ARIES: A Phase 2, Open-Label Study to Evaluate Rucaparib (PARP Inhibitor) in Combination with Nivolumab (Anti-PD-1 Antibody) in Patients with Ovarian Cancer

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INTRODUCTION

- Rucaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, has antitumor activity in ovarian cancer associated with homologous recombination deficiency (HRD), a phenomenon characterized by a deleterious mutation in *BRCA1*, *BRCA2*, or other homologous recombination repair gene, and/or genomic loss of heterozygosity (LOH)^{1,2}
- Nivolumab is a human immunoglobulin monoclonal antibody that binds to the programmed cell death receptor 1 (PD-1) and blocks its interaction with programmed cell death ligand 1 (PD-L1) and 2, releasing PD-1 pathway-mediated inhibition of the immune system, including antitumor immune response
- The rationale for combining rucaparib with nivolumab for ovarian cancer includes:
 - Compared with homologous recombination-proficient tumors, ovarian tumors associated with HRD have more neoantigens, which can attract tumor-infiltrating lymphocytes that express PD-L1,³ resulting in a preferential response to immune checkpoint inhibitors
 - DNA damage induced by PARP inhibition may increase neoantigens regardless of HRD status
 - In preliminary clinical study results, the combination of a PARP inhibitor with a PD-1 or PD-L1 blocking antibody demonstrated encouraging antitumor activity and a manageable safety profile in patients with ovarian cancer⁴⁻⁶
- Thus, we hypothesized that PARP inhibition by rucaparib may work synergistically with the PD-1 inhibitor nivolumab in patients with ovarian cancer by stimulating the tumor immune microenvironment to enhance immune-mediated antitumor activity

ARIES TRIAL OVERVIEW

- ARIES (CO-338-097; NCT03824704) is an open-label, 2-stage, 2-cohort, phase 2 study evaluating rucaparib plus nivolumab combination treatment for platinum-sensitive, recurrent, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer (**Figure 1**)
 - Cohort A1:** Patients with germline *BRCA* wild-type cancer (ie, all patients, except those with germline *BRCA* mutation)
 - Cohort A2 (exploratory):** Patients with deleterious germline *BRCA*-mutant cancer
- Simon 2-stage design will be used for Cohort A1 after ≥18 patients have either completed 16 weeks of treatment or discontinued treatment
 - If ≥3 of 18 patients have a confirmed complete or partial response per investigator, the trial will continue enrollment
- Cohort B, designed to include patients with locally advanced or metastatic urothelial cancer, was removed before enrolling any patients because preliminary efficacy results from the ATLAS trial in patients with recurrent, locally advanced or metastatic urothelial cancer (NCT03397394) did not meet protocol-defined continuance criteria

Primary Endpoints

Cohort A1 only:

- Investigator-assessed ORR per RECIST

Exploratory Cohort A2 only:

- Effect of rucaparib on the tumor immune microenvironment through analysis of pre- and post-treatment tumor samples

Secondary Endpoints

Cohort A1 only:

- ORR per RECIST and GCIG CA-125 criteria
- Investigator-assessed ORR per RECIST in:
 - BRCA* wild type/high LOH
 - BRCA* wild type/low LOH
 - BRCA* wild type/indeterminate LOH
 - Somatic *BRCA* mutation
- PFS
- DOR

Cohorts A1 and A2:

- Safety and tolerability of rucaparib + nivolumab

CA-125, cancer antigen 125; DOR, duration of response; GCIG, Gynecologic Cancer InterGroup; LOH, loss of heterozygosity; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Figure 1. ARIES Trial Schema

*Tumor tissue sample to be analyzed by the central laboratory (Foundation Medicine, Inc.) for sequencing of *BRCA* genes and analysis of genomic LOH; patients may enroll prior to sample analysis provided there is confirmation that tumor tissue has been received by the central laboratory. †Prior PARP inhibitor treatment is permitted if used as a frontline maintenance therapy without disease progression while on PARP inhibitor treatment. ‡Confirmed by local assessment. §Treatment will be initiated with a 1-cycle run-in of rucaparib; a mandatory post-treatment tumor sample will be collected prior to first dose of nivolumab on day 1 of cycle 2. BID, twice daily; CA-125, cancer antigen 125; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; LOH, loss of heterozygosity; PARP, poly(ADP-ribose) polymerase; PO, by mouth; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q24W, every 24 weeks; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

TRIAL ENROLLMENT

- Approximately 15 sites will enroll patients in the United States (**Figure 2**), with a target enrollment of ~53 patients (43 in Cohort A1 and 10 in Cohort A2)

Figure 2. Currently Enrolling Sites in ARIES

SUMMARY

- The open-label, 2-cohort, 2-stage trial ARIES is assessing the efficacy of rucaparib plus nivolumab in patients with platinum-sensitive, recurrent, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer
- ARIES aims to evaluate whether PARP inhibition stimulates the immune microenvironment and whether rucaparib plus nivolumab treatment shows enhanced immune-mediated antitumor activity in patients with germline *BRCA* wild-type (Cohort A1) or with deleterious germline *BRCA*-mutated ovarian cancer (Cohort A2)
- Results of ARIES may support a new treatment option for patients with platinum-sensitive, recurrent, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer

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