TREATMENT OF B-CELL MALIGNANCIES BY A COMBINATION JAK AND PI3K INHIBITOR

This application claims the benefit of priority of 61/976,815, filed April 8, 2014, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

This invention relates to methods of treating B-cell malignancies using a combination of inhibitors of JAK1 and/or JAK2 and inhibitors of PI3Kδ.

BACKGROUND

The B-cell receptor (BCR) is present on both normal and most malignant B-cells. Engagement of the BCR provides important survival signals, and interruption of the BCR signal can lead to B-cell death. Studies performed with siRNA to inhibit BCR expression have shown that constitutive signaling by the BCR is critical for the survival and proliferation of human B-cell lymphomas. The primary role of BCR signaling in these cells appears to be activation of spleen tyrosine kinase (Syk) which in turn leads to several downstream events that promote cell survival, including activation of Bruton tyrosine kinase (BTK), phosphatidylinositol 3 kinase (PI3K), and AKT. A number of B-cell malignancies, including diffuse large B-cell lymphomas (DLBCL), have been shown to be particularly dependent upon BCR survival signals as evidenced by their sensitivity to genetic and pharmacological inhibition of BCR signaling components in vitro. It has been shown that DLBCL cells engage PI3K, augmenting anti-apoptotic NF-kB signaling and survival signals and that inhibition of the PI3K/AKT pathway synergizes with NF-kB inhibition in killing DLBCL cell lines *in vitro*.

Aberrant activation of JAKs, through production of cytokines and growth factors, has also been associated with increased malignant cell proliferation and survival in a number of tumor types. JAKs activate a number of downstream pathways implicated in the proliferation and survival of malignant cells including the STATs, a family of important latent transcription factors. Of clinical relevance, levels of serum IL-10 and IL-6, which signal through the JAKs, have been found to be elevated in patients with