Lorbrena® (lorlatinib) – New orphan drug approval

- On November 2, 2018, Pfizer announced the FDA approval of Lorbrena (lorlatinib), for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on the following:
    - Xalkori® (crizotinib) and at least one other ALK inhibitor for metastatic disease; or
    - Alecensa® (alectinib) or Zykadia® (ceritinib) as the first ALK inhibitor therapy for metastatic disease.
    - This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

- The American Cancer Society estimates that 234,030 new cases of lung cancer will be diagnosed and 154,050 will die from the disease in 2018.
    - NSCLC accounts for about 85% of lung cancer cases.
    - About 75% of NSCLC patients are diagnosed late with metastatic or advanced disease where the five-year survival rate is only 5%.
    - Epidemiology studies suggest that approximately 3 – 5% of NSCLC tumors are ALK-positive.

- Lorbrena is a tyrosine kinase inhibitor with *in vitro* activity against ALK and ROS1 as well as other gene mutations. Lorbrena demonstrated *in vitro* activity against multiple mutant forms of the ALK enzyme, including some mutations detected in tumors at the time of disease progression on crizotinib and other ALK inhibitors.

- The efficacy of Lorbrena was demonstrated in a non-randomized, dose-ranging study enrolling 215 patients with ALK-positive metastatic NSCLC previously treated with one or more ALK kinase inhibitors. The major efficacy outcome measures were overall response rate (ORR) and intracranial ORR.
    - The ORR was 48% (95% CI: 42, 55).
    - Intracranial ORR was assessed in 89 patients as 60% (95% CI: 49, 70).
    - In addition, duration of response (DOR) was 12.5 months (95% CI: 8.4, 23.7) and intracranial DOR was 19.5 months (95% CI: 12.4, not reached).

- Lorbrena is contraindicated in patients concomitantly using strong CYP3A inducers.

- Other warnings and precautions of Lorbrena include risk of serious hepatotoxicity with concomitant use of strong CYP3A inducers, central nervous system effects, hyperlipidemia, atrioventricular block, interstitial lung disease/pneumonitis, and embryo-fetal toxicity.

- The most common adverse effects (≥ 20%) with Lorbrena use were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea.

- The recommended dose of Lorbrena is 100 mg orally once daily, with or without food, until disease progression or unacceptable toxicity.

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- Pfizer’s launch plans for Lorbrena are pending. Lorbrena will be available as 25 mg and 100 mg tablets.