UPGRADE: Phase 1 Combination Trial of the NaPi2b-directed Antibody-Drug Conjugate (ADC) Upifitamab Rilsodotin (UpRi; XMT-1536) in Patients With Ovarian Cancer

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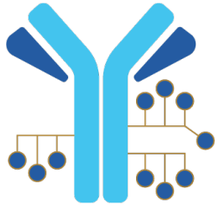
BACKGROUND

Unmet Need for Platinum-Sensitive Recurrent HGSOC[1–3]

- 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
  - Paclitaxel is associated 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, GI 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

Upifitamab Rilsodotin (UpRi): Investigational First-in-Class NaPi2b-targeting ADC[4,5]

- **NaPi2b** is a sodium-dependent phosphate transport protein broadly expressed in solid tumors, including high-grade serous epithelial ovarian, fallopian tube, and primary peritoneal cancer, with limited expression in normal tissue
- It is believed that approximately two-thirds of patients with HGSOC have high NaPi2b expression based on an IHC tumor proportion score (TPS) of at least 75%
- Based on the encouraging single-agent safety and efficacy data, we hypothesize that UpRi in combination with other therapies can provide additional clinical benefit and improved tolerability over current standard of care



Antibody: Humanized monoclonal anti-SLC34A2 (NaPi2b)

Linker: Fleximer polymer scaffold; cleavable ester linker stable in circulation

Payload: AF-HPA (DolaLock-controlled bystander effect); selectively toxic to rapidly dividing cells

Drug-to-Antibody Ratio (DAR): ~10

There Is Rationale for Combination Therapy With Carboplatin[3,6,7]

- To address this unmet medical need, novel platinum-based combinations must be developed that:
  - Can be continued as maintenance treatment following completion of platinum-based chemotherapy
  - Specifically contain targeted agents with favorable therapeutic index and lack appreciable overlapping toxicity with carboplatin
  - Have non-overlapping mechanisms of action with other agents typically combined with carboplatin
- ADCs, such as UpRi, may represent a promising strategy in combination with carboplatin to optimize therapeutic index for patients

METHODS

Study Design and Eligibility

UPGRADE-A is a cohort under the UPGRADE umbrella study evaluating UpRi in combination with other therapies (NCT04907968), specifically a Phase 1 dose escalation and expansion study evaluating UpRi in combination with carboplatin in patients with platinum-sensitive[a] 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[a] 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 = 0–1

Dose Escalation (BOIN Design; N=18)

UpRi (3 dose levels) + carbo AUC 5 q4w × 6 → **UpRi q4w** until PD or unacceptable AE

Primary Endpoint
- MTD for UpRi with carboplatin AUC 5

Secondary Endpoints
- AEs, PK for UpRi, PK for carboplatin, immunogenicity for UpRi, ORR, PFS, OS

Dose Expansion (N=30)

UpRi MTD + carbo AUC 5 q4w × 6 → **UpRi q4w** until PD or unacceptable AE

Primary Endpoint
- Feasibility

Secondary Endpoints
- AEs, PK for UpRi, PK for carboplatin, immunogenicity for UpRi, ORR, PFS, OS, efficacy by NaPi2b expression

[a] Patients with platinum-sensitive disease are defined as having achieved either a partial or complete response to 4 or more cycles in their last platinum-containing regimen and their disease progressing more than 6 months after completion of the last dose of platinum-containing therapy.

Statistical Considerations

Dose escalation

- 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

Dose expansion

- Primary objective of expansion cohort is to determine feasibility at MTD determined by ≥60% of participants completing at least 4 cycles of UpRi/carboplatin combination without discontinuing treatment earlier for reasons other than disease progression
- Secondary objectives include assessing correlation of tumor expression of NaPi2b and objective tumor response

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
- UPGRADE-A is a cohort under the umbrella study, UPGRADE, evaluating UpRi in combination with carboplatin 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: NCT04907968

ACKNOWLEDGMENTS

We would like to thank the patients, their families, and the site staff for making this study possible.

This study is sponsored by Mersana Therapeutics, Inc.

Editorial support for this poster was provided by BluPrint Oncology.

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ADDITIONAL INFORMATION

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For more information on UPGRADE, visit ClinicalTrials.gov page NCT04907968 via QR code provided or contact medicalinformation@mersana.com

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; AF-HPA, auristatin F-hydroxypropylamide; AUC, area under the curve; BOIN, Bayesian optimal interval; carbo, carboplatin; DAR, drug-to-antibody ratio; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; 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; PARP, Poly (ADP-ribose) polymerase; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PS, performance status; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SLC34A2, solute carrier family 34 member 2 gene; TPS, tumor proportion score; TRAE, treatment-related adverse event; UpRi, upifitamab rilsodotin.