Krazati™ (adagrasib) – New orphan drug approval

- On December 12, 2022, Mirati Therapeutics announced the FDA approval of Krazati (adagrasib), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.
    - This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial(s).
- NSCLC accounts for approximately 85% of all lung cancer cases. KRAS G12C is the most common KRAS mutation in NSCLC, present in approximately 14% of patients with lung adenocarcinoma, and is a biomarker mutation of poor prognosis.
- Krazati is an irreversible inhibitor of KRAS G12C. Krazati inhibits tumor cell growth and viability in cells harboring KRAS G12C mutations.
- The efficacy of Krazati was established in KRYSTAL-1, a single-arm, open-label expansion cohort study. The efficacy population included 112 patients with KRAS G12C-mutated advanced NSCLC who previously received treatment with a platinum-based regimen and an immune checkpoint inhibitor. The major outcome measures were confirmed ORR and DOR.
    - The ORR was 43% (95% CI: 34, 53).
    - The median DOR was 8.5 months (95% CI: 6.2, 13.8).
- Warnings and precautions for Krazati include gastrointestinal adverse reactions, QTc interval prolongation, hepatotoxicity, and interstitial lung disease/pneumonitis.
- The most common adverse reactions (≥ 25%) with Krazati use were nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, renal impairment, edema, dyspnea, and decreased appetite.
- The most common Grade 3 or 4 (≥ 2%) laboratory abnormalities with Krazati use were decreased lymphocytes, decreased hemoglobin, increased alanine aminotransferase, increased aspartate aminotransferase, hypokalemia, hyponatremia, increased lipase, decreased leukocytes, decreased neutrophils, and increased alkaline phosphatase.
- The recommended dosage of Krazati is 600 mg orally twice daily until disease progression or unacceptable toxicity.
    - Patients should be selected for treatment based on the presence of KRAS G12C mutation in plasma or tumor specimens. If no mutation is detected in a plasma specimen, tumor tissue should be tested. Information on FDA-approved tests for the detection of a KRAS G12C mutation is available at: https://www.fda.gov/CompanionDiagnostics.
- Mirati Therapeutics' launch plans for Krazati are pending. Krazati will be available as a 200 mg tablet.