

Abstract:

Neoplastic cells evade death by upregulating anti-apoptotic proteins such as Inhibitor of Apoptosis Proteins (IAPs). SMAC mimetics are a drug class that bind IAPs causing their degradation and are actively being investigated in cancer clinical trials. The addition of tumor necrosis factor-alpha (TNF) is required for SMAC mimetics to induce death in normal cells. However, *JAK2*^{V617F} mutant myeloproliferative neoplasm (MPN) cells are sensitive to SMAC mimetics alone. Therefore, we hypothesize that combining the SMAC mimetic LCL-161 with an anti-TNF agent will target the *JAK2*^{V617F}-mutant cells in MPN while preserving normal cells. We will test this hypothesis using primary human MPN peripheral blood cells as well as MPN mouse models. These data will provide the rationale for the design of an investigator initiated trial testing LCL-161 in combination with a TNF blocking agent in MPN patients.