ENGOT-OV44/FIRST Study: An Adaptive Randomized Phase 3 Comparison of Standard Platinum-Based Treatment Versus Platinum + Dostarlimab (TSR-042) Followed by Niraparib + Dostarlimab Maintenance Therapy in Patients with Stage 3/4 Nonmucinous Epithelial Ovarian Cancer

BACKGROUND

- Despite surgery and standard-of-care systemic treatment (platinum and carboplatin ± bevacizumab), 5-year survival rates remain low for patients with high-risk stage 3/4 ovarian cancer (OC).
- Niraparib (ZEJULA®) is the first selective poly(ADP-ribose) polymerase inhibitor (PARPi) approved in the United States and Europe for maintenance treatment in patients with recurrent OC regardless of BRCAmut status.1,2
- Predicational data show synergy with PARPi + anti-programmed death 1 (PD-1) blockade.
- Niraparib + pembrolizumab has shown clinical efficacy in patients with platinum-resistant or refractory OC regardless of biomarker status.
- Dostarlimab (formerly TSR-042) is an anti-PD-1 humanized monoclonal antibody with encouraging clinical activity as monotherapy in early phase trials.
- A novel feature of the first study (INTACT02589) is the facility to adjust the inclusion of niraparib vs placebo in control arms for specific patient subpopulations based on external data from ongoing PARPi trials to ensure an optimal control group while also preventing randomization of patients to ineffective treatment.

METHODS

Key Eligibility

- All Stage III or IV patients with inoperable or with macroscopic residual tumor following primary debulking surgery are eligible.
- All patients with Stage III or IV disease to be treated with radiotherapy will be stratified by surgery and postoperative chemotherapy are eligible regardless of postoperative tumor burden.

Stratification

- Patients will be randomized to the following stratification factors: concurrent bevacizumab use, homologous recombination repair (HRR) mutation status (ie, gBRCAmut, non-gBRCA HRRpos, non-gBRCA HRRneg/determined), and disease burden.

Adaptive Study Design

- The study design is adapted with the evolution of the standard of care. After SOLO-1 positive results, all gBRCAmut patients will be randomized to either arm 2 or arm 3, to ensure they will receive niraparib and not the placebo

Objective

Primary Objective

- To compare the progression-free survival (PFS) of patients based on investigation of assessment of patients with Stage III or IV epithelial nonmucinous epithelial OC treated with platinum-based therapy and dostarlimab followed by niraparib and dostarlimab maintenance therapy with standard platinum-based therapy.

Secondary Objectives

- PFS by blinded independent central review
- Patient-reported outcomes
- Overall survival (OS)

Key Secondary Objectives

- Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- ORR per immune-related (iRECIST)
- Health-related quality of life (HRQL)
- Time to first subsequent therapy (TST)
- Time from treatment randomization to the earliest date of assessment of progression on the next anticancer therapy following study treatment or death by any cause (PFS2)
- RECIST v1.1 or CA2-129 QLQ
- Safety and tolerability of all treatments

Exploratory Objectives

- To retrospectively evaluate biomarkers related to OC, PARPi inhibition, and PD-1 therapy (eg, DNA repair pathway, immune check point pathways)

Figure 1. Trial Design

Figure 2. Participating Sites

Table 1. Key Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>Female ≥18 years old</td>
<td>Patient has mucinous, germ cell, transitional cell or undifferentiated tumor</td>
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<tr>
<td>Histologically confirmed diagnosis of nonmucinous epithelial ovarian cancer that is Stage III or IV according to International Federation of Gynecology and Obstetrics (FIGO) or tumor, node, and metastasis staging criteria</td>
<td>Low-grade or grade 1 epithelial ovarian cancer</td>
</tr>
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<td>Eastern Cooperative Oncology Group (ECOG) performance status of 0-1</td>
<td>Patients with stage IIC with no macroscopic residual disease if aggregate extra-pelvic disease involvement &lt;5 cm</td>
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<td>All patients with Stage IV disease eligible, including inoperable disease, patients who have received primary debulking, in those where neoadjuvant chemotherapy is planned</td>
<td>Diagnosed and/or treated with any therapy for invasive cancer &lt;5 years from study enrollment</td>
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<td>Patients with Stage III disease eligible if high-risk Stage IIIC or neoadjuvant chemotherapy is planned</td>
<td>Completed adjuvant chemotherapy and/or targeted therapy &lt;3 years from enrollment, or completed adjuvant hormonal therapy &lt;4 years from enrollment</td>
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<td>Participants must provide blood sample and tumor tissue sample, have adequate organ function, and must be HIV and HCV negative</td>
<td>Investigational therapy administered within 4 weeks or within a time interval &lt;1 half-lives of investigational agent, whichever is longer</td>
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<td>Adequate bone marrow suppression, with a minimum absolute lymphocyte count of 1500/mm³</td>
<td>Known contraindication or uncontrolled hypersensitivity to components of paclitaxel, carboplatin, niraparib, bevacizumab, dostarlimab, or their excipients</td>
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Table 2. Therapy and Dosing by Treatment Arm

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<td>Dostarlimab</td>
<td>500 mg Q3W</td>
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SUMMARY

- Projected enrollment is up to 912 patients.
- Patients will be stratified by concurrent bevacizumab usage, HRR mutation status, and disease burden.
- Adaptive design allows for modification of the control arm to follow the evolution of the standard of care.
- This study aims to assess the efficacy of dostarlimab followed by niraparib and dostarlimab maintenance therapy with standard platinum-based therapy in patients with Stage III or IV epithelial nonmucinous epithelial OC treated with platinum-based therapy.
- Safety, pharmacokinetics, and patient-reported outcomes will also be evaluated.
- This study is currently recruiting patients. Contact clinicaltrials@tesarobio.com with questions.

REFERENCES


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