Houk-Jung **Organic Colloquium**

"Prioritizing the patient - The discovery of lorlatinib, a macrocyclic ALK inhibitor for the treatment of resistant and metastatic NSCLC"

Abstract: Primary and secondary mutations in anaplastic lymphoma kinase (ALK) are oncogenic. Insights into ALK acquired resistance were used to define a drug design strategy that led to the discovery of lorlatinib (Lorbrena; PF-06463922), a novel ATP-competitive macrocyclic inhibitor of ALK and ROS1 kinases. Structure based drug design, lipophilic efficiency and physicochemical property-based optimization provided inhibitors with overlapping broad-spectrum potency, low transporter efflux, and brain penetration. The small, cyclic design provided a unique structure with unique properties. NMR and other analytical methods were used to study the unique molecular properties, including atropisomerism for some analogues. Protein dynamics from x-ray crystallographic data and molecular dynamics simulations performed on ALK mutants shed light on the mechanisms of acquired resistance. Research culminated in the discovery of a first in patient candidate, Lorbrena, which was given Breakthrough Therapy status by the FDA in 2016 and approved in late 2018 for the treatment of patients with refractory ALK positive non-small cell lung cancer (NSCLC). Lorbrena is the first and only ALK tyrosine kinase inhibitor (TKI) approved for use after second-generation ALK TKIs. Recently, a Phase 3 study of Lorbrena in patients with previously untreated ALK-positive, advanced NSCLC met its primary endpoint by demonstrating significantly improved progression-free survival, as compared to Xalkori, which is currently primary standard of care. The FDA has accepted for Priority Review the supplemental New Drug Application (sNDA) for Lorbrena as a first-line treatment for patients with ALK-positive NSCLC based on the pivotal data from the CROWN study.

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