Abstract:

Proviral integration site for Moloney murine leukemia virus (PIM) kinases are serine/threonine kinases and oncoproteins involved in tumorigenesis of many solid and hematopoietic malignancies including mantle cell lymphoma (MCL) and diffuse-large B-cell lymphoma (DLBCL). They were shown to promote growth and survival of cancer cells by phosphorylation of proteins involved in cell cycle regulation, transcription, translation and apoptosis. Their potential as therapeutic target is, however, complicated by existence of overlapping signaling pathways. Here we show that inhibition of PIM kinases with AZD1208, highly selective pan-PIM inhibitor, reduces growth of cell lines derived from MCL and DLBCL patients. Inhibition of PIM kinases results in decreased phosphorylation of proteins involved in apoptosis and cap-dependent translation. We further showed that concurrent inhibition of PIM-kinases with AZD1208 and signaling from B-cell receptor with ibrutinib (a Bruton’s tyrosine kinase (BTK) inhibitor) or idelalisib (a phosphatidylinositol 3-kinase (PI3K) inhibitor) synergistically reduces growth of MCL cell lines. Combination of AZD1208 and ibrutinib was accompanied by decreased phosphorylation of eukaryotic translation initiation factor 4E binding protein 1 (4E-BP1) and decreased expression of antiapoptotic MCL1. Despite significant improvement in the outcome of lymphoma patients achieved in recent 20 years new drugs and novel treatment approaches are needed for relapsed / refractory diseases. Our results thus show that PIM kinases present promising target for treatment of MCL and DLBCL patient especially in combination with ibrutinib or other inhibitors of BCR-mediated signaling.

Key words: PIM kinases, mantle cell lymphoma, diffuse-large B-cell lymphoma, cancer, AZD1208, ibrutinib, Bruton’s tyrosine kinase