Niraparib may improve response to checkpoint inhibitors by promoting an tolerable safety profile in patients with metastatic triple-negative breast cancer.

In the ENGOT-O11/NOVA trial (NCT02874724), 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.

In the QUADRA trial (NCT02354988), single-agent niraparib demonstrated clinical benefit in patients across a spectrum of biomarkers and chemosensitivity.

- A 27% objective response rate (ORR) was observed among patients with a BRCA mutation or platinum-resistant or -refractory disease.
- Regimens combining PARP inhibitors (PARPi) with synergistic mechanisms of action, such as antiangiogenic agents (e.g., bevacizumab) and/or immune checkpoint inhibitors, are actively being investigated to improve clinical outcomes.
- Hypoxia induces contextual synthetic lethality by impairing homologous recombination.

This could lead to synergy with PARPi-induced contextual synthetic lethality mechanisms.

- The phase 1 AVANOVA trial (NCT03543131) investigating niraparib plus bevacizumab is ongoing in patients with platinum-sensitive recurrent ovarian cancer. Preliminary data have provided evidence for the clinical activity and safety of the combination.

- 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.

- Niraparib may improve response to checkpoint inhibitors by promoting an increase in tumor-infiltrating lymphocytes.

- Preliminary results from the ongoing phase 1 DART trial (NCT03715264) 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.

- Preliminary data from the ongoing phase 1 TOPACIO study (NCT02678799) of niraparib and pembrolizumab suggest that the combination is active and has a tolerable safety profile in patients with metastatic triple-negative breast cancer and recurrent PRO, including those with BRCA1/2 disease.

- OPAL (NCT03534774) will evaluate combination therapy with niraparib, bevacizumab, and durvalumab 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 Model Syngeneic Model.

Study Design
- This is a multicenter, 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 antiangiogenic 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, durvalumab, and bevacizumab. Additional expansion cohorts may be opened to further evaluate the efficacy of the novel other niraparib combinations in PROC.

Figure 2: Study Design

- Safety: Safety assessments include 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) assess the extent of disease. Disease will be evaluated every 9 weeks while patients are on study treatment independent of clinical symptoms. Disease progression (also known as response, disease progression, or PD) includes death, withdrawal of consent, or loss to follow-up or scans and CA-125 testing will continue at the specified intervals (ie, every 9 weeks for the first year and every 2 years thereafter).

- Biomarkers: 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 durvalumab in patients with platinum-resistant recurrent ovarian cancer.

- Molecular profile analysis will evaluate the evolution of the tumor and tumor microenvironment.

- Potential molecular treatment-related biomarkers will be investigated.

- This study is currently recruiting patients. Contact clinicaltrials@tesarobio.com with questions.

ACKNOWLEDGMENTS

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