Clinical Activity of a Novel Multiple Tyrosine Kinase and Aurora Kinase Inhibitor, ENMD-2076, Against Multiple Myeloma: Interim Phase I Trial Results

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INTRODUCTION

1. Patient Characteristics

Despite recent improvements, multiple myeloma (MM) remains incurable, indicating the need for continued investigation of novel agents. ENMD-2076 is a novel, orally active molecule that has been shown to have significant activity against aurora and multiple receptor tyrosine kinases. Recently, we demonstrated that ENMD-2076 has significant pre-clinical in vitro and in vivo activity against MM cell lines and primary myeloma cells (Wang et al, Br J Haematol, 2010). Furthermore, ENMD-2076 inhibited critical pathways for MM cell survival and proliferation, including PI3K/AKT pathway with downregulation of synaptojanin and 30AP, and Aurora A and B kinase, inducing G2/M cell cycle arrest, inhibiting angiogenesis, and the FGFR3 pathway. We present the interim results of a phase I clinical trial of ENMD-2076 in patients with relapsed and refractory MM.

Methods: An open label, single agent, dose-escalation, safety and tolerability trial of ENMD-2076 is currently conducted in heavily pre-treated, relapsed and refractory patients who have previously failed standard therapy. Using a 3+3 design, dose escalation with ENMD-2076 is currently being studied at the doses: 150, 225, 325 mg/day orally for 28 days. Patients are redosed in subsequent 28-day cycles according to safety, tolerability, and absence of progression. Pharmacokinetics and pharmacodynamic studies, including effect on phosphorylated histone 3 (pH3) in purified bone marrow MM cells, effect on the PI3K pathway in peripheral blood mononuclear cells (PBMC), and circulating endothelial cell precursors are being investigated.

Results: Currently, dose-escalation for the first three dose levels has been completed. Nine patients of median age 54 (range, 48-78) years were treated. There were 5 males and 5 females. The median number of prior regimens was 3 (range, 2-5), with 8 patients having failed high-dose melphalan and autologous stem cell transplantation. The most commonly observed toxicities included grades 1-2 anorexia (n=2), nausea (n=2), diarrhea (n=1), fatigue (n=1), asymptomatic elevation of amylase (n=1) and lipase (n=1), anemia (n=2), leucopenia (n=1), thrombocytopenia (n=2), and heavy proteinuria (n=1). Grades 3 toxicities included hypertension (n=1), asymptomatic elevation of lipase (n=1), and thrombocytopenia (n=1). No dose-limiting toxicity was observed with all toxicities resolving promptly upon interruption or discontinuation of dosing. All patients treated on dose level 1 had progression of disease on treatment, 1 patient in dose level 2 had stable disease, and 2 patients on dose level 3 had stable disease although with 21% and 19% reduction in serum M-protein after 7 days rest for PK monitoring. Cycles 2 and beyond: ENMD-2076 daily for 28 days with dose-modification for grades 3-4 toxicity.

Conclusion: In the ongoing phase I clinical trial, ENMD-2076 appears safe and well-tolerated at the doses tested to date. ENMD-2076 may hold promise as a treatment for MM and further study is warranted.

ENMD-2076 is a novel, orally active molecule that has been shown to have significant activity against Aurora and multiple tyrosine kinases, including Flt3, c-Kit, VEGFR2, FGFR1, FGFR3, JAK2.

3. Disease Response

1. MTD of ENMD-2076 is not yet established in this ongoing trial, but dose-limiting toxicity of thrombocytopenia has been observed at 325 mg/day dose level. This cohort has been expanded to 6 patients (ongoing).

2. Clinical activity is noted at the 325 mg/day dose level, with 1 patient achieving a PR and 2 patients with stable disease (although with minor reduction in M-protein).

3. Pharmacokinetic and pharmacodynamic studies, including PI3K pathway inhibition in peripheral blood mononuclear cells and angiogenesis markers, are ongoing.

4. Change in p-H3 in CD138+ marrow cells

CONCLUSIONS

ENMD-2076 is a novel, orally active molecule that has been shown to have significant activity against Aurora kinases and multiple tyrosine kinases, including Flt3, c-Kit, VEGFR2, FGFR1, FGFR3, JAK2.

ENMD-2076 induces early apoptosis of MM cells with caspase activation, cleavage of PARP, and modulates the expression of anti- and pro-apoptotic proteins to favor cell death. In addition, ENMD-2076 inhibits the PI3K/Akt pathway, Aurora kinases A and B, signaling through FGFR3 and VEGFR, and induces G2/M cell cycle arrest.

Based on our preclinical studies, we initiated a phase I trial of ENMD-2076 in relapsed and refractory MM patients.

STUDY OBJECTIVE

Determine the maximum tolerated dose, safety and tolerability of ENMD-2076 as a single agent in patients with relapsed and refractory MM.

RESULTS

1. Patient Characteristics

<table>
<thead>
<tr>
<th>Age, median (range) years</th>
<th>Gender, male/female, n</th>
<th>lines of prior treatment, median (range)</th>
<th>Prior autologous transplantation, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>54 (48-78)</td>
<td>5:5</td>
<td>3 (2-5)</td>
<td>2 (2-5)</td>
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</table>

2. Toxicity*

Elevated lipase* Anorexia Nausea Diarrhea Dyspepsia Constipation Diarrhea Elevation amylase* Elevation lipase* Edema Hypertension Epistaxis Joint pain Albuminuria Hematological Anemia Neutropenia Thrombocytopenia Eosinophilia Neutropenia Fatigue Tremor

* All elevations of amylase, lipase, and transaminases were asymptomatic ** Toxicity during cycle 1 of treatment

Toxicities included hypertension (n=1), asymptomatic elevation of lipase (n=1), anemia (n=2), leucopenia (n=1), thrombocytopenia (n=2), and heavy proteinuria (n=1). Grades 3 toxicities included hypertension (n=1), asymptomatic elevation of lipase (n=1), and thrombocytopenia (n=1). No dose-limiting toxicity was observed with all toxicities resolving promptly upon interruption or discontinuation of dosing. All patients treated on dose level 1 had progression of disease on treatment, 1 patient in dose level 2 had stable disease, and 2 patients on dose level 3 had stable disease although with 21% and 19% reduction in serum M-protein after 7 days rest for PK monitoring. Cycles 2 and beyond: ENMD-2076 daily for 28 days with dose-modification for grades 3-4 toxicity.

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