

# **The Chemistry of Lorlatinib: From Discovery to Commercial Route Development**

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Lorlatinib is a macrocyclic inhibitor of EML4-ALK for the treatment of non-small cell lung cancer (NSCLC). The compound was initially designed to not only overcome resistance observed in the clinic to Xalkori but also to be brain penetrant in order to target brain metastases that are often observed in patients with NSCLC. The talk will focus on the design rationale behind the discovery of the molecule highlighting the difficulties in balancing potency with suitable physicochemical properties to enable the compound to cross the blood-brain barrier. Furthermore the synthetic challenges of developing a sustainable synthesis for a macrocyclic compound will be discussed as well as how the utilization of High Throughput experimentation (HTE) was utilized to expedite solutions to these.