UPLIFT (ENGOT-ov67/GOG-3048): A Pivotal Cohort of Upifitamab Rilsodotin (XMT-1536; UpRi), an NaPi2b-directed Dolaflexin Antibody Drug Conjugate (ADC) in Platinum-Resistant Ovarian Cancer

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BACKGROUND

➢ 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

➢ Upifitamab rilsodotin (UpRi; XMT-1536) is an investigational first-in-class antibody drug conjugate (ADC) targeting NaPi2b

Uplift Rilsodotin (UpRi): First-in-Class ADC Targeting NaPi2b

Hydrophilic Polymer Scaffold

DolaLock Payload With Controlled Bystander Effect

- Selectively toxic to rapidly dividing cells
- Initially released payload (AF-AHP) is freely permeable and bystander capable
- Intracellular conversion to AF diminishes permeability and controls bystander effect
- Accumulates in tumor, not a PGp substrate
- Induces immunogenic cell death

METHODS

RATIONALE

➢ Effective and well-tolerated treatments for platinum-resistant ovarian cancer remain a substantial unmet medical need

➢ SOC treatment, such as single-agent chemotherapy, have limited efficacy, with response rates of 4–12%, median PFS of 3–4 months, and median OS of less than 12 months10

➢ UPLIFT was designed as a Phase 2 single-arm registrational trial for platinum-resistant ovarian cancer as part of the ongoing Phase 1b study

- Based on the available emerging safety and efficacy profile of UpRi
- Designed to provide an opportunity for accelerated development and streamlined pathway to regulatory submission

DOISING

➢ Single-agent UpRi dosed at 36 mg/m2 up to a maximum of approximately 80 mg, administered IV Q4W

UPLIFT Cohort Key Eligibility Criteria

Primary Cancer

High-grade serous ovarian, fallopian tube, or primary peritoneal

Patient Population

Platinum-resistant (progressed within 6 months of last dose of platinum)

- 1–4 prior lines of therapy
- Prior bevacizumab required for patients with 1 or 2 prior lines of therapy, but not required for patients with 3–4 prior lines of therapy
- Excludes primary platinum-refractory disease

Baseline Neopathy

Allowed Grade 1–2; excludes patients with baseline neopathy Grade 3 or higher

Tissue Availability

Fresh OR archival

Biomarker Positivity

Not required (retrospectively assessed)

OBJECTIVES

Primary Objective

- Investigator-assessed confirmed ORR in patients with platinum-resistant ovarian cancer and high NaPi2b expression

Secondary Objectives

- Investigator-assessed confirmed ORR in overall platinum-resistant ovarian cancer population
- DoR
- Safety

Study Population for UPLIFT

Platinum-resistant ovarian cancer

- 1–4 prior lines in platinum-resistant
- High-grade serous histology
- Archived tumor and fresh biopsy (if medically feasible)
- Prior bevacizumab for those with 1–2 prior lines of therapy

Assessments

- Tumor imaging (MRI or CT) baseline and every 8 weeks
- Response assessed per RECIST v.1.1

STATISTICAL CONSIDERATIONS

➢ Sample Size: N=up to 180 total patients, including ~100 patients with high NaPi2b expression

➢ NaPi2b Cutoff: Pre-defined threshold of TPS ≥75% in retrospectively evaluated tissue specimens

➢ Power: Sample size of ~100 for high NaPi2b expressors provides ≥90% power to rule out the maximum SOC ORR of 12% with a 1-sided 97.5% exact binomial confidence interval

SUMMARY

➢ Upifitamab rilsodotin (UpRi) is an investigational first-in-class ADC targeting the sodium-dependent phosphate transport protein NaPi2b

➢ UPLIFT will evaluate the relevance of NaPi2b as a biomarker in both the UpRi-high and overall populations, with the goal of better understanding how NaPi2b can be used in further development to enrich patient outcomes

➢ Tumor samples (fresh or archival) will be collected prior to enrollment for retrospective tumor tissue evaluation of NaPi2b expression

➢ ≥90% power to rule out the maximum SOC ORR of 12%

➢ Study is being conducted in collaboration with ENGOT (ENGOT-ov67) and GOG (GOG-3048)

➢ ClinicalTrials.gov registry: NCT03319628

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REFERENCES


ADDITIONAL INFORMATION

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For more information on UPLIFT, visit ClinicalTrials.gov page NCT03319628 via QR code provided below.

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* TPS as determined by an IHC method.

Abbreviations: AF - antifade agent F, AF-AHP - auristatin F-hydrophilic polymer, AST - assay transfer, CT - computed tomography, DAR - drug-to-antibody ratio, DCR - disease control rate, DoR - duration of response, ENGOT - European Network for Gynecological Oncological Trial Groups, GOG - Gynecology Oncology Group, HPC - immunohistochemistry, IV - intravenous, MRI - magnetic resonance imaging, NaPi2b - sodium-dependent phosphate transport protein, OR - overall response rate, OS - overall survival, PARP - poly (ADP-ribose) polymerase, Q4W - every 4 weeks, RECIST - Response Evaluation Criteria in Solid Tumors, SOC - standard of care, TIPS - tiered priority score, TRAE - treatment-related adverse event.