IMO-8400, a selective antagonist of TLRs 7, 8 and 9, inhibits MYD88 L265P mutation-driven signaling and cell survival: A potential novel approach for treatment of B-cell lymphomas harboring MYD88 L265P mutation

Lakshmi Bhagat, Daqing Wang, Weifen Jiang and Sudhir Agrawal, Idera Pharmaceuticals, 167 Sidney Street, Cambridge, MA 02139

Abstract

• Emerging biology has identified novel therapeutic targets for the treatment of B-cell lymphomas
  – Constitutive activation of nuclear factor (NF)κB and Jak/STAT signaling has been shown to promote cell survival in the activated B-cell like (ABC) subtype of diffuse large B-cell lymphomas (DLBCL)
  – A highly recurrent oncogenic mutation affecting MYD88 in ABC-DLBCL tumors has been identified
    – MYD88 is an adapter protein that mediates Toll-like receptor (TLR) signaling; L265P was the most prevalent MYD88 mutation observed
  – Reported in 29% of patients with ABC-DLBCL, in over 90% of patients with Waldenström’s macroglobulinemia (WM) and in other B-cell lymphomas
  – The MYD88 L265P oncogenic mutation is shown to promote cell survival by initiating signaling through IRAK-1, IRAK-4, NF-kB, JAK/STAT, and secretion of IL-6 and IL-10
  – Recently, it has been shown that knockdown of TLR7 or TLR9 expression, but not other TLRs, blocked NF-kB signaling and survival of cells expressing MYD88 L265P oncogenic mutation
  – TLR7 and 9 are expressed on B-cells and dendritic cells

Introduction

Research Objectives: Validate the rationale for targeting TLR7 and TLR9 for treatment of B-cell lymphomas harboring MYD88 L265P oncogenic mutation

• Evaluate effect of IMO-8400, an antagonist of TLR7, TLR9, and TLR3, on signaling pathways in human lymphoma cells with the MYD88 L265P oncogenic mutation
• Evaluate effect of IMO-8400 treatment on tumor cell proliferation and survival
  – In vitro and in vivo in mouse xenograft models
• Evaluate specificity of TLR7/9 inhibition to the MYD88 L265P oncogenic mutation
• Rationale: Upstream inhibition of the TLR/MYD88 pathway may be more appropriate to lymphomas characterized by MYD88-L265P compared to downstream inhibition of specific proteins such as IRAK-4 and BTK
  – IRAK-4 is employed by all TLRs except TLR3; the blocking of IRAK-4 may have an impact on all TLR functions in other cells, including B-cells
  – Patients harboring MYD88 L265P mutation as the only identified oncogenic mutation showed no response to treatment with bortezomib, a BTK inhibitor

In vitro Studies in MYD88 L265P-Positive ABC-DLBCL Cell Lines

IMO-8400, an antagonist of TLR7, 8 and 9, inhibits survival of cells harboring MYD88 L265P oncogenic mutation

Decreased cell viability is associated with inhibition of cytokines

Effect of Gene-Silencing Oligonucleotide (GSO) knockdown of TLR7, TLR9 or MYD88 on cell survival harboring MYD88 L265P oncogenic mutation is consistent with previous reports

Tumor Models of MYD88 L265P-Positive ABC-DLBCL

Treatment with IMO-8400 prolongs mouse survival in OCI-Ly10 disseminated xenograft model

- Inhibition of tumor growth is associated with suppression of key tumor-associated cytokines
- Treatment with IMO-8400 inhibits tumor growth in OCI-Ly10 xenograft model

IMD-800 inhibits key cell signaling pathways in OCI-Ly10 cells

IMO-8400 inhibits key cell signaling pathways in OCI-Ly10 cells

IMO-8400 inhibits cell survival and cell signaling pathways in OCI-Ly10 cells

IMO-8400 inhibits key cell signaling pathways in OCI-Ly10 cells

Summary

• Knockdown of TLR7 and TLR9 in MYD88-L265P mutant cells led to decreased cell survival and inhibition of cell survival, in agreement with previous reports
• Treatment with IMO-8400, an antagonist of TLRs 7, 8 and 9, of ABC-DLBCL cells expressing MYD88 L265P oncogenic mutation in vitro and in mouse xenograft models led to inhibition of cell survival and tumor growth, respectively, and:
  – Inhibition of cytokine induction including IL-10
  – Down-regulation of gene expression in the NF-κB and Jak/STAT pathways
  – Inhibition of IRAK-4, NF-κB, STI1, p38, and BTK signaling pathways
• Furthermore, treatment of established tumors (500 mm³) with IMO-8400 led to delayed tumor growth
• IMO-8400 treatment of Waldenström macrophage-burden lymphomas expressing MYD88 L265P oncogenic mutation led to similar inhibitory effects on cell signaling and survival
• No activity was seen in a GCB-DLBCL cell line, SU-DHL-6, lacking MYD88 L265P oncogenic mutation, in vitro or in vivo

IMO-8400 antitumor activity is specific to tumors with MYD88 L265P oncogenic mutation

References


Current Clinical Development

• IMO-8400 is in clinical development for the treatment of B-cell lymphomas harboring MYD88 L265P oncogenic mutation
• Patient enrollment is now open in a Phase 1/2 trial of IMO-8400 in Waldenström macrophage-burden lymphomas
• A protocol for Phase 1/2 trial in patients with DLBCL harboring the MYD88 L265P oncogenic mutation has been submitted to the FDA

IMO-8400, a selective antagonist of TLRs 7, 8 and 9, inhibits MYD88 L265P mutation-driven signaling and cell survival: A potential novel approach for treatment of B-cell lymphomas harboring MYD88 L265P mutation

Lakshmi Bhagat, Daqing Wang, Weifen Jiang and Sudhir Agrawal, Idera Pharmaceuticals, 167 Sidney Street, Cambridge, MA 02139

References