As a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

- The efficacy of Lazcluze was established in MARIPOSA, a randomized, active-controlled study in patients required to have untreated locally advanced or metastatic NSCLC with either exon 19 deletions or exon 21 L858R substitution EGFR mutations, not amenable to curative therapy. Patients were randomized to Lazcluze in combination with Rybrevant, Tagrisso® (osimertinib) monotherapy, or Lazcluze monotherapy (an unapproved regimen for NSCLC) until disease progression or unacceptable toxicity. The major efficacy measure was progression-free survival (PFS). Additional efficacy measures included overall survival (OS), overall response rate (ORR) and duration of response (DOR). Efficacy was compared between the Lazcluze plus Rybrevant arm and the Tagrisso arm (N = 858 patients).

    - Median PFS was 23.7 months in the Lazcluze plus Rybrevant arm vs. 16.6 months in the Tagrisso arm (hazard ratio 0.70, 95% CI: 0.58, 0.85; p = 0.0002).
    - The ORR was 78% (95% CI: 74, 82) in the Lazcluze plus Rybrevant arm vs. 73% (95% CI: 69, 78) in the Tagrisso arm.
    - Median DOR was 25.8 months (95% CI: 20.1, not estimable) in the Lazcluze plus Rybrevant arm vs. 16.7 months (95% CI: 14.8, 18.5) in the Tagrisso arm.
    - While OS results were immature at the current analysis, with 55% of pre-specified deaths for the final analysis reported, no trend towards a detriment was observed.

- Warnings and precautions for Lazcluze include venous thromboembolic events (VTE); interstitial lung disease/pneumonitis; dermatologic adverse reactions; ocular toxicity; and embryo-fetal toxicity.

- The most common adverse reactions (≥ 20%) with Lazcluze plus Rybrevant use were rash, nail toxicity, infusion-related reaction (Rybrevant), musculoskeletal pain, edema, stomatitis, VTE, paresthesia, fatigue, diarrhea, constipation, COVID-19, hemorrhage, dry skin, decreased appetite, pruritus, nausea, and ocular toxicity. The most common grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased albumin, decreased sodium, increased alanine aminotransferase, decreased potassium, decreased hemoglobin, increased aspartate transferase, increased gamma-glutamyl transferase, and increased magnesium.

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- The recommended dosage of Lazcluze is 240 mg orally once daily administered in combination with Rybrevant. Treatment should be continued until disease progression or unacceptable toxicity. Lazcluze can be administered any time prior to Rybrevant when given on the same day.
    - Rybrevant intravenous dosing is based on body weight. Refer to the Rybrevant drug label for complete dosing recommendations for all of its NSCLC uses.
- J&J's launch plans for Lazcluze are pending. Lazcluze will be available as an 80 mg and 240 mg tablet.

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