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

FIRST CLINICAL TRIAL

BACKGROUND

- Despite surgery and standard-of-care systemic treatment (paclitaxel 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 *BRCA*mut status.[1,2]
- Preclinical 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.[3]
- 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 (NCT03602859) is the facility to adapt 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 neoadjuvant chemotherapy followed by interval debulking surgery and postoperative chemotherapy are eligible regardless of postoperative tumor burden.

Stratification

- Patients will be randomized according to the following stratification factors: concurrent bevacizumab use, homologous recombination repair (HRR) mutation status (ie, g*BRCA*mut, non-g*BRCA* HRRpos, non-g*BRCA* HRRneg/not 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 g*BRCA*mut patients will be randomized to either arm 2 or arm 3, to ensure they will receive niraparib and not its placebo

Objectives

Primary Objective

- To compare the progression-free survival (PFS) based on investigator 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.

Key Secondary Objective

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

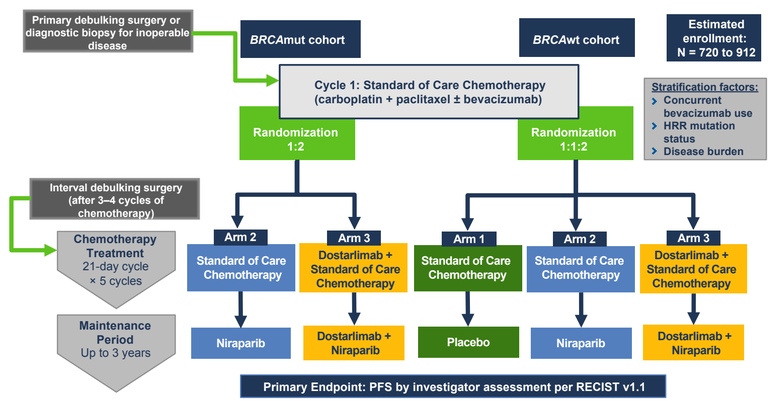
Secondary Objectives

- Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- ORR per immune-related (ir)RECIST
- Health-related quality of life (HRQoL)
- Time to first subsequent therapy (TFST)
- Time to second subsequent therapy (TSST)
- 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 CA-125 PFS
- Safety and tolerability of all treatments

Exploratory Objectives

- To retrospectively evaluate biomarkers related to OC, PARP inhibition, and PD-1 therapy (eg, DNA repair pathways, immune checkpoint pathways)

Figure 1. Trial Design



*BRCA*mut=*BRCA* mutated; *BRCA*wt=*BRCA* wild-type; HRR=homologous recombination repair; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

Table 1. Key Inclusion and Exclusion Criteria*

Inclusion Criteria	Exclusion Criteria
• Female ≥18 years old • 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 • Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 • All patients with Stage IV disease eligible, including inoperable disease, patients who have received primary debulking, or those where neoadjuvant chemotherapy is planned • Patients with Stage III disease eligible if high-risk Stage IIIC or neoadjuvant chemotherapy is planned • Patients must provide blood sample and tumor tissue sample, have adequate organ function, normal BP or adequately treated and controlled hypertension (SBP ≤140 mmHg and/or DBP ≤90 mmHg), agree to complete HRQoL questionnaires, and be able to take oral medication	• Patient has mucinous, germ cell, transitional cell or undifferentiated tumor • Low-grade or grade 1 epithelial ovarian cancer • Patients with stage IIIC with no macroscopic residual disease if aggregate extra-pelvic disease involvement is ≥5 cm • Diagnosed and/or treated with any therapy for invasive cancer <5 years from study enrollment • Completed adjuvant chemotherapy and/or targeted therapy <3 years from enrollment, or completed adjuvant hormonal therapy <4 weeks from enrollment • Investigational therapy administered within 4 weeks or within a time interval <5 half-lives of investigational agent, whichever is longer • Known contraindication or uncontrolled hypersensitivity to components of paclitaxel, carboplatin, niraparib, bevacizumab, dostarlimab, or their excipients

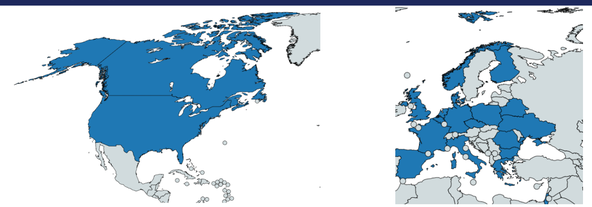
*For complete inclusion and exclusion criteria and other study information, please contact medinfo@tesarobio.com.

Table 2. Therapy and Dosing by Treatment Arm

Drug	Dosage	Mode of Administration	Arm 1[1]	Arm 2	Arm 3
Chemotherapy treatment period					
Paclitaxel	175 mg/m² Q3W	IV	✔	✔	✔
Carboplatin	AUC 5 or 6 mg/mL/min Q3W	IV	✔	✔	✔
Dostarlimab	500 mg Q3W	IV	-	-	✔
Bevacizumab	7.5 mg/kg or 15 mg/kg Q3W (up to 15 months)	IV	Optional treatment in all arms		
Maintenance treatment period					
Niraparib[2]	200 mg QD	PO	-	✔	✔
Dostarlimab[2]	1000 mg Q6W	IV	-	-	✔
Bevacizumab	7.5 mg/kg or 15 mg/kg Q3W (up to 15 months)	IV	May be continued from chemotherapy treatment period		

[1]No g*BRCA*mut patients will be randomized to arm 1.
[2]Placebo capsules and/or infusion will be administered in arms where active treatment is indicated as not provided.

Figure 2. Participating Sites



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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