INTRODUCTION

- The poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib inhibits the enzymes PARP1, PARP2, and PARP3, all of which play an important role in DNA repair.
- Rucaparib has antitumour activity in ovarian carcinomas associated with homologous recombination deficiency (HRD), a phenomenon characterised by a deleterious mutation in BRCA1, BRCA2, or other homologous recombination repair genes (e.g., RAD51C, RAD51D, and germline loss of heterozygosity (LOH)).
- LOH is a genomic association lost with 1% of a copy or chromosomal region.
- In the ARIEL3 (NCT01968213) study, rucaparib maintenance treatment significantly improved progression-free survival (PFS) in all patient populations regardless of biomarker status.
- Nirbulumab, a human immunoglobulin G1 monoclonal antibody, blocks programmed death receptor-1 (PD-1) and blocks its interaction with programmed death ligand-1 (PD-L1) and PD-L2, releasing PD-L1 and PD-L2 from the tumour cell, thereby blocking an important immune checkpoint.
- The rationale for combining rucaparib with nirbulumab includes:
  - Tumours with a deleterious BRCA1 mutation express novel, tumour-specific protein sequences (neocantiens), which can attract tumor-infiltrating lymphocytes that express PD-L1.
  - Ovarian cancer tumours associated with HRD have more neocantiens relative to those that have homologous recombination proficiency and may respond poorly to other immune checkpoint inhibitors.
- Rucaparib in combination with a PD-1 or PD-L1 checkpoint inhibitor demonstrated improved antitumour activity in a syngeneic ovarian cancer BRCA (BRCA1/2)-PD-(L)1/mouse model (Figure 1).
- In preliminary clinical study results, the combination of a PARP inhibitor with a PD-1 or PD-L1 blocking antibody demonstrated encouraging antitumour activity and a manageable safety profile in patients with ovarian cancer.
- The phase 3 study ATHENA will evaluate whether patients with ovarian cancer benefit from rucaparib + nirbulumab administered in combination as maintenance treatment following response to standard treatment (surgery and platinum-based chemotherapy) in the frontline setting.

TRIAL OVERVIEW

- ATHENA (GOG-3020/ENGOT-ov45; NCT03322246) is a randomised, multinational, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of rucaparib + nirbulumab as maintenance treatment following frontline platinum-based chemotherapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (Figure 2).

Figure 2. ATHENA Trial Schema

- Key eligibility criteria:
  - Newly diagnosed, stage III/IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.
  - Investigator-ascertained CR or PR without disease progression or rise in CA-125 at any time during frontline platinum doublet chemotherapy.
  - Completed cytoreductive surgery (if permitted), either prior to chemotherapy or following progression on neoadjuvant chemotherapy, with sufficient residual disease available for analysis.
  - ECOG PS 0 or 1.
  - No prior treatment for ovarian cancer, including any maintenance treatment other than first-line platinum regimen.

- Key endpoints will be evaluated using an ordered step-down procedure in 3 independent comparisons: Arm A vs Arm B, Arm A vs Arm D, and Arm B vs Arm D (Figures 3 and 4).

Figure 3. Planned Analyses for ATHENA

- Endpoints evaluated using an ordered step-down procedure:
  - Primary endpoint: Investigator-assessed PFS per RECIST.
  - Key secondary endpoints: BICR-assessed PFS per RECIST, OS, and Investigator-assessed ORR.

- Analysis of each endpoint will stop down through the subgroups in Figure 4 before proceeding to analysis of endpoint.

- Figure 4. Ordered Step-Down Procedure of Each Subgroup and Endpoint

- At least 25 countries will participate in ATHENA (Figure 5), with a target enrolment of 1000 patients across 270 sites.

Figure 5. Countries Participating in ATHENA

- SUMMARY

  - The phase 3 study ATHENA will investigate the efficacy and safety of rucaparib + nirbulumab as maintenance treatment following surgery and chemotherapy in patients with newly diagnosed stage III-IV ovarian cancer.
  - The goal of using this combination is to extend PFS following standard treatment (e.g., surgery and platinum-based chemotherapy) for ovarian cancer in the frontline setting.

References