To address this unmet medical need, novel platinum-based combinations must be developed that:

- inhibit maintenance therapy
- Dose-limiting toxicities, such as thrombocytopenia and neutropenia, limit duration of platinum-based therapy
- although platinum therapy, this improvement is associated with additional toxicity, with response rates diminishing
- Standard of care for patients with newly diagnosed and platinum-sensitive recurrent HGSOC consists of platinum therapy, but outcomes are limited by toxicity (neutropenia), alopecia, peripheral neuropathy, and myalgia or arthralgia

Alcohol dehydrogenase (ADH), alcohol-dehydrogenase; ADC, antibody-drug conjugate; AE, adverse event; AFH, anti-fibroblast growth factor receptor; AUC, area under the curve; BION, baseline optical image; carbo, carboplatin; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; GOG, gynecologic oncology group; HGSOC, high-grade serous ovarian cancer; MTD, maximum tolerated dose; NaPi2b, sodium-dependent phosphate transport protein 2B; OC, ovarian cancer; ORR, objective response rate; OS, overall survival; primary peritoneal cancer; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tumor proportion score; TRAE, treatment-related adverse event; UpRi, upifitamab rilsodotin.

**BACKGROUND**

Unmet Need for Platinum-Sensitive Recurrent HGSOC

- Standard of care for patients with newly diagnosed and platinum-sensitive recurrent HGSOC consists of platinum-based chemotherapy with or without bevacizumab, often followed by bevacizumab and/or PARP inhibitor maintenance therapy
- Although platinum-containing combination therapies offer improvement in outcomes over single-agent platinum therapy, this improvement is associated with additional toxicity, with response rates diminishing through subsequent therapies
- Pathflux in association with high incidence of TRAEs, including hypersensitivity reactions, hematologic toxicity (neutropenia), alopecia, peripheral neuropathy, and myalgia or arthralgia
- Bevacizumab has been shown to cause additional AEs including hypertension, proteinuria, G1 events (perforations, abscesses, and fistulas), thromboembolism, high-grade pain, and wound disruption
- Dose-limiting toxicities, such as thrombocytopenia and neutropenia, limit duration of platinum-based therapy (usually 6 cycles) in the recurrent disease setting
- Poor response rates beyond first line indicate that there is a clear need for effective therapies in the treatment of platinum-sensitive recurrent OC

**METHODS**

**Study Design and Eligibility**

**UPGRADE**: A cohort is under the UPGRADE umbrella study evaluating UpRi in combination with other therapies (NCT04907668), specifically a Phase 1 dose escalation and expansion study evaluating UpRi in combination with carbo in patients with platinum-sensitive recurrent OC who have received 1–2 prior lines of therapy. Patients are not selected for NaPi2b expression. The trial is currently enrolling patients. Additional combination cohorts will be added.

**Key Enrollment Criteria**

- Recurrent, platinum-sensitive high-grade serous ovarian cancer, including fallopian tube or primary peritoneal cancer
- 1–2 prior platinum-based regimens
- Tissue (fresh or archival) will be collected for retrospective assessment of NaPi2b expression
- RECIST v1.1 measurable disease
- ECOG PS ≤ 2

**Dose Escalation (BOIN Design; N=18)**

<table>
<thead>
<tr>
<th>UpRi (3 dose levels)</th>
<th>carbo AUC 5 q4w ≥ 6</th>
<th>UpRi q4w until PD or unacceptable AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>MTD for UpRi with carboplatin AUC 5</td>
<td></td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>AEs, PK for UpRi, PK for carboplatin, immunogenicity for UpRi, DOR, FRS, OS, efficacy by NaPi2b</td>
<td></td>
</tr>
</tbody>
</table>

**Dose Expansion (N=36)**

<table>
<thead>
<tr>
<th>UpRi MTD</th>
<th>carbo AUC 5 q4w ≥ 6</th>
<th>UpRi q4w until PD or unacceptable AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>MTD for UpRi with carboplatin AUC 5</td>
<td></td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>AEs, PK for UpRi, PK for carboplatin, immunogenicity for UpRi, DOR, FRS, OS, efficacy by NaPi2b</td>
<td></td>
</tr>
</tbody>
</table>

**Statistical Considerations**

- Bayesian optimal interval (BOIN) design will be used to determine the MTD among the 3 dose levels to be evaluated in this study
- If additional dose levels/schemes are planned to be evaluated, then the maximum sample size will be increased by 6 patients for every dose level/scheme planned to be evaluated

- Primary objective of expansion cohort is to determine feasibility at MTD determined by ≥26% of participants completing ≥4 cycles of UpRi/carboplatin combination without discontinuing treatment earlier for reasons other than disease progression
- Secondary objectives include assessing correlation of tumor progression with maintenance treatment following completion of the dose

**CONCLUSIONS**

- Upifitamab rilsodotin (UpRi) is an investigational first-in-class ADC targeting the sodium-dependent phosphate transport protein NaPi2b
- Based on available emerging data, we hypothesize that UpRi in combination with other therapies may provide additional clinical benefit and improved tolerability over current standard of care
- UpRi is a cohort under the umbrella study, UPGRADE, evaluating UpRi in combination with carbo in patients with platinum-sensitive (progressing ≥6 months after completion of last dose of platinum) recurrent OC who have received 1–2 prior lines of therapy
- Primary objectives for the dose escalation and expansion cohorts are to identify the MTD and to assess the feasibility of the combination. Secondary endpoints include safety and tolerability, PK, and preliminary anti-neoplastic activity
- Enrollment to the dose escalation cohort is underway
- ClinicalTrials.gov registry: NCT04907668

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**REFERENCES**


**ADDITIONAL INFORMATION**

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For more information on UPGRADE, visit ClinicalTrials.gov page NCT04907668 via QR code provided or contact medicalinformation@mersana.com