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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*$^+$ AND *ROS1*$^+$ 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 reversible 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 (3 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 *ROS1* 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. ■

Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicenter, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol 2017 Oct 23 [Epub ahead of print].

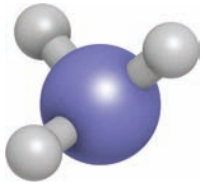
Metabolism

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 metabolism of labeled glutamine [^{15}N(amide)-glutamine]. In estrogen receptor (ER)–positive breast cancer cells, ^{15}N(amide)-glutamine was incorporated into asparagine and nucleotides, and labeled nitrogens were also unexpectedly present in proline, aspartate, branched chain amino acids, and glutamate, which had not been previously linked to glutamine metabolism. The labeled nitrogen was freed as ammonia before incorporation into these glutamine derivatives. Glutaminase converts glutamine to glutamate and ammonia, and treatment with the glutaminase inhibitor Bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide (BPTES) reduced the production of labeled glutamate, proline, and aspartate, whereas nucleotides and asparagine remained labeled, as they are involved in direct glutamine 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$^+$ breast cancer xenografts, intraperitoneal injection of $^{15}NH_4Cl$ 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. ■

Spinelli JB, Yoon H, Ringel AE, Jeanfavre S, Clish CB, Haigis MC, et al. Metabolic recycling of ammonia via glutamate dehydrogenase supports breast cancer biomass. Science 2017 Oct 12 [Epub ahead of print].

AACR American Association for Cancer Research

CANCER DISCOVERY

Breast Cancer Cells Recycle Ammonia to Generate Amino Acids

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