Interim Results From a Phase 1/2, Open-Label, Dose-Escalation Trial of IMO-8400 in Patients with Relapsed or Refractory Waldenström's Macroglobulinemia

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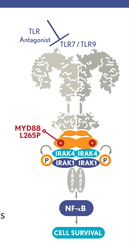
Rationale for Toll-like Receptor Antagonism as a Potential Therapeutic Approach in Waldenström's Macroglobulinemia

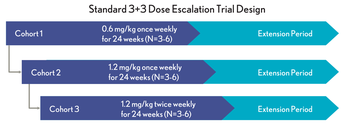
- Waldenström's macroglobulinemia (WM) is a rare, indolent B-cell lymphoma characterized by lymphoplasmacytic cell infiltration of bone marrow and elevated serum levels of immunoglobulin M (IgM) protein
- About 90% of WM patients harbor the MYD88 L265P oncogenic mutation; MYD88 is an adapter protein in the Toll-like receptor (TLR) pathway
- In preclinical studies, the MYD88 L265P mutation was shown to amplify TLR7 and 9 signaling, and knockdown of these TLRs potently suppressed NF-κβ activity and promoted apoptosis in B-cell lymphoma cell lines harboring the mutation[1]
- TLR7, 8 and 9 are expressed on the endosome of human B-cells and dendritic cells and recognize nucleic acid ligands
- IMO-8400 is a novel investigational oligonucleotide-based antagonist of TLR7, 8 and 9
  - In preclinical studies in human cell lines of WM harboring the MYD88 L265P mutation, IMO-8400 inhibited key cell signaling pathways, including NF-κβ, BTK, STAT-3 and IRAK-4[2]
  - In preclinical tumor models harboring the MYD88 L265P mutation, IMO-8400 inhibited tumor growth and immunoglobulin M (IgM) protein production. In addition, tumor growth inhibition was correlated with suppression of systemic cytokines such as IL-10, IL-2R, IP-10 and MIG[2]
  - In Phase 1 and 2 clinical trials in healthy subjects (N=30) and in patients with autoimmune disease (N=35), IMO-8400 was generally well tolerated and demonstrated evidence of clinical activity[3,4]
- Based on these data, we initiated a Phase 1/2 clinical trial of IMO-8400 in WM, the first study of a drug candidate specifically targeting the MYD88 L265P mutation



[1] Lim, et al. AACR, 2013. [2] Bhagat, et al. AACR, 2014. [3] Bhagat, et al. FOCIS, 2013. [4] Balak, et al. AAD, 2015.

Graphic adapted from: Cancer Res. 2013, 73 Suppl. 1.2332.

Design of an Open-Label Phase 1/2 Dose-Escalation Clinical Trial in Patients with WM



- IMO-8400 administered by subcutaneous injection
- Serum IgM and M-protein assessed at screening, Weeks 9, 17, 23, end of treatment, and end of study
- Bone marrow biopsies conducted at screening and end of treatment
- Serum collected at screening, Week 1 of every 8 week cycle, and end of treatment for cytokine assessment
- PCR-based genetic screening used to determine MYD88 L265P mutation status following enrollment

Study Objectives

Primary

- Safety and tolerability

Secondary

- Preliminary evidence of efficacy based on international guidelines for classifying a clinical response[1]
- Identification of an optimal dose for further clinical evaluation
- Characterization of the pharmacokinetics of escalating dose levels

Exploratory

- Associations between the treatment effect of IMO-8400 and selected immunologic markers of disease activity (e.g., serum cytokines)

[1] Owen, et al. British Journal of Haematology, 2012.

Eligibility Criteria

Major Inclusion Criteria

- Primary diagnosis established according to criteria of the Second International Workshop on WM[1]
- Received at least one course of therapy consistent with the recommendations for "first-line therapy" from the Fourth International Workshop on WM[2]
- Relapsed or refractory based on the criteria for assessing response from the Sixth International Workshop on WM[3]
- Serum monoclonal immunoglobulin M-protein ≥0.5 g/dL at screening

Major Exclusion Criteria

- Received cytotoxic chemotherapy within the past 3 weeks or rituximab within the past 2 months
- At initiation of study drug, receiving concomitant chronic systemic corticosteroid therapy >20 mg of prednisone daily
- Active autoimmune cytopenia (anemia, thrombocytopenia, leukopenia) requiring concomitant therapy

[1] Owen, et al. Seminars in Oncology, 2003. [2] Dimopoulos, et al. Journal of Clinical Oncology, 2009. [3] Treon, et al. Clinical Lymphoma, Myeloma and Leukemia, 2011.

Patient Disposition and Analysis Populations

- 19 patients were enrolled as of August 2015 data cut-off
  - Efficacy evaluable population (N=15) excluded 2 patients who initiated treatment within 1 week of data cut-off and 2 patients who did not complete at least 1 cycle of therapy
- Median follow-up of 24 weeks (range 3-50 weeks)
- 13 activated clinical sites in the United States

Population	0.6 mg/kg/wk	1.2 mg/kg/wk	2.4 mg/kg/wk	Overall
Enrolled / safety population	6	5	8	19
Patient status				
• Ongoing	0	0	3 (38%)	3 (16%)
• Completed 24 weeks of therapy	5 (83%)	2 (40%)	3 (38%)	10 (53%)
• Discontinued study				
- Due to dose-limiting toxicity	0	0	1 (12%)	1 (5%)
- Due to adverse event	0	0	0	0
- Disease progression	0	2 (40%)	0	2 (11%)
- Other	1 (17%)	1 (20%)	1 (12%)	3 (16%)
Efficacy evaluable population*	5 (83%)	4 (80%)	6 (75%)	15 (79%)
• Completed ≥1 cycle of IMO-8400	5 (83%)	4 (80%)	5 (62%)	14 (74%)

* Includes patients who completed ≥1 cycle of therapy or those who discontinued due to progressive disease or dose-limiting toxicity

Baseline Patient Characteristics

Characteristic	Total (N=19)
Median age (range) – year	68 (48-94)
Sex – n (%)	
Male	13 (68%)
Female	6 (32%)
IPSSWM – n (%)	
Low	7 (37%)
Medium	10 (53%)
High	2 (11%)
Disease status – n (%)	
Relapsed	15 (79%)
Refractory*	4 (21%)
Median paraprotein levels	
Serum IgM (range) – mg/dL	2225 (785-5750)
M-protein (range) – g/dL	0.96 (0.06-2.71)
Median hemoglobin (range) – g/dL	11.3 (7.6-13.9)
Median serum β2-microglobin (range) – mg/L	3.42 (1.28-13.10)
Median platelet count (range) – thousand/mm³	240 (50-479)
MYD88 L265P mutation status – n (%)	
Positive	15 (79%)
Negative	3 (16%)
Indeterminate/ Missing	1 (5%)

* Refractory defined as last treatment regimen received within prior 6 months

History of Prior Treatment

Characteristic	Total (N=19)
Median no. of previous treatment regimens (range)	2 (1-7)
Most Common Therapies** – n (%)	
Rituximab	17 (89.5%)
Bortezomib	8 (42.1%)
Cyclophosphamide	8 (42.1%)
Cladribine	7 (36.8%)
Dexamethasone	5 (26.3)
Prednisone	4 (21.1%)
Fludarabine	3 (15.8%)
Experimental	2 (10.5%)
Vincristine	2 (10.5%)
Ibrutinib	1 (5.3%)

** Excludes treatments/regimens reported only once, with the exception of ibrutinib

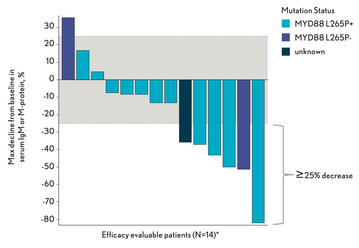
Summary of Treatment-Emergent Adverse Events

- IMO-8400 was generally well tolerated at all dose levels
- Most reported adverse events (AEs) deemed related or possibly related to study drug were mild or moderate (CTCAE grade 1 or 2)
- The most common AEs observed were fatigue, injection site erythema, headache, injection site pain, nausea and pain in extremity
- Reported injection site reactions included grade 1 erythema, grade 1 pain and grade 1 induration
  - No injection site blistering, necrosis, pruritus, ulceration or tenderness were reported
- Grade 3 AEs reported as possibly or probably related to study drug included neutropenia, anemia and arthritis
  - 1 of 8 patients treated with 2.4 mg/kg in the safety population had a dose-limiting toxicity (DLT) deemed possibly related to study drug. This patient experienced a grade 3 probable flare of pre-existing arthritis
- No deaths or grade 4 events were reported

Incidence of Frequently Reported Treatment-Emergent Adverse Events (AEs Experienced by Two or More Patients)

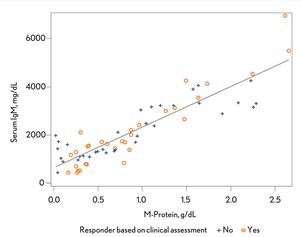
Preferred Term	Subjects Experiencing All Grades
Fatigue	3 (16%)
Injection site erythema	3 (16%)
Headache	3 (16%)
Injection site pain	3 (16%)
Nausea	3 (16%)
Pain in extremity	3 (16%)
Arthralgia	2 (10%)
Anemia	2 (10%)
Dehydration	2 (10%)
Diarrhea	2 (10%)
Hematoma	2 (10%)
Neutropenia	2 (10%)
Night sweats	2 (10%)
Upper respiratory tract infection	2 (10%)

Maximal Decrease in Serum IgM or M-protein (Best Observed of Either) in Efficacy Evaluable Patients



* 1 evaluable patient discontinued due to a DLT before a follow-up IgM level was obtained

Serum IgM and M-protein Were Highly Correlated Regardless of Response Status



- Correlation analysis of serum IgM and M-protein included values at multiple time points for the efficacy evaluable population (N=15)

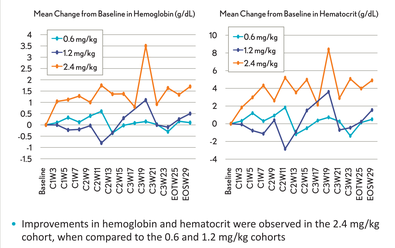
Summary of Responses, Based on International Guidelines for Classifying a Clinical Response*

Dose Level (mg/kg)	Number of Prior Therapies	Regimen Prior to Study 401	Best Clinical Response	Time to Best Response	Bone Marrow Response
0.6	1	rituximab, ~2 months prior	MR	~24 wks	Not assessed
0.6	2	rituximab, ~11 months prior	PR	~24 wks	Not assessed
1.2	2	bortezomib/ dexamethasone, ~2 months prior	MR	~28 wks	Yes
2.4	6	ibrutinib, ~2 months prior	PR	~8 wks	Yes
2.4	1	rituximab/ bortezomib/ cyclophosphamide, ~5 years prior	MR	~16 wks	No (stable)
2.4	2	cladribine, ~3 years prior	MR	~8 wks	Yes

* Clinical response criteria include serum IgM or M-protein, extramedullary disease assessment, bone marrow assessment and disease symptoms

- Among 6 evaluable patients treated at the highest dose level studied to date (2.4 m/kg), 3 had responses and 2 had stable disease
- Trend in time to first response:
  - ~25 weeks for the 0.6 and 1.2 mg/kg cohorts combined
  - ~11 weeks for the 2.4 mg/kg cohort

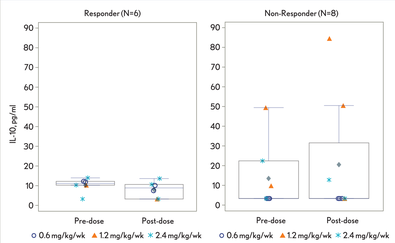
Dose-Dependent Changes in Hemoglobin and Hematocrit



- Improvements in hemoglobin and hematocrit were observed in the 2.4 mg/kg cohort, when compared to the 0.6 and 1.2 mg/kg cohorts

* No observations for 1.2 mg/kg cohort at C3W17 due to 2 unevaluable samples

Change in Serum IL-10 from Baseline to Last Observation



- Responders had a 16.5% median decrease in serum IL-10; at baseline, these patients had a median serum IL-10 level above the lower limit of detection
- Non-responders had a median serum IL-10 level below the lower limit of detection at baseline, and no change was observed through the last observation
- There was a significant correlation between change in M-protein and change in IL-10 (rho=0.71, p=0.01)

Summary of IMO-8400 Pharmacokinetics

Dose mg/kg	Frequency	Number of Patients [Week 1 / Week 13]	$AUC_{0-\tau}$, ng·h/mL (SD) [Week 13]	Accumulation Ratio [Week 13 / Week 1]
0.6	1x weekly	6 / 5	2990 (± 1244)	1.17
1.2	1x weekly	4 / 2	7308 (± 378)	0.90
1.2	2x weekly	8 / 3	7992 (± 1244)	1.00

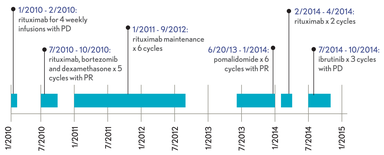
Methods: Sample Time Points: pre-dose, 1, 2 and 4 hours post-dose on Week 1, Week 5 and Week 13. Plasma (K2-EDTA) samples were analyzed using a validated hybridization ELISA method. For human plasma the assay LLOQ is 10.0 ng/mL. Pharmacokinetic analysis of plasma assay results was performed using Phoenix WinNonlin (version 6.4, Certara, Princeton, NJ). Non-compartmental methods (liner trapezoidal interpolation) were used to calculate pharmacokinetic parameters, where possible.

Summary of Pharmacokinetic (PK) Data

- PK results showed evidence of dose-dependent exposure
- Twice weekly compared to once weekly administration of 1.2 mg/kg did not impact PK
- There was no evidence of drug accumulation at Week 13

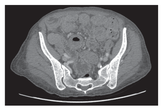
Case Report: Partial Response in a Patient with Refractory Disease

- 67-year-old white female first diagnosed with WM in Nov. 2009
- Previously treated with 6 regimens:

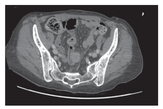


- Symptoms prior to initiating IMO-8400 treatment included diarrhea and fatigue
- Started treatment with IMO-8400 at a dose of 2.4 mg/kg per week
- Achieved PR by Week 9 on study
- PR was associated with an improvement in: baseline symptoms, intestinal wall thickening, hemoglobin (3.2 g/dL increase), β-2-microglobulin (46% decrease)
- Bone marrow disease burden decreased from 15% (baseline) to 10% (end of treatment)
- Completed full course of treatment on study, but did not roll over to extension study due to one episode of grade 3 neutropenia

Pre-treatment: 1/2/15



End of Treatment: 7/13/15



- CT imaging of the pelvis showed diffuse bowel wall thickening at baseline, with improvement demonstrated at end of treatment

CONCLUSIONS

Safety

- IMO-8400 was generally well tolerated at dose levels of 0.6, 1.2 and 2.4 mg/kg (1.2 mg/kg twice) per week
- The Maximum Tolerated Dose of IMO-8400 has not yet been identified

Clinical activity

- In the highest dose cohort studied to date (2.4 mg/kg):
  - There were 3 responses and 2 stable disease out of 6 patients with evaluable disease treated to date
  - Median time to first response ~10.5 weeks
  - Improvements in symptoms, hemoglobin and bone marrow were seen
- One of these responders was refractory to ibrutinib

Summary

- These data in patients with WM provide the first clinical evidence supporting inhibition of the TLR pathway as a potential therapeutic approach for B-cell lymphomas harboring the MYD88 L265P oncogenic mutation
- Exploration of higher IMO-8400 dose levels in this patient population is warranted

Disclosures: Idera Pharmaceuticals is the sponsor of this clinical trial. S Thomas, W Harb, T Beck, N Gabrail, ML Palomba, S Ansell, H Eradat, E Libby, R Advani, J Hajdenberg, J Hoffman and D Vesole are investigators who received research funding from Idera related to the conduct of this trial. L Simov, N Wyant, J Brevard, S Agrawal and J O'Leary are employees of Idera.