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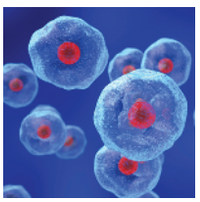
Preclinical Studies

Major finding: Crenolanib is a type I kinase inhibitor with activity against FLT3-ITD and secondary FLT3 mutants.

Clinical relevance: Crenolanib synergizes with sorafenib to inhibit FLT3-ITD–positive AML cell growth.

Impact: Crenolanib may be effective in FLT3-ITD–positive AML and overcome resistance to FLT3 inhibitors.

CRENOLANIB IS EFFECTIVE AGAINST SECONDARY *FLT3* MUTATIONS IN AML



Internal tandem duplication (ITD) mutations of fms-related tyrosine kinase 3 (FLT3) are frequently observed in acute myeloid leukemia (AML) and associated with poor outcome. Type II tyrosine kinase inhibitors (TKI) such as sorafenib and quizartinib that preferentially bind and stabilize inactive kinase conformations have shown clinical activity in patients with FLT3-ITD–positive AML, but resistance quickly develops as a result of secondary kinase domain (KD) mutations that lock FLT3 in an auto-activated state. Hypothesizing that type I kinase inhibitors capable of binding active FLT3 might be effective against secondary FLT3 KD mutations, Zimmerman and colleagues tested the activity of crenolanib, a potent, well-tolerated platelet-derived growth factor receptor inhibitor that also has high affinity for FLT3. Crenolanib had greater affinity for FLT3-ITD and FLT3 KD mutants than sorafenib and had higher affinity for active, phosphorylated kinases than inactive, nonphosphorylated kinases, indicating that crenolanib is a type I kinase inhibitor. Crenolanib potently inhibited the growth of AML cell lines expressing FLT3-ITD *in vitro* and *in vivo* and synergized with sorafenib to induce tumor regression and significantly prolong survival time in mice, suggesting that combining type I and type II kinase inhibitors may be an effective strategy to treat FLT3-ITD–positive AML. Crenolanib also potently reduced the viability of AML cell lines expressing FLT3 KD mutants associated with acquired sorafenib and quizartinib resistance and moderately inhibited the growth of cells harboring both ITD and KD mutations *in vitro*. Furthermore, unlike sorafenib, crenolanib significantly blocked the leukemic infiltration of AML cells expressing drug-resistant FLT3 mutants and inhibited the *ex vivo* growth of primary blasts from two patients with TKI-resistant FLT3-ITD–positive AML. These preclinical studies support further study of crenolanib in TKI-naïve and TKI-resistant FLT3-ITD–positive AML. ■

Zimmerman EI, Turner DC, Buaboonnam J, Hu S, Orwick S, Roberts MS, et al. Crenolanib is active against models of drug-resistant FLT3-ITD–positive acute myeloid leukemia. Blood 2013 Sept 17 [Epub ahead of print].

Clinical Trials

Major finding: Alisertib, an Aurora A kinase inhibitor, shows efficacy in aggressive B- and T-cell lymphomas.

Clinical Relevance: Response to alisertib is independent of *AURKA* amplification and Aurora A protein expression.

Impact: Aurora A inhibitors warrant further study in single-agent and combination clinical trials.

ALISERTIB IS ACTIVE IN RELAPSED AND REFRACTORY NON-HODGKIN LYMPHOMAS

Upregulation of the oncogenic mitotic kinase Aurora A (encoded by *AURKA*) is frequently detected in aggressive non-Hodgkin lymphomas and is correlated with poor prognosis, implicating Aurora A as a potential therapeutic target. In preclinical studies, alisertib, a selective, small-molecule Aurora A kinase inhibitor, induced mitotic arrest and apoptosis in lymphoma cell lines and suppressed tumor growth in a mouse model of diffuse large B-cell lymphoma (DLBCL). To further investigate the therapeutic potential of Aurora A inhibition, Friedberg and colleagues evaluated the safety and efficacy of alisertib in a phase II trial of 48 patients with various subtypes of relapsed or refractory aggressive non-Hodgkin lymphomas. Alisertib was generally well tolerated and several patients continued therapy beyond 1 year; the most common treatment-related grade 3–4 adverse events consisted of cytopenias, stomatitis, and fatigue, and dose reductions were associated with higher trough plasma concentrations of alisertib. Single-agent treatment with alisertib resulted in an overall response rate of 27% (13 of 48 patients), including complete responses in 10% of patients, partial responses in 17% of patients, and stable disease in 33% of patients. Clinical responses were observed across the various subtypes of non-Hodgkin lymphoma in 3 of 21 patients with DLBCL, 3 of 13 patients with mantle-cell lymphoma, 2 of 5 patients with transformed follicular lymphoma, 4 of 8 patients with noncutaneous T-cell lymphoma, and 1 of 1 patient with Burkitt lymphoma. However, this clinical benefit was not correlated with *AURKA* gene amplification or Aurora A kinase protein expression in tumor samples. These results support additional clinical trials of alisertib, alone or in combination with other therapeutic agents that may synergize with or sensitize tumors to Aurora A inhibition, in aggressive B- and T-cell lymphomas. ■

Friedberg JW, Mahadevan D, Cebula E, Persky D, Lossos I, Agarwal AB, et al. Phase II study of alisertib, a selective Aurora A kinase inhibitor, in relapsed and refractory aggressive B- and T-cell non-Hodgkin lymphoma. J Clin Oncol 2013 Sept 16 [Epub ahead of print].

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AACR American Association for Cancer Research

CANCER DISCOVERY

Alisertib Is Active in Relapsed and Refractory Non-Hodgkin Lymphomas

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