Vitrakvi® (larotrectinib) – New orphan drug approval

- On November 26, 2018, the FDA announced the approval of Loxo Oncology's Vitrakvi (larotrectinib), for the treatment of adult and pediatric patients with solid tumors that: (1) have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, (2) are metastatic or where surgical resection is likely to result in severe morbidity, and (3) have no satisfactory alternative treatments or that have progressed following treatment.
    - This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- Research has shown that the NTRK genes, which encode for tropomyosin receptor kinase (TRK) proteins, can become fused to other genes abnormally, resulting in growth signals that support the growth of tumors. NTRK fusions are rare but occur in cancers arising in many sites of the body.
    - Prior to the approval of Vitrakvi, there had been no treatment for cancers that frequently express this mutation, like mammary analogue secretory carcinoma, cellular or mixed congenital mesoblastic nephroma and infantile fibrosarcoma.
- Vitrakvi is the second cancer treatment approved based on a common biomarker across different types of tumors rather than the location in the body where the tumor originated.
- Vitrakvi is a kinase inhibitor. Based on *in vitro* and *in vivo* tumor models, Vitrakvi has anti-tumor activity in cells with constitutive activation of TRK proteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression.
- The efficacy of Vitrakvi was evaluated in three open-label, single-arm studies of 55 pediatric and adult patients with unresectable or metastatic solid tumors that had an identified NTRK gene fusion. All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR).
    - The ORR was 75% (95% CI: 61, 85) across different types of solid tumors.
    - The DOR ranged from 1.6+ to 33.2+ months; 73% of responses lasted at least 6 months and 39% lasted a year or more at the time results were analyzed.
- Warnings and precautions of Vitrakvi use include neurotoxicity, hepatotoxicity, and embryo-fetal toxicity.
- The most common adverse reactions (≥ 20%) with Vitrakvi use were fatigue, nausea, dizziness, vomiting, increased AST, cough, increased ALT, constipation, and diarrhea.
- The recommended dosage of Vitrakvi is 100 mg orally twice daily in adult and pediatric patients with body surface area (BSA) of ≥ 1.0 m^2. In pediatric patients with BSA < 1.0 m^2, the recommended dosage is 100 mg/m^2 orally twice daily.
    - Patients should be selected for treatment with Vitrakvi based on the presence of a NTRK gene fusion in tumor specimens. An FDA-approved test for the detection of NTRK gene fusion is not currently available.

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- Loxo Oncology plans to launch Vitrakvi immediately. Vitrakvi will be available as 25 mg and 100 mg capsules and a 20 mg/mL oral solution