Initial efficacy and safety results from ENGOT-ov60/GOG-3052/RAMP 201: A phase 2 study of avutometinib (VS-6766) ± defactinib in recurrent low-grade serous ovarian cancer (LGSO)

Robert W. Holloway1, Susanis N. Banerjee1, Karl L. Ring1, Els Van Niewenhuizen2, Michel Fabbro2, Carol Aghajanian3, Ana Okain4, Nicolotta Cobolmo1, Alessandro D. Santin1, Andrew R. Clapp1, Kathleen N. Moore1, Peter G. Rose5, David M. O'Malley5, Hye Sook Chon6, Erin A. Salinas3, Emily N. Prendergast7, Stephanie Lustgarten1, Manuel Rodrigues1, Christine Gennings1, Bradley J. Monk1, Rachel N. Grisham1

1. Department of Obstetrics and Gynecology, Emory University School of Medicine, Atlanta, GA, USA; 2. Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver, CO, USA; 3. Department of Radiation Oncology, University of Virginia Health System, Charlottesville, VA, USA; 4. Department of Obstetrics and Gynecology, Medical College of Wisconsin, Milwaukee, WI, USA; 5. Department of Obstetrics and Gynecology, Emory University Hospital, Atlanta, GA, USA; 6. Department of Obstetrics and Gynecology, Metz Medical Centre, Metz, Lorraine, France; 7. Department of Obstetrics and Gynecology, McGill University, Montreal, QC, Canada

BACKGROUND

- LGSOC is a RAS/RAF pathway-driven cancer that constitutes ≤10% of ovarian cancer.1,2
- Current treatment options in recurrent LGSOC have shown responses ranging between 0.2%-6%.4
- There are no FDA or EMA-approved treatments specifically for LGSOC.
- Avutometinib is a first-in-class oral RAF/MEK inhibitor that potently inhibits MEK kinase activity and also blocks the compensatory reactivation of MEK by upstream RAF.5,6 (Figure 1).
- Defactinib is a selective inhibitor of focal adhesion kinase (FAK), which has been shown to mediate resistance to RAF/MEK inhibition.6,7 (Figure 1).

Avutometinib + defactinib has demonstrated a high rate of confirmed and durable responses (objective response rate [ORR] ≥46%, median progression free survival [mPFS] >23 mos) in recurrent LGSOC (KRAME, NCT03878522), forming the basis for an FDA Breakthrough Therapy Designation and for the ENGOT-ov60/GOG-3052/RAMP 201 study.2

Herein, we present initial efficacy and safety (Parts A & B) results from a planned interim analysis of the registration-directed phase 2 ENGOT-ov60/GOG-3052/RAMP 201 (RAMP 201) trial evaluating avutometinib (VS-6766) ± defactinib in LGSOC (NCT04625270).

Efficacy

- Confirmed ORRs of 45% (15/2/19; 95% CI: 21%, 64%) and 10% (3/32; 95% CI: 2%, 24%) were observed on the combination and monotherapy arms, respectively.8,9
- mPFS: 10/81 mos vs 21/28 days for avutometinib vs. placebo (HR = 0.13; 95% CI: 0.06-0.28; p < 0.001) (Figure 2).
- Tumor shrinkage was observed in the vast majority of patients on the combination and monotherapy arms, 89% (25/28) and 50% (16/32) respectively.
- Responses observed in 314 patients who received prior MEK inhibition therapy in combination arm (1/10 in monotherapy arm).
- Median time to response in combination arm 5.5 months (range: 1.6-14.6 months) and monotherapy arm: 7.3 months (range 2.1-11.1 months).

Table 1: Baseline Characteristics of RAMP 201 Part A

Percent Change in Baseline Tumor Assessment

Table 2: RAMP 201 Part A Patient Disposition

<table>
<thead>
<tr>
<th>Patient Disposition</th>
<th>Avutometinib</th>
<th>Defactinib</th>
<th>Both</th>
<th>Either</th>
<th>Neither</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>81</td>
<td>81</td>
<td>81</td>
<td>81</td>
<td>0</td>
</tr>
<tr>
<td>Evaluable Patients</td>
<td>72</td>
<td>72</td>
<td>72</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>Censored</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Died</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3: RAMP 201 Part A Efficacy Results per BICR (Efficacy Evaluative Patient Population)

CONCLUSIONS

- Key objectives for Part A of the ENGOT-ov60/GOG-3052/RAMP 201 study were achieved.
- Avutometinib (2.3 mg PO twice weekly) ± defactinib (200 mg PO BID 21/28 days) has been selected as the go-forward regimen in patients with recurrent LGSOC.
- The combination of avutometinib + defactinib demonstrated exceptionally high responses in heavily-pretreated recurrent LGSOC, regardless of KRAS status.9
- Confirmed ORR: 46% (mPFS >23 mos vs. 21/28 days).
- Tumor shrinkage was observed in the vast majority of patients in both monotherapy (50%) and combination (89%) arms.
- The safety profile was consistent with previously reported safety results for avutometinib + defactinib.
- Majority of AEs were grade 1-2.
- Limited number of patients experienced dose reductions or discontinuations.
- Enrollment in combination arm of the ENGOT-ov60/GOG-3052/RAMP 201 continues in all patients with recurrent LGSOC, irrespective of KRAS mutation status.

REFERENCES