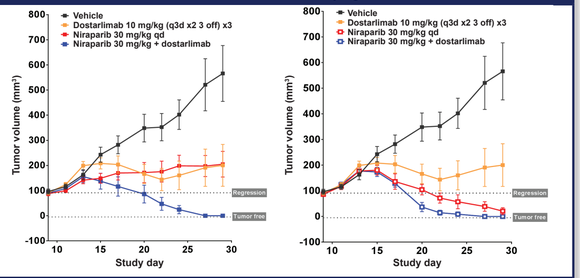
An Open-Label Phase 2 Study of Combination of Dostarlimab (TSR-042), Bevacizumab, and Niraparib in Patients with Platinum-Resistant Ovarian Cancer: Cohort A of the OPAL Trial

BACKGROUND

- While most patients with advanced-stage ovarian cancer will respond to their initial chemotherapy, the majority of them will eventually experience recurrence. Platinum-resistant ovarian cancer (PROC) is defined as disease recurrence within 6 months of platinum-based chemotherapy[1] and carries a worse prognosis than platinum-sensitive disease,[2] with a median overall survival (OS) of <12 months.[3] Optimal treatment of PROC remains an unmet medical need.
- Niraparib (ZEJULA®) is a selective, orally available poly(ADP-ribose) polymerase (PARP)1/2 inhibitor approved in the United States and Europe 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]
- In the ENGOT-OV16/NOVA trial (NCT01847274), single-agent niraparib significantly improved progression-free survival (PFS) compared with placebo in platinum-sensitive recurrent ovarian cancer regardless of *BRCA* mutation or homologous recombination deficiency (HRD) status.[6]
- In the QUADRA trial (NCT02354586), single-agent niraparib demonstrated clinical benefit in patients across a spectrum of biomarkers and chemotherapy sensitivity.[7]
  - A 27% objective response rate (ORR) was observed among patients with a *BRCA* mutation and platinum-resistant or -refractory disease.
- Regimens combining PARP inhibitors (PARPi) with synergistic mechanisms of action, such as antiangiogenesis agents (eg, bevacizumab) and/or immune checkpoint inhibitors, are actively being investigated to improve clinical outcomes.[8]
- Hypoxia induces contextual synthetic lethality by impairing homologous recombination. This could lead to synergy with PARPi-induced contextual synthetic lethality mechanisms.
  - The phase 1/2 AVANOVA trial (NCT02354131) investigating niraparib plus bevacizumab is ongoing in patients with recurrent platinum-sensitive ovarian cancer. Preliminary data have provided evidence for the clinical activity and safety of the combination.[9]
- Preclinical evidence suggests synergy between immune checkpoint inhibitors and PARPi (**Figure 1**).
  - PARPi can increase the number of CD8+ T cells and natural killer cells, as well as their production of interferon gamma and tumor necrosis factor alpha.[11,12]
  - Niraparib may improve response to checkpoint inhibitors by promoting an increase in tumor-infiltrating lymphocytes.[13]
  - Preliminary results from the ongoing phase 1 GARNET trial (NCT02715284) show that dostarlimab (antiprogrammed death [PD]-1 monoclonal antibody, formerly TSR-042) is clinically active in heavily pretreated patients and well tolerated, with a predictable safety profile.[14]
- Preliminary data from the ongoing phase 1/2 TOPACIO study (NCT02657889) of niraparib and pembrolizumab suggest that this combination is active and has a tolerable safety profile in patients with metastatic triple-negative breast cancer and recurrent PROC, including those with *BRCA*wt disease.[15]
- OPAL (NCT03574779) will evaluate triple combination therapy with niraparib, bevacizumab, and dostarlimab in PROC patients.
  - Additional cohorts may be added as new data become available.

Figure 1. Niraparib Enhanced the Antitumor Response of Dostarlimab in a *BRCA*-Deficient Ovarian Cancer Mouse Syngenic Model[10]



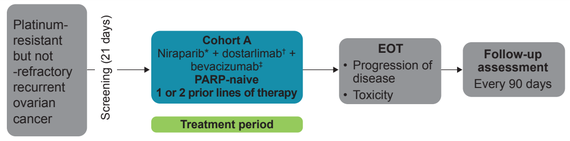
(q3d x2 3 off) x3=twice a week for 2 weeks followed by 3 weeks off, repeated 3 times; qd=once daily.

METHODS

Study Design

- This is a multicenter, multicohort, open-label, phase 2 study to evaluate the efficacy and safety of niraparib novel combinations in patients with advanced, relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 1 or 2 prior lines of anticancer therapy and have platinum-resistant but not -refractory disease (**Figure 2**). Additional study arms may be added to test other novel combinations as data become available.
- All patients will be treated with the combination of niraparib, dostarlimab, and bevacizumab. Additional expansion cohorts may be opened to further evaluate the efficacy of other novel niraparib combinations in PROC.

Figure 2. Study Design



***Niraparib** Starting dose is: - 300 mg in patients with baseline body weight ≥77 kg *and* platelets ≥150,000/μL - 200 mg in patients with baseline weight <77 kg *or* baseline platelet count <150,000/μL - administered on days 1 to 21 q3w until progression of disease
†Dostarlimab 500 mg on day 1 q3w for 4 cycles, followed by 1000 mg every other cycle (q6w) beginning on day 1/cycle 5
‡Bevacizumab 15 mg/kg on day 1 of every 21-day cycle q3w

EOT=end of treatment; PARP=poly(ADP-ribose) polymerase; q3w=every 3 weeks; q6w=every 6 weeks.

- This study will consist of a 28-day screening period, a treatment period, an end-of-treatment period when the study drug is discontinued for any reason, a safety follow-up visit 30 days after the last dose of study drug, and a follow-up assessment every 90 days. Treatment begins on cycle 1/day 1 and will continue until disease progression or unacceptable toxicity.

Key Inclusion Criteria

- The study will be conducted in patients with histologically diagnosed recurrent high-grade epithelial ovarian, fallopian tube, primary peritoneal cancer, or recurrent carcinosarcoma of the ovary, and 1 or 2 prior anticancer therapies. Patients with high-grade mixed histology are also eligible.
- Patients must have measurable disease according to RECIST v1.1.
- Patients must be considered resistant to their last platinum-based therapy.
- Patients who received prior bevacizumab are eligible only if they did not discontinue bevacizumab due to toxicity, as established by the investigator.
- Patients must be PARPi naive.
- Patients are required to provide archival tumor tissue or a fresh biopsy.
- Patients must have adequate organ function, and have recovered (ie, to grade ≤1 or to baseline) from prior chemotherapy-induced adverse events.

Key Exclusion Criteria

- Patients previously treated with anti–PD-1 or anti–PD-L1 agents.
- Patients who have immunodeficiency or are receiving systemic steroid therapy.
- Patients with active autoimmune disease requiring systemic treatment within the past 2 years.
- Patients with bowel obstruction, bowel obstruction within the past 3 months, or patients at high risk for bowel obstruction related to underlying disease as determined by the investigator.
- Patients cannot have proteinuria at screening.
- Patients with primary platinum-refractory disease are not eligible.

Objectives

Primary Objective

- ORR, defined as the percentage of patients who achieve CR or PR per RECIST v1.1

Secondary Objectives

- PFS
- OS
- Duration of response
- Disease control rate
- Safety and tolerability of niraparib combinations

Exploratory Objectives

- Evaluate the evolution of the molecular profile of the tumor and tumor microenvironment in response to treatment
- Identify potential disease- or treatment-related biomarkers, including *BRCA* status, homologous recombination repair gene status, HRD score, tumor mutational burden, and PD-L1 levels

Study Assessments

Safety

- Symptom-directed physical examination, vital signs, electrocardiograms, Eastern Cooperative Oncology Group (ECOG) performance status, and clinical laboratory assessments.

Clinical Activity

- Radiographic evaluations (computed tomography/magnetic resonance imaging of chest, abdomen, and pelvis) to assess the extent of disease will be conducted every 9 weeks while patients are on study treatment independent of cycle delays and/or dose interruptions and at any time when progression of disease is suspected.
  - After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks. If a patient discontinues treatment for a reason other than disease progression, death, withdrawal of consent, or loss to follow-up, scans and CA-125 testing will continue at the specified intervals (ie, every 9 weeks for the first year and every 12 weeks thereafter).

Biomarkers

- Blood sampling for biomarker evaluations will be conducted. The incidence/changes of biomarkers will be summarized using descriptive statistics. Correlation of clinical activity with biomarker subpopulations may be performed.

SUMMARY

- Preclinical data suggest that PARPi combined with bevacizumab or immune checkpoint inhibitors may act synergistically.
- The OPAL trial will assess the efficacy and safety of niraparib combined with bevacizumab and dostarlimab in patients with platinum-resistant recurrent epithelial ovarian cancer.
- Molecular profile analysis will evaluate the evolution of the tumor and tumor microenvironment.
- Potential disease- or treatment-related biomarkers will be investigated.
- This study is currently recruiting patients. Contact clinicaltrials@tesarobio.com with questions.

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