Drug Resistance

Major finding: F1174L-mutated ALK shows reduced sensitivity to crizotinib inhibition.

Concept: The F1174L mutation enhances the ATP-binding affinity of ALK.

Clinical relevance: Patients with F1174L-mutated ALK may benefit from higher crizotinib doses.

ALK MUTANTS SHOW DIFFERENTIAL RESPONSE TO CRIZOTINIB

Neuroblastoma, an often fatal neuroendocrine tumor that arises from the developing autonomic nervous system, remains the most common cancer in infants. In familial and approximately 10% of sporadic neuroblastoma cases, activating point mutations have been identified in the gene encoding anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase that normally functions in the developing nervous system. The two most common *ALK* mutations found in sporadic neuroblastomas are F1174L and R1275Q, located in key regulatory regions of the receptor's kinase domain. Recently, the U.S. Food and Drug Administration approved a small-molecule inhibitor of ALK—crizotinib—for use in ALK fusion-dependent non-small cell lung cancers. In order to inform the use of ALK inhibitors in neuroblastoma patients, Bresler, Wood, and colleagues evaluated the effects of the F1174L and R1275Q mutations on both ALK activity and sensitivity to crizotinib inhibition. Both mutations activated ALK; however, compared with the R1275Q mutant or amplified wild-type, F1174L-mutated ALK was relatively resistant to crizotinib inhibition in human neuroblastoma cells and xenografts. Using biochemical analyses, the authors then demonstrated enhanced ATP-binding affinity of the F1174L ALK mutant. This finding explains the reduced sensitivity of F1174L to crizotinib, which competes with ATP for binding to the kinase active site. Therefore, the data suggest that patients who carry the F1174L mutation may benefit from higher concentrations of crizotinib or from treatment with higher-affinity competitive inhibitors. Although additional clinical studies are warranted, the mechanistic insights presented here will likely translate into improved treatment options for neuroblastoma patients.

Bresler SC, Wood AC, Haglund EA, Courtright J, Belcastro LT, Plegaria JS, et al. Differential inhibitor sensitivity of anaplastic lymphoma kinase variants found in neuroblastoma. Sci Transl Med. 2011;3:108ra114.

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