IMO-8400 Inhibits Tumor Growth and Signaling Pathways in Waldenström's Macroglobulinemia: a Novel Therapeutic Approach in Development

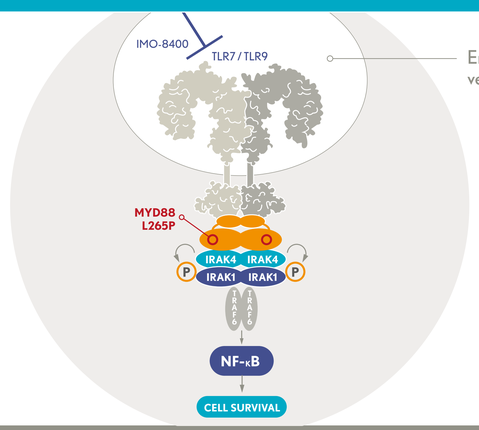
Wayne Jiang, Daqing Wang and Lakshmi Bhagat | Idera Pharmaceuticals, Inc. Cambridge, MA 02139, U.S.A.

idera PHARMACEUTICALS

RATIONALE AND OBJECTIVES

- MYD88 L265P is an oncogenic mutation present in over 90% of patients with Waldenström's macroglobulinemia (WM)[1] and in other B-cell lymphomas[2]
- 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[3]
- TLR signaling activates IRAK1/IRAK4, TRAF6, BTK, and NF-κB and JAK/STAT pathways
- Human B-cells express TLR7 and TLR9
- We hypothesize that antagonizing TLR7/TLR9 will block MYD88 L265P-driven signaling and inhibit tumor cell viability,[4] providing a novel potential approach to the treatment of WM
- 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 models, including an xenograft tumor model

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

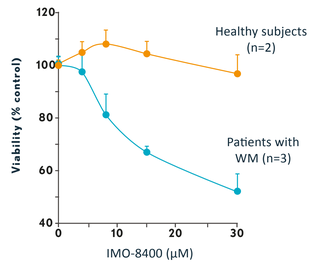


EXPERIMENTAL CONDITIONS

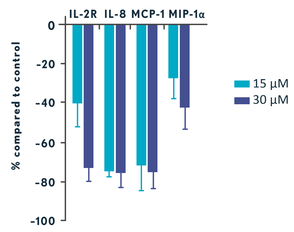
- Primary bone marrow cells from WM patients
  - N=3, all MYD88 L265P–positive by allele-specific PCR
  - Cell cultures incubated for 48 to 72 h with IMO-8400 at varying concentrations
- MWCL-1 cell culture and xenograft model
  - MYD88 L265P mutation shown by Sanger sequencing
  - Cell cultures incubated 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 mm^3

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

INHIBITION OF CELL VIABILITY



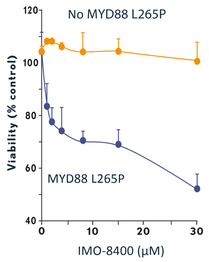
INHIBITION OF CYTOKINE SECRETION



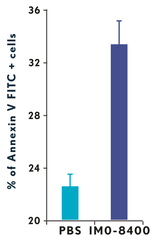
INHIBITION OF CELL SIGNALING PATHWAY GENE EXPRESSION

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

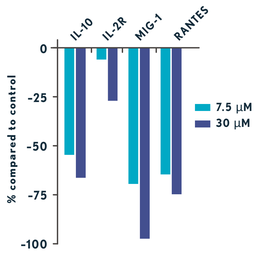
INHIBITION OF CELL VIABILITY



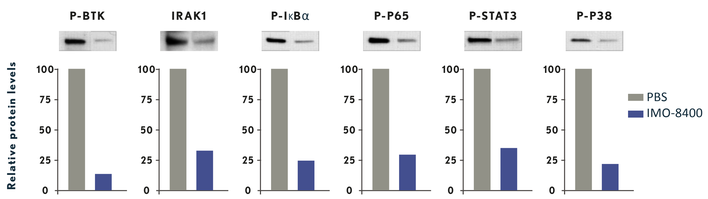
INDUCTION OF APOPTOSIS



INHIBITION OF CYTOKINE SECRETION

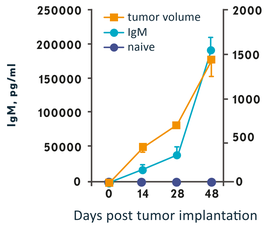


INHIBITION OF CELL SIGNALING PATHWAYS

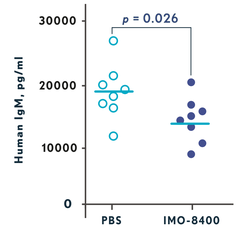


IMO-8400 TREATMENT INHIBITS TUMOR GROWTH IN A MYD88 L265P-POSITIVE MWCL-1 XENOGRAFT MODEL

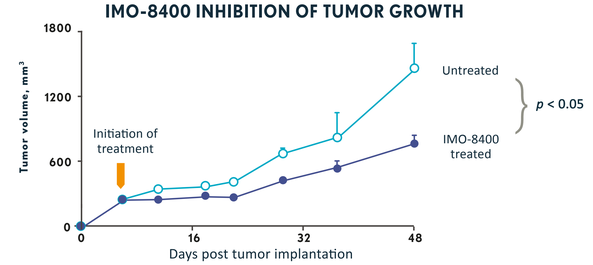
TUMOR GROWTH ASSOCIATED WITH HUMAN IgM SECRETION



IMO-8400 INHIBITION 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**

1. Treon SP, Hunter ZR. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. *Blood.* 2013 May 30;121(22):4434-6.
2. Ngo VN, Staudt LM et al. Oncogenically active MYD88 mutations in human lymphoma. *Nature.* 2011; 470:115-9.
3. Lim K-H, Barton GM, Staudt LM. Oncogenic MYD88 mutants require Toll-like receptors. *Cancer Res.* 2013; 73, Suppl 1: 2332.
4. Bhagat L et al. 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. AACR 2014 Abstract #2570.

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