IMO-8400 Inhibits Tumor Growth and Signaling Pathways in Waldenström’s Macroglobulinemia: a Novel Therapeutic Approach in Development
Wayne Jiang, Daqing Wang and Lakshmi Bhagat | Idera Pharmaceuticals, Inc. Cambridge, MA 02139, U.S.A.

RATIONALE AND OBJECTIVES

- MYD88 L265P is an oncogenic mutation present in over 90% of patients with Waldenström’s macroglobulinemia (WM) and in other B-cell lymphomas.
- MYD88 is an adaptor molecule in toll-like receptor (TLR) signaling; the L265P mutation oncogenic activity recently was associated with over-activation of the TLR signaling pathway.
- TLR signaling activates IRAK1/IRAK4, TRAF6, BTK, and NF-κB and JAK/STAT pathways.
- Human B-cells express TLR7 and TLR9.
- TLR signaling activates IRAK1/IRAK4, TRAF6, BTK, and NF-κB and JAK/STAT pathways.
- MYD88 is an adaptor molecule in toll-like receptor (TLR) signaling; the L265P mutation oncogenic activity recently was associated with over-activation of the TLR signaling pathway.
- IMO-8400 is an antagonist of TLR7/TLR9 that has been well tolerated in prior clinical trials and has shown clinical activity in patients with an autoimmune disease.
- Current objectives are to evaluate IMO-8400 effects on signaling pathways and tumor cell survival in MYD88 L265P-positive WM primary bone marrow cells, including an xenograft tumor model.

EXPERIMENTAL CONDITIONS

- Primary bone marrow cells from WM patients
- N=1, all MYD88 L265P-positive by allele-specific PCR
- Cell cultures incubated for 48 to 72 h with IMO-8400 at varying concentrations
- MWCL-1 cell culture and xenograft model
- MYD88 L265P mutation shown by Sanger sequencing
- Cell cultures incubated for 24 to 72 h with IMO-8400 at varying concentrations
- Xenograft studies in NOD-SCID mice (n=8) dosed by i.p. injection with IMO-8400 (25 mg/kg) or saline (PBS) twice/week for 3 weeks followed by once/week for 3 weeks. Treatment was initiated when mean tumor volumes reached approximately 270 mm³.

IMO-8400 INHIBITS MYD88 L265P-DRIVEN SIGNALING AND CELL SURVIVAL

IMO-8400 BLOCKS SIGNALING PATHWAYS AND INHIBITS CELL VIABILITY IN WM PRIMARY BONE MARROW CELLS BEARING MYD88 L265P

IMO-8400 TREATMENT INHIBITS TUMOR GROWTH IN A MYD88 L265P-POSITIVE MWCL-1 XENOGRAFT MODEL

IMO-8400 BLOCKS SIGNALING PATHWAYS AND INHIBITS CELL VIABILITY IN MWCL-1 CELL LINE BEARING MYD88 L265P

IMO-8400 INHIBITS ONCOGENIC MUTATION-DRIVEN SIGNALING AND INHIBITS CELL VIABILITY OF HUMAN IGM SECRETION

IMO-8400 INHIBITION OF TUMOR GROWTH

CONCLUSIONS

- IMO-8400 inhibits cell growth, cytokine secretion, and key cell signals including IRAK1/IRAK4, BTK, and NF-κB and JAK/STAT in MYD88 L265P-positive WM primary bone marrow cells.
- Implantation of MYD88 L265P-positive MWCL-1 cells in immunocompromised mice produces tumor growth that correlates with increased human IgM.
- Studies in the MWCL-1 mouse model show that IMO-8400 reduces tumor growth, consistent with cell culture studies showing IMO-8400 inhibits cell signaling, induces cancer cell apoptosis, and inhibits cell viability.
- Based on promising preclinical data from studies of IMO-8400 in cell-based assays and tumor models and clinical safety in early trials, IMO-8400 is currently being evaluated in a Phase 1/2 clinical trial in patients with WM.
- This is the first clinical approach to block the activity of the oncogenic mutation present in over 90% of patients with WM; for further information visit www.iderapharma.com or www.clinicaltrials.gov/show/NCT02092909

All authors are employees of Idera Pharmaceuticals and hold stock options.