**Clinical Trials**

**Major finding:** Lorlatinib achieved systemic and intracranial responses in patients with ALK- and ROS1-positive NSCLC.

**Clinical relevance:** Lorlatinib achieved objective responses in a proportion of heavily pretreated ALK-positive patients.

**Impact:** Lorlatinib may be an effective therapy for patients who have failed on available targeted therapies.

**LORLATINIB IS WELL TOLERATED AND HAS ACTIVITY IN ALK\(^{\text{+}}\) AND ROS1\(^{\text{+}}\) NSCLC**

Patients with ALK- or ROS1-rearranged non-small-cell lung cancer (NSCLC) are sensitive to tyrosine kinase inhibitors (TKI) including the standard first-line therapy crizotinib, but resistance eventually develops. The second-generation ALK TKIs ceritinib, alectinib, and brigatinib can overcome crizotinib resistance in ALK-rearranged tumors, but next-generation inhibitors are needed when resistance inevitably develops. Lorlatinib is a third-generation irreversible ATP-competitive TKI, designed to cross the blood-brain barrier, that potently and selectively targets ALK and ROS1. In preclinical studies lorlatinib had antitumor activity in a variety of ALK/ROS-positive xenograft models, including tumors with the ALK Gly1202Arg or ROS1 Gly2032Arg resistance mutations and ALK-positive intracranial tumors. Based on these findings, Shaw and colleagues enrolled 54 patients with locally advanced or metastatic NSCLC (41 with ALK rearrangements, 12 with ROS1 rearrangements, and 1 with unconfirmed ALK/ROS1 status) in a first-in-human, open-label, phase I dose-escalation study to assess the safety, maximum tolerated dose, and antitumor activity of lorlatinib. The primary endpoint was dose-limiting toxicity, and secondary endpoints included safety, pharmacokinetics, and overall response. Overall, 19 of 41 (46%) ALK-positive patients achieved an objective response (37 complete and 16 partial responses), including 11 of 26 (42%) patients who had been previously treated with two or more TKIs, including a second-generation ALK TKI. Partial responses were observed in 6 of 12 (50%) of patients with ROSI rearrangements. Of the 24 patients with measurable central nervous system (CNS) lesions, 11 (46%) had intracranial objective responses. Lorlatinib was well tolerated and the maximum tolerated dose was not reached. One dose-limiting toxicity occurred at 200 mg, and the recommended phase II dose was selected as 100 mg daily. Collectively, these findings demonstrate that lorlatinib is well tolerated and has systemic and intracranial antitumor activity in patients with advanced ALK- or ROS1-rearranged NSCLC. Lorlatinib may be an effective therapy for ALK- or ROS1-positive patients who have relapsed on available TKIs, including patients with progressive CNS metastasis.


**Metabolism**

**Major finding:** Ammonia generated from glutamate metabolism enhances the proliferation of breast cancer cells.

**Mechanism:** GDH catalyzes reductive amination to assimilate ammonia for the generation of amino acids.

**Impact:** Ammonia is a nitrogen source for amino acid synthesis in breast tumors, not merely a toxic by-product.

**BREAST CANCER CELLS RECYCLE AMMONIA TO GENERATE AMINO ACIDS**

In rapidly proliferating cells, increased nutrient consumption generates excess metabolic waste. In the tumor microenvironment, this can lead to accumulation of lactate and ammonia. Ammonia has been considered a toxic by-product, and it is not clear how tumor cells handle the high levels of ammonia generated by amino acid catabolism. Spinelli and colleagues hypothesized that ammonia might be incorporated into central metabolism. To test this hypothesis, metabolic tracing analysis with hydrophilic interaction LC/MS-MS was performed to determine the fate of ammonia generated from glutamate metabolism. Mechanistically, glutamate dehydrogenase (GDH) catalyzed reductive amination to recycle ammonia generated from glutaminolysis into the generation of glutamate and downstream metabolites including proline and aspartate. Ammonia was not toxic to breast cancer cells in vitro, and the addition of ammonia resulted in a GDH-dependent increase in proliferation. In ER\(^{\text{+}}\) breast cancer xenografts, intraperitoneal injection of \(^{15}\)NH\(_4\)Cl resulted in labeled proline and aspartate in the tumor, whereas the liver assimilated ammonia via the urea cycle. Further, depletion of GDH in tumor xenografts suppressed tumor growth in vivo. Altogether, these findings suggest that ammonia accumulation in the tumor microenvironment promotes the growth of breast cancer cells by serving as a nitrogen source for amino acid synthesis.

CANCER DISCOVERY

Lorlatinib Is Well Tolerated and Has Activity in $ALK^+$ and $ROS1^+$ NSCLC


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