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

Kathleen Moore,[1] Lara Maloney,[2] Karl Redhead,[3] Sandra Goble,[2] Jowell Go,[2] Owen Bowles,[2] Kevin K. Lin,[2] Abhishek Tripathi[1]

[1]Stephenson Cancer Center, The University of Oklahoma, Oklahoma City, OK, USA;
[2]Clovis Oncology, Inc., Boulder, CO, USA; [3]Clovis Oncology UK Ltd., Cambridge, UK

Abstract 0435

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 cancer[4-6]
- 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:
1) Investigator-assessed ORR per RECIST

Exploratory Cohort A2 only:
1) Effect of rucaparib on the tumor immune microenvironment through analysis of pre- and post-treatment tumor samples

Secondary Endpoints

Cohort A1 only:
1) ORR per RECIST and GCIG CA-125 criteria
2) Investigator-assessed ORR per RECIST in:
   - *BRCA* wild type/high LOH
   - *BRCA* wild type/low LOH
   - *BRCA* wild type/indeterminate LOH
   - Somatic *BRCA* mutation
3) PFS
4) DOR

Cohorts A1 and A2:
1) 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

Screening

Key eligibility criteria

Cohorts A1 (n=18–43) and A2 (n=10)
- Relapsed, platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Received 1 or 2 prior anticancer regimens, including ≥1 prior platinum-containing therapy; last therapy must have been platinum based
- Mandatory tumor tissue collected ≤42 days before the first dose of rucaparib or archival tumor tissue with no intervening antitumor therapy*
- ECOG PS 0 or 1
- No prior PARP inhibitor† or immune checkpoint inhibitor treatment

Cohort A1 only
- Germline *BRCA* wild-type ovarian cancer (ie, all patients, except those with germline *BRCA* mutation)‡
- Measurable disease per RECIST version 1.1

Cohort A2 only
- Deleterious germline *BRCA*-mutant ovarian cancer‡

Treatment

Rucaparib PO 600 mg BID + Nivolumab IV 480 mg Q4W

28-day cycle§

- Treatment for up to 24 months after initiation of combination treatment, until radiographic disease progression, unacceptable toxicity, or other reason for discontinuation
- Tumor assessment per RECIST Q8W after start of combination treatment for up to 18 months, then Q12W thereafter
- Blood samples to assess CA-125 collected each cycle
- Mandatory tumor tissue biopsy at cycle 1 day 28
- Safety assessment at each cycle

Post-treatment

- **End of treatment visit**
- **Follow-up visits**
  - 28 days after last dose of treatment
  - 100 days after last dose of nivolumab

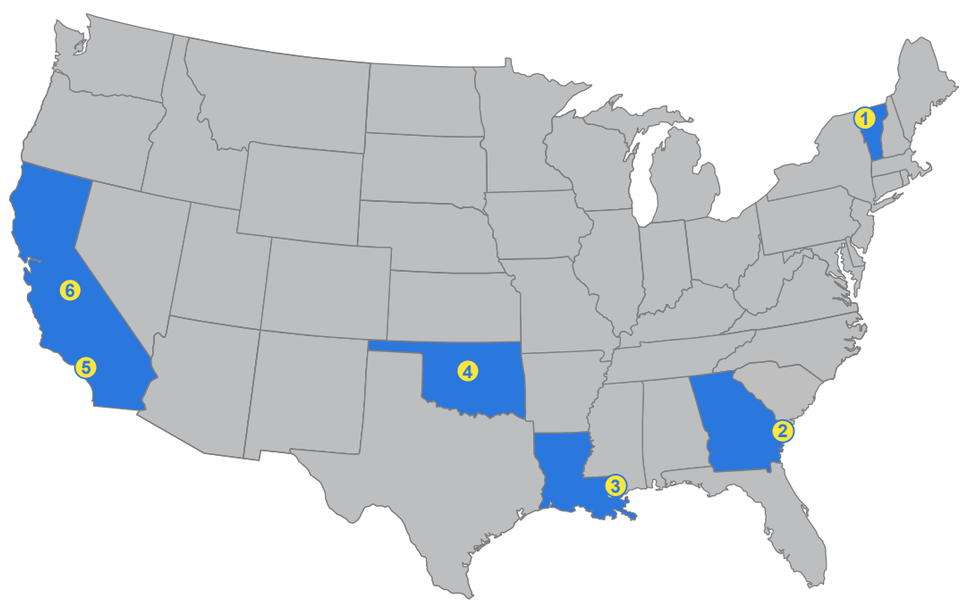
Long-term follow-up
- Tumor assessments Q12W for up to 18 months, then every Q24W thereafter for patients who discontinue for reason other than progression
- All patients to be followed Q12W for survival, subsequent treatments, disease progression, and secondary malignancies

*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



1. University of Vermont Medical Center, Burlington, VT
2. Memorial Health University Medical Center, Savannah, GA
3. Women's Cancer Care, Covington, LA
4. The University of Oklahoma Health Sciences Center, Oklahoma City, OK
5. Cedars-Sinai Medical Center, Los Angeles, CA
6. University of California, San Francisco, Fresno, CA

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

REFERENCES

1. Coleman et al. *Lancet*. 2017;390:1949-61.
2. Swisher et al. *Lancet Oncol*. 2017;18:75-87.
3. Strickland et al. *Oncotarget*. 2016;7:13587-98.
4. Lee et al. *J Clin Oncol*. 2017;35:2193-202.
5. Friedlander et al. *J Clin Oncol*. 2017;35:3013-13.
6. Konstantinopoulos et al. *J Clin Oncol*. 2018;36:106.

ACKNOWLEDGMENTS

This study is funded by Clovis Oncology, Inc. Medical writing and editorial support funded by Clovis Oncology was provided by Ritu Pathak and Shannon Davis of Ashfield Healthcare Communications.

Corresponding author: Kathleen Moore; email: Kathleen-Moore@ouhsc.edu.