ATHENA (GOG-3020/ENGOT-ov45): A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Rucaparib + Nivolumab Following Frontline Platinum-Based Chemotherapy in Ovarian Cancer

Abstract CT158

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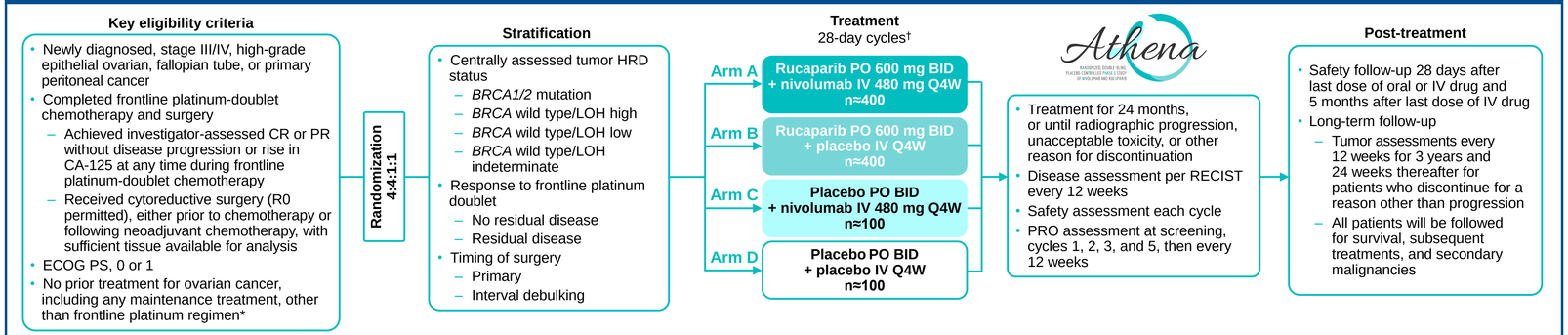
INTRODUCTION

- Rucaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor with antitumor activity in ovarian carcinomas associated with homologous recombination deficiency (HRD), a phenomenon characterized by a deleterious mutation in *BRCA1*, *BRCA2*, or other homologous recombination repair gene (eg, *RAD51C, RAD51D*), and/or genomic loss of heterozygosity[1-5]
- In the ARIEL3 (NCT01968213) study, rucaparib maintenance treatment significantly improved progression-free survival (PFS) for women with platinum-sensitive, recurrent ovarian cancer in all patient populations regardless of biomarker status[3]
- Nivolumab, a human immunoglobulin monoclonal antibody, binds programmed cell death receptor 1 (PD-1) and blocks its interaction with programmed cell death ligand 1 (PD-L1) and PD-L2, releasing PD-1–mediated inhibition of the immune response, including antitumor immune response
- The rationale for combining rucaparib with nivolumab includes the following:
  - Tumors with a deleterious *BRCA* mutation express novel, tumor-specific protein sequences (neoantigens), which can attract tumor-infiltrating lymphocytes that express PD-L1[6]
  - Ovarian carcinomas associated with HRD have more neoantigens relative to those that are homologous recombination proficient[6] and may respond preferentially to immune checkpoint inhibitors
  - Rucaparib in combination with a PD-1 or PD-L1 checkpoint inhibitor demonstrated improved antitumor activity in a syngeneic ovarian cancer BrKras (*BRCA1*$^{-/-}$*; TP53*$^{-/-}$*; MYC; KRAS-G12D; AKT*) model[7]
  - Furthermore, it is hypothesized that 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[8-11]
- The phase 3 study ATHENA is evaluating whether patients with ovarian cancer benefit from rucaparib + nivolumab 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; NCT03522246) is a randomized, multinational, double-blind, placebo-controlled, phase 3 study to evaluate the safety and efficacy of rucaparib + nivolumab as maintenance treatment following frontline platinum-based chemotherapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (**Figure 1**)
- 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 2** and **3**)

Figure 1. ATHENA Trial Schema



*Bevacizumab is allowed during the chemotherapy phase, but not during maintenance, ie, during treatment in this study. †First dose of IV study drug will be administered on day 1 of cycle 2; study treatment will continue on day 1 of every 28-day cycle thereafter.
BID, twice daily; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRD, homologous recombination deficiency; IV, intravenous; LOH, loss of heterozygosity; PO, by mouth; PR, partial response; PRO, patient-reported outcome; Q4W, every 4 weeks; R0, total cytoreduction; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Figure 2. Planned Analyses for ATHENA

Endpoints evaluated using an ordered step-down procedure

Primary endpoint
1) Investigator-assessed PFS per RECIST[12]

Key secondary endpoints
2) BICR-assessed PFS per RECIST[12]
3) OS
4) Investigator-assessed ORR

Analysis of each endpoint will step down through the subgroups in Figure 3 before proceeding to analysis of the next endpoint

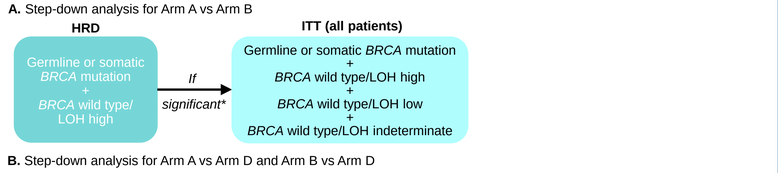
Endpoints not adjusted for multiplicity

Additional secondary endpoints
- Investigator-assessed DOR
- Safety

Key exploratory endpoints
- PFS2
- Contribution of nivolumab to efficacy of combination
- HRQoL
- PROs
- Mutation in other HRR genes and PD-L1 expression as molecular markers of efficacy
- ctDNA as marker of response and resistance
- PK of rucaparib and nivolumab

BICR, blinded independent central review; ctDNA, circulating tumor DNA; DOR, duration of response; HRQoL, health-related quality of life; HRR, homologous recombination repair; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PFS2, PFS after subsequent line of treatment; PK, pharmacokinetics; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Figure 3. Ordered Step-Down Procedure of Each Subgroup and Endpoint

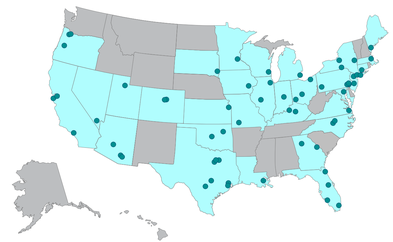


*Investigator-assessed PFS will be tested at a 1-sided 0.0083 significance level; once statistical significance is not achieved for a given analysis, statistical significance will not be declared for all subsequent analyses.
HRD, homologous recombination deficiency; ITT, intent to treat; LOH, loss of heterozygosity; PFS, progression-free survival.

TRIAL ENROLLMENT

- At least 25 countries will participate in ATHENA, with a target enrollment of 1000 patients across >270 sites
- At least 63 sites in the United States will be included (**Figure 4**)

Figure 4. US Sites Participating in ATHENA



SUMMARY

- The phase 3 study ATHENA is investigating the efficacy and safety of rucaparib + nivolumab 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 (eg, surgery and platinum-based chemotherapy) for ovarian cancer in the frontline setting

REFERENCES

1. Oza et al. *Gynecol Oncol*. 2017;147:267-75.
2. Kristeleit et al. *Clin Cancer Res*. 2017;23:4095-106.
3. Coleman et al. *Lancet*. 2017;390:1949-61.
4. Kondrashova et al. *Cancer Discov*. 2017;7:984-98.
5. Swisher et al. *Lancet Oncol*. 2017;18:75-87.
6. Strickland et al. *Oncotarget*. 2016;7:13587-98.
7. Nguyen et al. *Cancer Res*. 2018;78:abst 1716.
8. Lee et al. *J Clin Oncol*. 2017;35:2193-202.
9. Friedlander et al. *J Clin Oncol*. 2017;35:3013-13.
10. Konstantinopoulos et al. *Gynecol Oncol*. 2018;149: abst LBA3.
11. Drew et al. *Gynecol Oncol*. 2018;149:abst LBA4.
12. Eisenhauer et al. *Eur J Cancer*. 2009;45:228-47.

ACKNOWLEDGMENTS

This study is funded by Clovis Oncology, Inc. Medical writing and editorial support funded by Clovis Oncology was provided by Nathan Yardley and Shannon Davis of Ashfield Healthcare Communications. The ATHENA study design was previously presented at the IGCS Meeting, September 14–16, 2018, Kyoto, Japan.

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