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Background

- Despite surgery and standard-of-care systemic treatment (carboplatin/paclitaxel ± bevacizumab), 5-year survival rates remain low for patients with high-risk stage III/IV 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 mutation status1,2
- Data from clinical proof show synergy with PARPi + anti-programmed cell death 1 (PD-1) blockade
- Niraparib + pembrolizumab has shown clinical efficacy in patients with platinum-resistant or -refractory OC regardless of biomarker status3
- Dostarlimab (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 (NCT03602859) study is the facility to adapt the inclusion of niraparib versus placebo in control arms for specific patient subpopulations based on external data from ongoing PARPi trials to ensure an optimal control group, as well as to prevent randomization of patients to ineffective treatment

Methods

Key Eligibility

- All patients with stage III/IV OC with an operable or macroscopic residual tumor following primary debulking surgery are eligible
- All patients with stage III/IV disease who are 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, patients with germline BRCA-mutated [gBRCAmut], non-gBRCAmut HRR-positive, and non-gBRCAmut HRR-negative [not determined disease]), and disease burden

Adaptive Study Design

- The study has an adaptive design for modification of the control arm to follow the evolution of the standard of care. After positive results from the SOLO-1 trial, all patients with gBRCAmut disease will be randomized to Arm 2 or Arm 3 to ensure they receive niraparib and not placebo

Objectives

Primary Objective

- To compare investigator-assessed progression-free survival (PFS) from Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) among patients with stage III/IV 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

Secondary Objectives

- Objective response rate (ORR) per RECIST v1.1
- ORR per immune-related RECIST
- Health-related quality of life
- Time to first subsequent therapy
- Time to second subsequent therapy

Table 1. Key inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>≥18 years old</td>
<td>Patient has mucinous, germ cell, transitional cell, or undifferentiated tumor</td>
</tr>
<tr>
<td>Histologically confirmed diagnosis of nonmucinous epithelial OC 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 OC</td>
</tr>
<tr>
<td>Patients with stage III disease are eligible</td>
<td>Diagnosed and/or treated with any therapy for invasive cancer &lt;5 years from study enrolment</td>
</tr>
<tr>
<td>Patients must provide blood and tumor tissue samples, have adequate organ function, normal BP or adequately treated and controlled hypertension (SBP ≤140 mm Hg and/or DBP ≤90 mmHg), agree to complete HRQoL questionnaires, and be able to take oral medication</td>
<td>Completed adjuvant chemotherapy and/or targeted therapy &gt;3 years from enrolment, or completed adjuvant hormonal therapy &gt;4 weeks from enrolment</td>
</tr>
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Summary

- Projected enrollment is up to 912 patients
- Patients will be stratified by concurrent bevacizumab use, 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/IV nonmucinous epithelial OC treated with platinum-based therapy
- Safety, pharmacokinetics, and patient-reported outcomes will also be evaluated
- This study is currently recruiting patients.

Table 2. Therapy and Dosing by Treatment Arm

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Mode of Administration</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>platinum-based chemotherapy</td>
<td>QD</td>
<td>oral</td>
<td>175 mg/m² IV</td>
<td>500 mg Q3V</td>
<td>7.5 mg/kg (up to 15 months)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC of 5 or 15 mg/mL/min</td>
<td>IV</td>
<td>1000 mg Q2W</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>Niraparib</td>
<td>200 mg QD</td>
<td>PO</td>
<td>1000 mg Q2W</td>
<td>——</td>
<td>——</td>
</tr>
<tr>
<td>Dostarlimab</td>
<td>500 mg Q3V</td>
<td>IV</td>
<td>Optional treatment in all arms</td>
<td>——</td>
<td>——</td>
</tr>
</tbody>
</table>

References

4. ZEJULA (niraparib) [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; 2019.

Acknowledgments

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

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