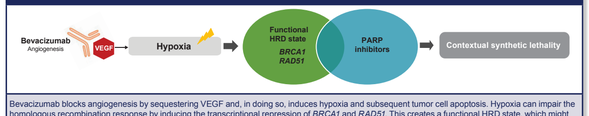
A Phase 2, Single-Arm, Open-Label Study to Evaluate the Safety and Efficacy of Niraparib Combined with Bevacizumab as Maintenance Treatment in Patients with Advanced Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer Following Frontline Platinum-Based Chemotherapy with Bevacizumab (OVARIO)

BACKGROUND

- Most women with ovarian, fallopian tube, or primary peritoneal cancer present with advanced-stage disease (stage 3 or 4) and have a 70%–95% chance of recurrence.[1] During periods of watchful waiting after chemotherapy, the possibility of recurrence is a major source of anxiety.
- Maintenance therapy is one approach to slow disease recurrence and increase the interval between platinum-based chemotherapy regimens. Targeted therapies such as poly(ADP-ribose) polymerase (PARP) inhibitors and antiangiogenesis agents have the potential to offer important advantages in maintenance therapy, including better tolerability and extended progression-free survival (PFS) compared with chemotherapy.[2,3]
- Niraparib (ZEJULA®) is a selective, orally active PARP-1 and -2 inhibitor approved for the maintenance treatment of adult patients with recurrent ovarian cancer who are in complete or partial response (CR or PR) to platinum-based chemotherapy.[4,5]
- Approximately 50% of high-grade serous ovarian cancers have germline or somatic abnormalities in homologous recombination repair, a critical DNA damage response pathway.[6] Mutations in genes such as *BRCA1, BRCA2,* and *RAD51* lead to homologous recombination deficiency (HRD). In the absence of genetic defects, hypoxia can induce transcriptional downregulation of homologous recombination-related genes, including *RAD51* and *BRCA1*, creating a functional HRD state.[7]
- PARP inhibitors induce apoptosis in hypoxic tumor regions in vivo, supporting the idea of contextual synthetic lethality between hypoxia-induced functional HRD and PARP inhibition.[7]
- Stress resulting from angiogenesis inhibitors such as bevacizumab, an anti–vascular endothelial growth factor (VEGF) monoclonal antibody, leads to tumor hypoxia.[8] This hypoxia-induced functional HRD state is expected to increase tumor sensitivity to PARP inhibitors (**Figure 1**).

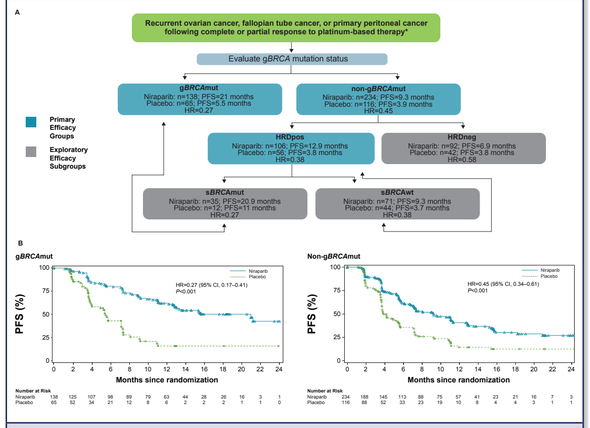
Figure 1. Synergy Between PARP Inhibitors and Bevacizumab



Bevacizumab blocks angiogenesis by sequestering VEGF and, in doing so, induces hypoxia and subsequent tumor cell apoptosis. Hypoxia can impair the homologous recombination response by inducing the transcriptional repression of *BRCA1* and *RAD51*. This creates a functional HRD state, which might be leveraged to target tumor cells via contextual synthetic lethality.
HRD=homologous recombination deficiency; PARP=poly(ADP-ribose) polymerase; VEGF=vascular endothelial growth factor.

- The ENGOT-OV16/NOVA trial (NCT01847274)[2] showed that niraparib monotherapy as a maintenance treatment significantly improved PFS in all 3 primary efficacy arms: g*BRCA* (HR=0.27), non-g*BRCA* (HR=0.45), and HRDpos (HR=0.38) compared with placebo (**Figure 2**).
  - A clinically significant benefit was also seen in the HRDnegative subgroup, which comprised ≈40% (n=134) of the non-g*BRCA* cohort (*BRCA*wt and non-HRD), HR=0.58. mPFS for niraparib was 6.9 months (95% CI, 5.6–9.6) vs. placebo is 3.8 months (95% CI, 3.7–5.6); *P*=0.0226 for placebo (**Figure 2**).

Figure 2. Niraparib Extended Progression-free Survival Regardless of *BRCA* or HRD Status in ENGOT-OV16/NOVA



A. Progression-free survival and hazard ratios for primary efficacy cohorts and exploratory efficacy subgroups in the ENGOT-OV16/NOVA trial.
B. Kaplan-Meier survival curves for g*BRCA*mut and non-g*BRCA*mut cohorts. *Patients who had a complete or partial response to penultimate platinum-based therapy lasting ≥6 months. CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficiency; mut=mutation; PFS=progression-free survival; wt=wild type.

- Neither *BRCA* mutation nor HRD status, as assessed by the Myriad myChoice HRD test was sufficient to predict individual responses to niraparib. However, longer median PFS was observed for the cohorts with these biomarkers, suggesting that mutations in HRD genes may confer greater sensitivity to niraparib (**Figure 2**).
  - Niraparib's strong efficacy regardless of biomarker status, may also be due to its ability to accumulate in tumors at high concentration. In a patient-derived xenograft mouse model, niraparib tumor exposure was >30-fold higher than olaparib.[9]
- In the ENGOT-OV16/NOVA trial, grade 3 or 4 hematologic abnormalities, fatigue, and hypertension were observed (**Table 1**). These adverse events (AEs) were generally manageable with dose interruption or adjustment. Importantly, patients' quality of life (QoL) was not affected over the course of treatment in the maintenance setting.[10]

Table 1. Treatment-Emergent Grade 3/4 AEs Occurring in ≥5% of Patients in ENGOT-OV16/NOVA[a]

Event, n (%)	Niraparib (N=367)	Placebo (N=179)
Thrombocytopenia[b]	124 (33.8)	1 (0.6)
Anemia[c]	93 (25.3)	0
Neutropenia[d]	72 (19.6)	3 (1.7)
Fatigue[e]	30 (8.2)	1 (0.6)
Hypertension	30 (8.2)	4 (2.2)

Myelodysplastic syndrome and/or acute myeloid leukemia occurred in 5 of 367 patients who received niraparib (1.4%) and 2 of 179 patients who received placebo (1.1%).
[a]There were no grade 5 AEs.
[b]Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count. No grade 3 or 4 bleeding events were associated with thrombocytopenia.
[c]Anemia includes reports of anemia and decreased hemoglobin counts.
[d]Neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.
[e]Fatigue includes reports of fatigue, asthenia, malaise, and lethargy.
AE=adverse event.

- Currently, the combination of niraparib and bevacizumab is being explored in patients with recurrent platinum-sensitive ovarian cancer as part of an ongoing phase 1/2 study (AVANOVA, NCT02354131).[3] Preliminary data suggest that this combination is clinically active with a predictable and manageable toxicity profile.
- The preliminary disease control rate from the phase 1 portion of AVANOVA was 92% and the overall response rate was 50%, including 1 CR and 5 PRs. The preliminary median PFS was 49 weeks (**Table 2**). The median duration of treatment was 46 weeks.[3]

Table 2. Preliminary Clinical Activity from AVANOVA: Response Evaluation

Response	n (%)
Complete response	1 (8)
Partial response	5 (42)
Stable disease	5 (42)
Progressive disease	1 (8)
Total	12 (100)

- AEs observed in the phase 1 portion of AVANOVA included anemia, constipation, fatigue, hypertension, nausea, and thrombocytopenia and were readily managed through routine laboratory testing, clinical surveillance, and adherence to the recommended dose modifications (**Table 3**).[3]

Table 3. Preliminary Grade 2–4 Toxicity at All Treatment Cycles from AVANOVA

Cohort	Grade	No. of events	Description
Cohort 1 (n=3)	2	1	Fatigue
	3	2	Hypertension
Cohort 2 (n=3)	2	5	Hypertension (1); nausea (2); fatigue (1); constipation (1)
	3	2	Anemia
Cohort 3 (n=6)	2	2	Nausea
	3	6	Hypertension (3), anemia (1), proteinuria (1)
	4	1	Thrombocytopenia

- Based on one dose-limiting toxicity, grade 4 thrombocytopenia, observed in cohort 3 from the phase 1 AVANOVA trial, the recommended phase 2 dose of the combination was determined to be 15 mg/kg every 3 weeks for bevacizumab and 300 mg once a day for niraparib (or 200 mg once a day for niraparib in patients with body weight <77 kg or a baseline platelet count <150,000/µL).[3]
- In this phase 2 OVARIO study (NCT03326193), niraparib plus bevacizumab will be evaluated as a maintenance treatment in patients with advanced (stage IIIB–IV) ovarian cancer who have received prior frontline platinum-based chemotherapy with bevacizumab and have recovered from primary debulking surgery.

METHODS

Study Design*

- This is a multicenter, phase 2, single-arm, open-label study to evaluate niraparib combined with bevacizumab as maintenance treatment in patients with newly diagnosed advanced (stage IIIB–IV) epithelial ovarian, fallopian tube, or peritoneal cancer who are recovered from primary debulking surgery. The study will enroll 90 patients and will be conducted in the United States. Eligibility criteria are set out in **Table 4**.

*This study will be conducted in accordance with the International Council for Harmonisation and Good Clinical Practice guidelines consistent with the Declaration of Helsinki as well as applicable national and local regulatory requirements.

Table 4. Key Eligibility Criteria

Inclusion Criteria

- Female ≥18 years old who is able to understand the study procedures and provides written informed consent to participate
- Newly diagnosed FIGO stage IIIB–IV epithelial ovarian, fallopian tube, or peritoneal cancer and recovered from debulking surgery
- High-grade serous or endometrioid or high-grade predominantly serous or endometrioid histology, regardless of HRD or g*BRCA* mutation status. Nonmucinous epithelial ovarian cancer and g*BRCA* mutation
- Completed frontline, platinum-based chemotherapy with CR, PR, or NED and have first study treatment dose within 12 weeks of the first day of the last cycle of chemotherapy:
  - ≥6 and ≤9 cycles of platinum-based therapy
  - IV, intraperitoneal, or neoadjuvant platinum-based chemotherapy; interval debulking
- Prior to enrollment, received ≥3 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy or underwent interval debulking surgery if she had received only 2 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy
- CA-125 in the normal range or CA-125 decrease by more than 90% during frontline therapy that is stable for at least 7 days (ie, no increase >15% from nadir)
- 1 attempt at optimal debulking surgery
- Agrees to undergo tumor HRD testing at screening
- ECOG performance status score of 0–1 and adequate organ function

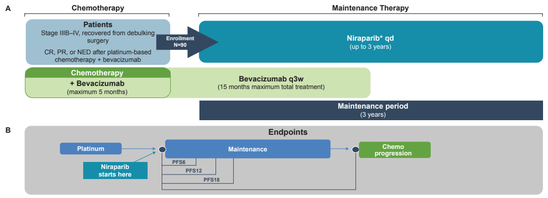
Exclusion Criteria

- Ovarian tumors of nonepithelial origin (eg, germ cell tumors) or any low-grade tumors
- Clinically significant cardiovascular disease, gastrointestinal disease, or abnormalities that would interfere with absorption of study treatment; a history of bowel obstruction, proteinuria as demonstrated by urine protein:creatinine ratio ≥1.0 at screening or urine dipstick for proteinuria ≥2; increased bleeding risk due to concurrent conditions; immunocompromised; or known active hepatic disease or QT interval prolongation >480 ms at screening
- Other than ovarian cancer, diagnosis or treatment for invasive cancer <5 years prior to study enrollment
- Poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection
- Prior treatment with a known PARP inhibitor
- Known history or current diagnosis of myelodysplastic syndrome or acute myeloid leukemia

CA-125=cancer antigen 125; CR=complete response; ECOG=Eastern Cooperative Oncology Group; FIGO=International Federation of Gynecology and Obstetrics; g*BRCA*=germline *BRCA*; HRD=homologous recombination deficiency; IV=intravenous; NED=no evidence of disease; PARP=poly(ADP-ribose) polymerase; PR=partial response.

- Patients who achieve CR, PR, or NED following platinum based-chemotherapy plus bevacizumab will receive maintenance treatment with niraparib combined with bevacizumab. Treatment will be discontinued in the case of disease progression, unacceptable toxicity, patient withdrawal, investigator's decision, or death (**Figure 3**).

Figure 3. Study Design and Efficacy Endpoints



*Dosage based on body weight and platelet count.
Chemo=chemotherapy; CR=complete response; NED=no evidence of disease; q3w=every 3 weeks; qd=daily; PD=progression of disease; PFS=time from initation of combined niraparib–bevacizumab treatment to disease progression; PFS6=PFS rate at 6 months from treatment initiation; PFS12=PFS rate at 12 months from treatment initiation; PFS18=PFS rate at 18 months from treatment initiation.

- The starting dose of niraparib will be based on the patient's baseline body weight or platelet count. Patients with a baseline body weight of ≥77 kg and a screening platelet count of ≥150,000/µL will start at 300 mg daily. Patients with a baseline actual body weight of <77 kg and/or a screening platelet count of <150,000/µL will start at 200 mg daily.
  - The dose of bevacizumab will be 15 mg/kg.

Objectives

Primary Objective

- Landmark analysis of 18-month PFS in patients who have achieved CR, PR, or no evidence of disease (NED) following frontline, platinum-based chemotherapy with bevacizumab

Secondary Objectives

- PFS by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 or cancer antigen 125 (CA-125) measurement
- Overall survival
- Patient-reported outcomes (PROs)
- Safety and tolerability

Exploratory Objectives

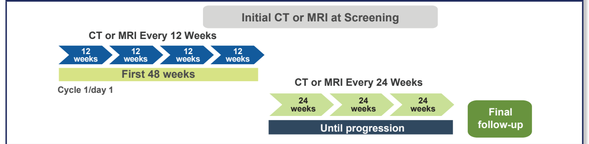
- PFS at 6 and 12 months
- Retrospective analysis of HRD status to investigate whether it predicts response to the niraparib-bevacizumab combination

Study Assessments

Efficacy

- Progressive disease will be determined using RECIST v1.1 based on radiologic scans (computed tomography or magnetic resonance imaging) performed according to the schedule in **Figure 4**.

Figure 4. Tumor Assessment via CT or MRI



CT or MRI will be done initially at screening, then every 12 weeks from cycle 1/day 1 visit for the first 48 weeks, then every 24 weeks until disease progression, at which point a final follow-up will be scheduled.
CT=computed tomography; MRI=magnetic resonance imaging.

HRD Status

- HRD status will be determined using pretreatment archival tumor samples. For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained prior to study treatment initiation. While all patients must submit to HRD testing, HRD status will be used retrospectively and not affect eligibility for OVARIO.

Safety

- All AEs and serious AEs, regardless of causality, will be collected and recorded for each patient from the day the informed consent form is signed until 90 days after the last dose of study treatment.
- AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
- AEs of special interest will be myelodysplastic syndrome and acute myeloid leukemia, secondary cancers, pneumonitis, and embryo-fetal toxicity.

SUMMARY

- Maintenance therapy requires clinicians to balance toxicity with QoL and extending remission. New approaches in this setting with combination targeted therapies such as PARP inhibitors plus bevacizumab can potentially extend PFS and improve QoL compared with chemotherapy.
- The OVARIO study will assess the efficacy and safety of niraparib combined with bevacizumab as maintenance treatment in patients with stage III or IV ovarian cancer with CR, PR, or NED following frontline platinum-based chemotherapy. PROs will also be evaluated.
- A retrospective analysis to examine HRD as a predictor of response to the niraparib plus bevacizumab combination will be completed.
- This study is currently recruiting patients. Contact clinicaltrials@tesarobio.com for questions.

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