ALK Inhibitors

Tyrosine kinases, such as anaplastic lymphoma kinase (ALK), have become critical targets in the development of novel chemotherapy and anti-inflammatory drugs. ALK plays a crucial role in brain development and also accelerates the onset and progression of various cancers, including anaplastic large cell lymphoma, neuroblastoma, and non-small cell lung cancer.

Mutations in the ALK gene or its fusion with other genes often result in the production of abnormal or overexpressed proteins. Hyperactive ALK activates the JAK/STAT, PI3K/Akt, and ERK signaling pathways, leading to dysregulation of the cell cycle and abnormal cell survival and proliferation. Targeting ALK can block these aberrant signals, thereby inhibiting cancer cell signaling and tumor growth.

Some ALK inhibitors also inhibit IGF-1R, which is another critical target for blocking cancer cell growth.Notable dual-targeting products include **LDK378 (**L127618、L420413**)**, **AZD3463 (**A125664、A421354**)**, and **GSK-1838705A (**G610695**)**.

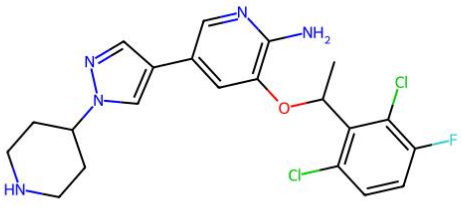

Figure 1 Chemical structure of Crizotinib

Crizotinib (C137735**)** is a well-studied ALK inhibitor that also inhibits the activity of ROS1 and c-MET. In cancer cells, this compound upregulates the expression of the

pro-apoptotic factor BIM and downregulates the expression of the anti-apoptotic protein survivin, thereby inducing apoptosis.

CH5424802 (C125242、C421077) targets both wild-type and mutant L1196M ALK, inducing the regression of brain metastases in non-small cell lung cancer.

Doramapimod (D125100)is an inhibitor of ALK, JNK, and p38 MAPK, demonstrating the ability to suppress pulmonary inflammation in both in vivo and in vitro experiments.

ASP-3026 (A128022、A420576) is an ALK inhibitor that reduces tumor burden in lung and thoracic tumor models.

References:

1. Grande E, Bolós MV, Arriola E. Mol Cancer Ther. 2011 Apr;10(4):569-79.

2. Yang B. Protein Kinases in Drug Discovery Conference. 2013.

3. Okamoto W, Okamoto I, Arao T, et al. Mol Cancer Ther. 2012 Jul;11(7):1557-64.

4. Kodama T, Hasegawa M, Takanashi K, et al. Cancer Chemother Pharmacol. 2014 Nov;74(5):1023-8.

5. Hoogendijk AJ, Pinhanços SS, van der Poll T, et al. Immunobiology. 2013 Apr;218(4):435-42.

Aladdin: https://www.aladdinsci.com/