IMO-8400, an Antagonist of Toll-like Receptors 7, 8, and 9, in Development for Genetically Defined B-cell Lymphomas: Safety and Tolerability in Phase 1 and Phase 2 Clinical Trials


BACKGROUND

Toll-like Receptors Have Central Roles in the Immune System

- Toll-like receptors (TLRs) are pattern-recognition molecular pattern recognition receptors of the innate immune system
- TLRs 7 and 8, which are expressed in human B-cells, respond to lipid- and nucleic acid-based ligands by initiating a signaling cascade mediated through MyD88, IRAK4, IRAK1, and JAK/STAT
- DNA- and RNA-sensing ligands for TLRs 7 and 8 are generated as damage-associated molecular patterns in certain infectious diseases and malignancies

B-cell Lymphomas: Safety and Tolerability in Phase 1 and Phase 2 Clinical Trials

IMO-8400, an Antagonist of TLRs 7, 8, and 9, in Development for Genetically Defined B-cell Lymphomas

Disclosure: Authors are employees of Idera Pharmaceuticals and hold stock in the company.

1. MYD88 L265P Oncogenic Mutation Over-activates TLR Signaling

- MYD88 is a key adaptor molecule in TLR signaling
- Recently, the oncogenic mutation MYD88 L265P has been described and reported to occur in patients with activated B-cell-like diffuse large B-cell lymphoma (PGC-DLBCL), Waldenström’s macroglobulinemia (WM), and other B-cell malignancies
- IMO-8400 blocks LPS-induced expression of TLR 7 and 8 signaling, creating an anti-tumor mechanism of action
- Recent epidemiological data confirm a strong association between the presence of MYD88 L265P and poor outcomes in patients with DLBCL

Ongoing Clinical Development of IMO-8400 for Genetically Defined Forms of B-cell Lymphoma

- Preclinical data presented at AACR 2016, including from von Einem tumor studies, showed that IMO-8400 inhibited cell growth and signaling and reduced tumor growth in WM and DLBCL, similar to the MYD88 L265P mutation
- Based on the preclinical data, clinical safety, and demonstration of efficacy in vivo, IMO-8400 has been advanced for the treatment of patients with MYD88 L265P and other B-cell malignancies

Phase 1 Clinical Trial in Healthy Volunteers (Study 8400-001)

- Multiple ascending dose (8 subjects)
- Placebo-controlled, single dose
- Safety population: 18 subjects

Phase 2 Selected Laboratory Parameters

- Anemia: Treatment-emergent decreases
  - Erythrocytes: Grade 3 or 4
    - All of the elevations were Grade 3
  - Hemoglobin: Treatment-emergent decreases
    - All of the elevations were Grade 3
  - Platelets: Treatment-emergent decreases
    - All of the elevations were Grade 3

- Neutrophil counts

- Lymphocytes

- Neutrophils

- Total white blood cells

- Absolute neutrophil counts

Summary of Phase 1 Safety Results

- No treatment-related deaths
- No treatment-related severe AEs
- No serious arrhythmias
- No patterns of treatment-related changes in laboratory tests

Phase 1 Clinical Trial in Patients with Pioriasis (Study 8400-201)

- Dose escalation
- Placebo-controlled, single dose
- Follow-up at 6-8 weeks

Comparison of IMO-8400 to Placebo

- Placebo-controlled, single dose
- Patients with moderate to severe plaque psoriasis

Dose Escalation Cohorts

- Cohort 1: 0.1 mg/kg
- Cohort 2: 0.3 mg/kg
- Cohort 3: 0.6 mg/kg

Phase 2 Clinical Trial in Waldenström’s Macroglobulinemia (Study 8400-401)

- Placebo-controlled, single dose
- Treatment-emergent decreases

- No treatment-related deaths
- No serious arrhythmias
- No treatment-related severe AEs

Summary of Phase 2 Safety Results

- No treatment-related deaths
- No treatment-related severe AEs
- No serious arrhythmias
- No patterns of treatment-related changes in laboratory tests

Response to therapy

- Patients treated with IMO-8400 had a 42% improvement in PASI 100
- Significant improvement in joint pain, fatigue, and quality of life

Cell Survival

- MYD88 L265P drives over-expression of TLR 7 and 9 signaling, creating an anti-tumor mechanism of action
- DNA- and RNA-based ligands for TLRs 7 and 9 also are generated as damage-associated molecular patterns in certain infectious diseases and malignancies

- The mechanism of action of IMO-8400, Phase 1/2 clinical trials of IMO-8400 are being conducted in both relapsed/refractory patients with WM and in patients with DLBCL

- Phase 1 safety results showed a reduced incidence of adverse events, with representing 10 scheduled site-monitoring per patient, or 1,000 for treatment group of patients

- Phase 1/2 clinical trials of IMO-8400 are being conducted in both relapsed/refractory patients with WM and in patients with DLBCL

- Phase 1 and Phase 2 clinical trials have shown no instances of ulceration or necrosis

- There has been no pattern of systemic AEs and no pattern of laboratory changes, including LFTs and cytopenias

- Across these experiences, there have been no treatment-related deaths
- No serious arrhythmias
- No treatment-related severe AEs

- Phase 2 clinical trials of IMO-8400 are being conducted in both relapsed/refractory patients with WM and in patients with DLBCL

- The most common treatment-related AE has been mild irritation of erythema and induration

- There have been no instances of ulceration or necrosis

- There has been no pattern of systemic AEs and no pattern of laboratory changes, including LFTs and cytopenias

- IMO-8400 represents a novel treatment for B-cell malignancies with the MYD88 L265P mutation. It has been well-tolerated in completed clinical trials to date

References

- Lim et al. AACR 2013 Abstract #2332.