A PHASE 2 STUDY OF ENMD-2076 IN PLATINUM RESISTANT OVARIAN CANCER

URSULA A. MATULONIS 1, JULIE LEE 1, BRIAN LASONDE 1, WILLIAM P. TEW 2, AFRA YEHWALASHET 2, DANIELA MATEI 3, KIAN BEHBAKHT 4, JILL GROTHUSEN 4, GINI FLEMING 5, NITA K. LEE 5, JAMIE ARNOTT 6, MARK R. BRAY 7, GRAFTHAM GERALD 7, VINCENT CASTONGUAY 8, HELEN MACKAY 8, CAROLYN F. Sidor 6, AMIT M. OZA 8.

1. DANA-FARBER CANCER INSTITUTE AND HARVARD MEDICAL SCHOOL, BOSTON, MA; 2. MEMORIAL SLOAN-KETTERING CANCER CENTER, NEW YORK, NY; 3. INDIANA UNIVERSITY SIMON CANCER CENTER, INDIANAPOLIS, IN; 4. UNIVERSITY OF COLORADO, AURORA CO; 5. UNIVERSITY OF CHICAGO, CHICAGO, IL; 6. ENTREMED INC.; 7. DURHAM, NC AND 8. TORONTO ON; 8. PRINCESS MARGARET HOSPITAL, TORONTO, ON.

INTRODUCTION

- ENMD-2076 is a novel, orally active, small molecule kinase inhibitor with anti-angiogenic and anti-proliferative mechanisms.
- ENMD-2076 has been shown to inhibit a unique profile of kinase targets including the Aurora kinase which is key regulators of the process of cell division and are often over-expressed in human cancers, and the VEGFR and FGFR families critical for angiogenesis.
- Multiple non-clinical investigations have provided encouraging results for the use of ENMD-2076 in the treatment of various cancers including ovarian cancer models as a single agent or in combination with chemotherapy (ref 1).
- Many of the kinase targets for ENMD-2076 are important in the pathogenesis of ovarian cancer and may play a role in the development of resistance to other therapies (ref 2).

- ENMD-2076 is Active Against Multiple Oncogenic Kinases

- In a Phase 1 study, ENMD-2076 showed activity in a number of indications including ovarian cancer (ref 4).
- Of the 20 ovarian cancer patients treated, there were 2 PRs per RECIST and 6 additional PRs based on CA-125; 5 patients were on study drug for 6 months or longer; one patient remains on study drug for over 3 years.
- The combination of ENMD-2076’s unique mechanism of action, preclinical activity and Phase 1 results makes it an excellent candidate for a Phase 2 study in platinum resistant ovarian cancer patients.

METHODS

Study Design
- Open-label, single arm, Phase 2 study of single agent ENMD-2076 taken daily orally for recurrent ovarian, peritoneal or tubal cancer.
- Starting dose of 2 mg/kg was reduced to 275mg/kg after the initial 23 patients enrolled because of treatment delays and side effects (for patients less than 1.65m, starting dose was 275mg reduced to 250mg).
- Study conducted at 6 cancer centers in the US and Canada.
- Tumor assessments every 2 cycles (28 day cycles) by RECIST v1.1 and at Day 180 (6 month time point); safety assessments per CTCAE versions 4.0.
- Patients were given home blood pressure monitoring devices with instructions to contact their site with abnormal readings.

Key Eligibility Criteria
- Platinum resistant ovarian, peritoneal or tubal cancers with progression within 6 months of completing platinum-based chemotherapy; no more than 3 prior regimens for recurrent disease including one non-platinum regimen.
- Measurable disease by RECIST v1.1.
- Normal organ function with ECOG of 0 or 1.
- Controlled blood pressure; QTC less than 470ms; normal electrojection fraction, no history of nephrotic syndrome or 2+ proteinuria at screening.
- Concurrent therapy with antiangiogenic or antiwarfarin allowed.
- Prior therapy with VEGF inhibitors allowed.
- Prior platinum refractory patients excluded.

Study Endpoints
- Progression free survival rate at 6 months (by RECIST v1.1).
- Response rate, duration of response, overall survival.
- Exploratory analyses of archival tissue for mitotic index and angiogenesis to correlate with response.
- Safety.

STATISTICAL PLAN

- The Safety Population is defined as any patient receiving at least one dose of ENMD-2076 (N=84).
- The Efficacy Population is defined as the patients in the safety population who met all major entry criteria. If a patient withdrew consent prior to the first tumor assessment for reasons other than unacceptable side effects, documented PD or death they were excluded from the Efficacy Population (N=57).
- Progression free survival rates are estimated from the Kaplan Meier distribution.
- Sample size calculations - Null hypothesis of a PFS rate at 6 months of 20% with an alternative hypothesis of 35% to support additional single agent studies in this patient population using a daily schedule (ref 5.6).
- One-sided test at the 5% level of significance.
- 80% power.

PHARMACOKINETICS

- Single determinations of ENMD-2076 and its active metabolite, ENMD-2050, were obtained at Day 1 of each cycle.
- Steady state plasma levels of ENMD-2076 averaged 356 ng/mL (N = 42).
- Steady state plasma levels of ENMD-2076 were not significantly different in those patients who discontinued due to an AE (343 ng/mL) compared to patients who were progression free and alive at 6 months (397 ng/mL).

Overall Best Response Assessment (Revised RECIST v1.1)

<table>
<thead>
<tr>
<th>Disease</th>
<th>CR</th>
<th>PR</th>
<th>NR</th>
<th>PD</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian cancer</td>
<td>13</td>
<td>52</td>
<td>23</td>
<td>1</td>
<td>68%</td>
</tr>
<tr>
<td>Peritoneal cancer</td>
<td>0</td>
<td>15</td>
<td>19</td>
<td>0</td>
<td>25%</td>
</tr>
<tr>
<td>Tubal cancer</td>
<td>0</td>
<td>10</td>
<td>22</td>
<td>0</td>
<td>25%</td>
</tr>
</tbody>
</table>

All Treatment-Emergent Adverse Events by Systems Organ Class and Preferred Term by Severity Safety Population (in at least 5%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>84 (100)</td>
<td>61 (72)</td>
<td>0</td>
<td>0</td>
<td>145</td>
</tr>
<tr>
<td>Nausea</td>
<td>84 (100)</td>
<td>51 (61)</td>
<td>0</td>
<td>0</td>
<td>135</td>
</tr>
<tr>
<td>Vomiting</td>
<td>84 (100)</td>
<td>42 (50)</td>
<td>0</td>
<td>0</td>
<td>126</td>
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<tr>
<td>Hematologic</td>
<td>84 (100)</td>
<td>47 (56)</td>
<td>0</td>
<td>0</td>
<td>131</td>
</tr>
<tr>
<td>Anorexia</td>
<td>84 (100)</td>
<td>60 (71)</td>
<td>0</td>
<td>0</td>
<td>144</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>84 (100)</td>
<td>63 (75)</td>
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<td>0</td>
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<tr>
<td>Alopecia</td>
<td>84 (100)</td>
<td>13 (15)</td>
<td>0</td>
<td>0</td>
<td>97</td>
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<tr>
<td>Leukopenia</td>
<td>84 (100)</td>
<td>25 (30)</td>
<td>0</td>
<td>0</td>
<td>109</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>84 (100)</td>
<td>25 (30)</td>
<td>0</td>
<td>0</td>
<td>109</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>84 (100)</td>
<td>13 (15)</td>
<td>0</td>
<td>0</td>
<td>97</td>
</tr>
<tr>
<td>Anemia</td>
<td>84 (100)</td>
<td>25 (30)</td>
<td>0</td>
<td>0</td>
<td>109</td>
</tr>
</tbody>
</table>

Potential Drug-Related Deaths: None
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**CONCLUSIONS**
- Single agent ENMD-2076 has activity in platinum resistant ovarian cancer patients with a progression-free survival rate of 6 months to 19 days.
- For patients meeting the primary endpoint, none had received prior anti-VEGF therapy and 38% had prior liposomal doxorubicin.
- Median OS has not yet been reached.
- The side effect profile is consistent with activity against the targets of ENMD-2076, in particular, VEGF2 and Aurora A.
- Dose reductions were required in 15% of patients treated before the starting dose was reduced compared to 11% following the reductions suggesting better tolerability at the lower starting dose of 250 mg/dl (250 mg/dl in patients less than 1.65m).
- The major non-cardiac vascular toxicities related to ENMD-2076 were hypertension (64% all grades / 21.9% grade 3 or 4), thromboembolism (6.3% all grades / 6.3% grade 3 or 4), hemorrage (14% all grades / 3.2% grade 3 or 4; including two patients with CNS hemorrhage) and reversible posterior leukoencephalopathy syndrome (1.8% all grades / 1.8% grade 3).
- Cytopenias occurred in 11% all grades / 3% grade 3 or 4.
- One patient reported reversible left ventricular dysfunction. No reports of QTc prolongation.
- Close monitoring and management of blood pressure and blood counts are required especially during the first two months of therapy with ENMD-2076 to minimize the risk for bleeding or hypertensive complications.
- No significant correlation has yet been observed between ENMD-2076 response and studied biomarkers of proliferation or p53 levels.
- A trend was observed among responding patients towards higher vascular densities on average than non-responders (4126 microvessels per mm² vs. 3115 microvessels per mm², p = 0.23).
- Further studies are in progress to evaluate potential markers of ENMD-2076 sensitivity.
- Final data on this Phase 2 study is expected 3Q2021.
- Clinical investigations with active chemotherapy agents and alternative schedules are warranted and planned in this patient population.
- Phase 2 clinical studies in other indications of interest include triple negative breast cancer, neuroendocrine cancers, hepatocellular cancer and colorectal cancer.

**REFERENCES**

**ACKNOWLEDGEMENTS**
- To thank the patients and their families for participation in this study.
- To thank SimplyMed, Inc., for their support in data collection and statistics.
- Sponsored by EndoHealth, Inc., Rod неделю, Ltd.