A Phase 1b Dose-escalation Study of Binimetinib (MEK162) in Combination with Weekly Paclitaxel in Patients with Platinum-resistant Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

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Introduction
The majority of women diagnosed with epithelial ovarian cancer will eventually become refractory or resistant to platinum-based and taxane-based chemotherapy. Past attempts to treat platinum-resistant disease have been challenging.

Methods
A multi-center, phase 1b, open-label, dose-escalation study was conducted to determine the safety, tolerability, and preliminary antitumor activity of binimetinib (BNI) in combination with weekly paclitaxel (PAC) in platinum-resistant or refractory epithelial ovarian, fallopian tube or primary peritoneal cancer patients (NCT01948217). Eligible patients had to have an ECOG PS ≤1, at least one measurable lesion, and prior platinum-based chemotherapy. Patients were sequentially assigned to 2 dosing schedules in combination with weekly PAC and assessed the safety, pharmacokinetics (PK) and preliminary antitumor activity in female patients with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. Dose-escalation was performed using a 3+3 design. Topicality and safety were evaluated every 2 weeks. 28-day cycles were used to determine the safety and tolerability of the agent ± PAC. Overall response, disease control rate (DCR), duration of objective response, and safety/tolerability were measured as endpoints and compared between the 2 dosing schedules.

Results
The majority of patients (20/34; 59%) were ≥65 years old. A total of 34 patients were enrolled across all dose levels of binimetinib (45 mg BID INTRM, 45 mg BID CONT, and 30 mg BID CONT) and 34 patients received PAC 60 mg/m² weekly.

Conclusions
The combination of BNI on both the 30 mg BID CONT and 45 mg BID INTERM schedules with weekly PAC (RP2Ds) had acceptable tolerability and PK profiles and could be moved forward into Phase 2.

Pharmacokinetics

Table 1: Geometric Mean Binimetinib Concentration vs. Time

<table>
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<th>Time (h)</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>24</th>
<th>48</th>
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Best Response in Patients with Measurable Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>histology</th>
<th>prior n</th>
<th>prior therapy</th>
<th>best response</th>
<th>confirmed CR</th>
<th>confirmed PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>LGS</td>
<td>3</td>
<td>first-line platinum-based and taxane-based chemotherapy</td>
<td>PD</td>
<td></td>
<td></td>
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<tr>
<td>Patient 2</td>
<td>HGS</td>
<td>6</td>
<td>first-line platinum-based and taxane-based chemotherapy</td>
<td>CR</td>
<td></td>
<td></td>
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<tr>
<td>Patient 3</td>
<td>LGS</td>
<td>5</td>
<td>first-line platinum-based and taxane-based chemotherapy</td>
<td>PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 4</td>
<td>HGS</td>
<td>4</td>
<td>first-line platinum-based and taxane-based chemotherapy</td>
<td>CR</td>
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</table>

Nineteen of 34 patients (56%) experienced an SAE, with a higher incidence observed for patients at 45 mg BID CONT (75%) compared to patients at 30 mg BID CONT (25%). The majority of SAEs were manageable, with 2 patients receiving treatment discontinuation. No DLTs were observed at the 30 mg BID CONT dose level. Two patients had treatment interruptions due to SAEs during the 22nd cycle (one patient had SAE grade 3 hepatic failure and the other had grade 3 abdominal pain), leading to an amended protocol to reduce this cycle to 1 cycle. Five patients remained on treatment during the 22nd cycle (one patient had grade 3 anemia, one had grade 3 neutropenia, one had grade 3 nausea and vomiting, and two had grade 3 abdominal pain).

Summary
The combination of BNI on both the 30 mg BID CONT and 45 mg BID INTERM schedules with weekly PAC (RP2Ds) had acceptable tolerability and PK profiles and could be moved forward into Phase 2. This combination of BNI on the 30 mg BID CONT and 45 mg BID INTERM schedules with weekly PAC had acceptable tolerability and PK profiles and could be moved forward into Phase 2. This combination of BNI on the 30 mg BID CONT and 45 mg BID INTERM schedules with weekly PAC did not increase toxicity of either agent based on their known single-agent safety profiles; however, the combination was well tolerated and led to objective responses in platinum-resistant ovarian cancer patients. These findings support further development of the study drug combination in platinum-resistant epithelial ovarian cancer patients with unmet medical need.

Narratives of Patients with RECIST v1.1 Responses

Confirmed Complete Responses in LGS Patient

- 65-year-old White female with LGS epithelial ovarian cancer (BRAF mutation).
- Prior venetoclax failed to achieve response with chemotherapy (best response CR).
- Initial treatment 45 mg BID CONT; 90 mg/m² PAC.
- Treatment discontinued (Day 113) due to Grade 2 fatigue.
- Both study drugs discontinued (Day 115). No evidence of disease progression at 16.5 months.
- Patient continues on venetoclax- alone treatment.

Confirmed Complete Responses in LGS Patient

- 71-year-old White female with LGS epithelial ovarian cancer (KIAA1549 mutation).
- Prior venetoclax failed to achieve response with chemotherapy (best response SD).
- Initial treatment 45 mg BID CONT; 90 mg/m² PAC.
- Treatment discontinued (Day 57) due to Grade 2 neuropathy; patient continued treatment on 45 mg BID CONT, 60 mg/m² PAC.
- Confirmed PR on Day 233 (ongoing; duration 15.2 months).
- Patient continues on venetoclax- alone treatment.

Confirmed Partial Responses in LGS Patient

- 71-year-old White female with LGS epithelial ovarian cancer (17p13.1 and 5q31 mutations).
- Prior sorafenib for treatment of advanced/metastatic disease.
- Initial treatment 45 mg BID CONT; 90 mg/m² PAC.
- Treatment discontinued (Day 65) due to Grade 2 fatigue.
- PAC discontinued (Day 7) due to Grade 2 neuropathy; patient continued treatment.
- Confirmed PR on Day 229 (ongoing; duration 12.4 months).
- Confirmed PR on Day 732 due to radiologic disease progression.

Confirmed Partial Responses in HIS Patient

- 75-year-old White female with HIS epithelial ovarian cancer (17p13.1 and 5q31 mutations).
- Prior carboplatin/pegylated liposomal Doxorubicin (best response PR) and Paclitaxel/Cisplatin (best response PD).
- Confirmed PR on Day 60; treatment discontinued (Day 120) due to Grade 2 fatigue.
- PAC discontinued (Day 7) due to Grade 2 neuropathy; patient continued treatment.
- Confirmed PR on Day 60 (duration 6 months).
- Treatment discontinued (Day 262) w/o radiologic disease progression.

Confirmed Partial Responses in HIS Patient

- 60-year-old White female with HIS epithelial ovarian cancer (genetic altered status unknown).
- Prior surgery (resection for advanced disease) and therapy with carboplatin, paclitaxel, and bevacizumab.
- Treatment discontinued (Day 272) due to high-grade toxicities.
- Confirmed PR on Day 30; treatment discontinued (Day 30).
- Confirmed PR on Day 357; patient remains on treatment and shows durable response.
- Treatment discontinued (Day 357); patient shows durable response.

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