Abstract 0326

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

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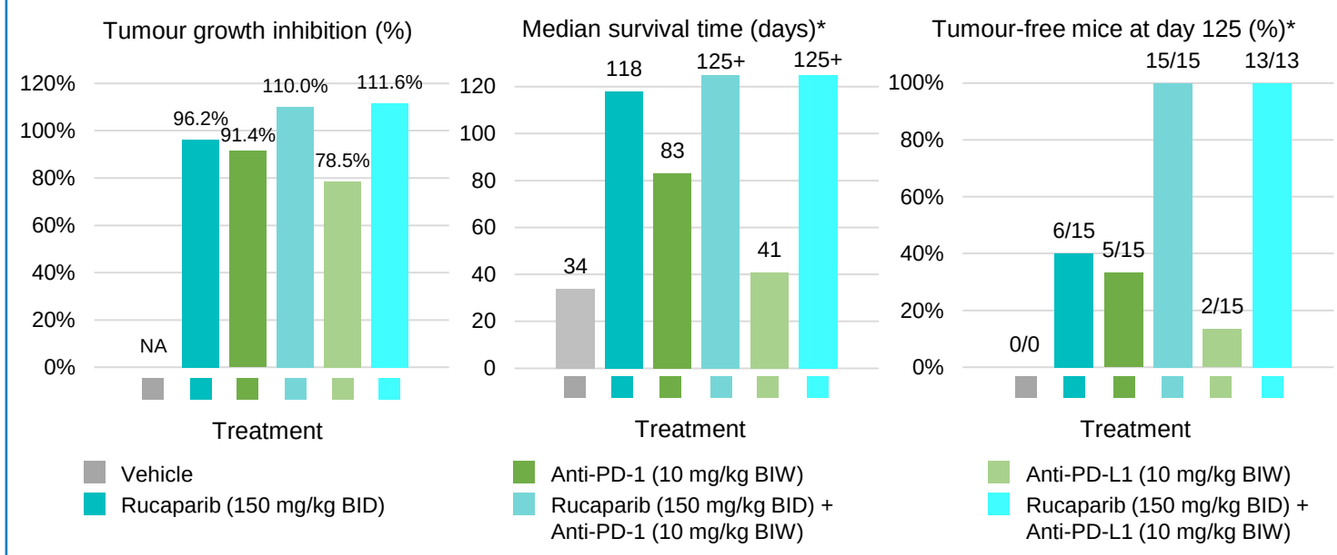
INTRODUCTION

- 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 gene (eg, *RAD51C, RAD51D*), and/or genomic loss of heterozygosity (LOH)[1-5]
  - LOH is a genomic scar associated with loss of 1 copy of a gene or chromosomal region[5-8]
- In the ARIEL3 (NCT01968213) study, rucaparib maintenance treatment significantly improved progression-free survival (PFS) in all patient populations regardless of biomarker status[3]
- Nivolumab, a human immunoglobulin monoclonal antibody, binds programmed death receptor-1 (PD-1) and blocks its interaction with programmed death ligand-1 (PD-L1) and PD-L2, releasing PD-1–mediated inhibition of the immune response, including antitumour immune response
- The rationale for combining rucaparib with nivolumab includes:
  - Tumours with a deleterious *BRCA* mutation express novel, tumour-specific protein sequences (neoantigens), which can attract tumour-infiltrating lymphocytes that express PD-L1[9]
  - Ovarian cancer tumours associated with HRD have more neoantigens relative to those that are homologous recombination proficient[9] and may respond preferentially to immune checkpoint inhibitors
  - Rucaparib in combination with a PD-1 or PD-L1 checkpoint inhibitor demonstrated improved antitumour activity in a syngeneic ovarian cancer BrKras (*BRCA1*$^{-/-}$*; TP53*$^{-/-}$*; MYC; KRAS-G12D; AKT*) model (**Figure 1**)[10]
  - 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[11-14]
- The phase 3 study ATHENA will evaluate 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

Figure 1. Improved Efficacy of Rucaparib when Combined with Anti-PD-1 or Anti-PD-L1 in *BRCA*$^{-/-}$ Syngeneic Ovarian Cancer Model

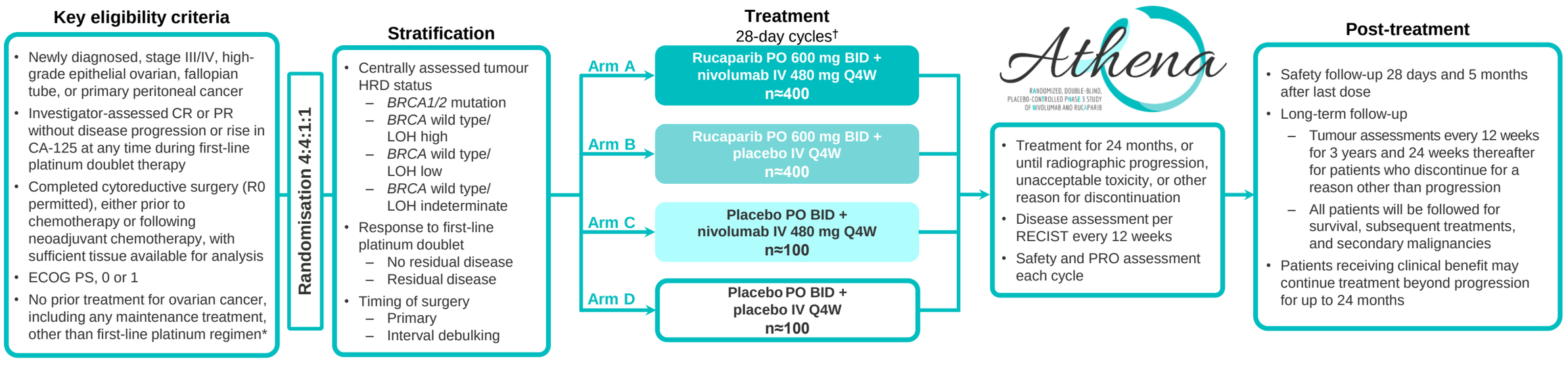


Anti-PD-L1 (10F.9G2; Bio X Cell, West Lebanon, NH) and anti-PD-1 (RMP1-14; Bio X Cell, West Lebanon, NH) were used in these experiments.
*Mice were sacrificed at day 125; all mice in the combination arms were alive at day 125.
BID, twice daily; BIW, twice weekly, NA, not applicable; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1.
Adapted from Nguyen et al. *Cancer Res*. 2018;78:abstr 1716 (Presented at AACR 2018).[10]

TRIAL OVERVIEW

- ATHENA (GOG-3020/ENGOT-ov45; NCT03522246) is a randomised, multinational, double-blind, placebo-controlled, phase 3 study to evaluate the safety and efficacy of rucaparib + nivolumab as maintenance treatment following front-line platinum-based chemotherapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (**Figure 2**)

Figure 2. 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 Tumours version 1.1.

- 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 3** and **4**)

Figure 3. Planned Analyses for ATHENA

Endpoints evaluated using an ordered step-down procedure

Primary endpoint

1) Investigator-assessed PFS per RECIST[15]

Key secondary endpoints

2) BICR-assessed PFS per RECIST[15]
3) OS
4) Investigator-assessed ORR

Analysis of each endpoint will step down through the subgroups in Figure 4 before proceeding to analysis of the next endpoint

Endpoints not adjusted for multiplicity

Additional secondary endpoints

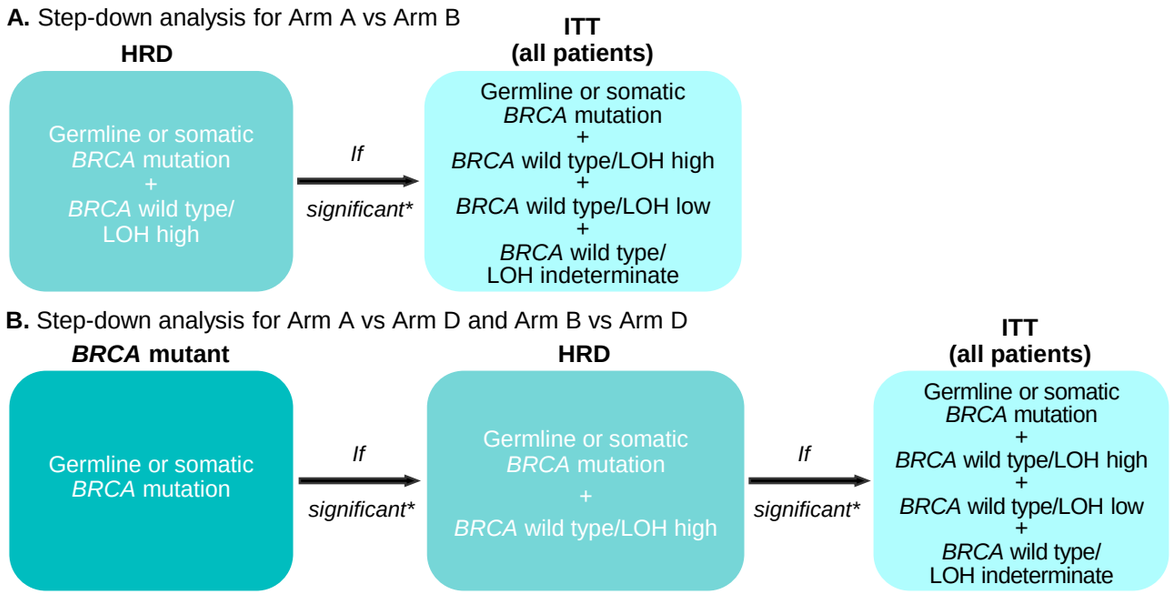
- Investigator-assessed DOR
- Safety

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 tumour 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; PK, pharmacokinetics; PFS, progression-free survival; PFS2, PFS after subsequent line of treatment; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria In Solid Tumours version 1.1.

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

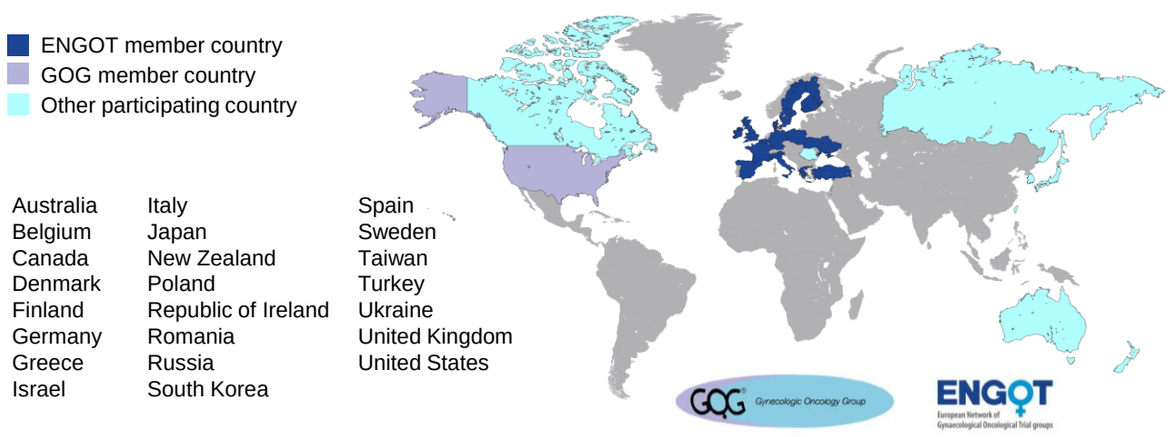


*Investigator-assessed PFS will be tested at a 1-sided 0.0083 significance level; once statistical significance is not achieved for a given analysis, statistical significance will not be declared for all subsequent analyses.
HRD, homologous recombination deficiency; ITT, intent to treat; LOH, loss of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

TRIAL ENROLMENT

- 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 + 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. Watkins et al. *Breast Cancer Res*. 2014;16:211.
7. Marquard et al. *Biomark Res*. 2015;3:9.
8. Sun et al. *Cancer Res*. 2018;78:abst 4544.
9. Strickland et al. *Oncotarget*. 2016;7:13587-98.
10. Nguyen et al. *Cancer Res*. 2018;78:abst 1716.
11. Lee et al. *J Clin Oncol*. 2017;35:2193-202.
12. Friedlander et al. *J Clin Oncol*. 2017;35:3013-13.
13. Konstantinopoulos et al. *Gynecol Oncol*. 2018;149:abst LBA3.
14. Drew et al. *Gynecol Oncol*. 2018;149:abst LBA4.
15. Eisenhauer et al. *Eur J Cancer*. 2009;45:228-47.

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