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Title: An open-label phase II study of dostarlimab (TSR-042), bevacizumab (bev), and niraparib combination in patients (pts) with platinum-resistant ovarian cancer (PROC): Cohort A of the OPAL trial

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Objectives: Preclinical evidence suggests that PARP inhibition (PARPi), anti-PD-1 therapy, and anti-angiogenic therapies have interactions that may support synergistic antitumor activity in pts with PROC. This phase 2 study evaluated activity of combination therapy with the PARPi niraparib, the PD-1 inhibitor dostarlimab, and bev in pts with PROC.

Methods: Eligible pts had high-grade, platinum-resistant (progressed ≤6 mo after completion of ≥ 4 cycles of platinum-based chemo), recurrent epithelial ovarian, fallopian tube, primary peritoneal cancer, or recurrent carcinosarcoma of the ovary (high-grade mixed histology permitted). Pts had 1–2 prior lines of anticancer therapy for OC, and no prior therapy with an anti-PD-1/-L1 or PARPi. Pts received a regimen of 500 mg dostarlimab Q3W x 4, then 1000 mg Q6W + 15 mg/kg bev Q3W + niraparib 300 mg or 200 mg (for weight <77 kg or platelet count <150,000/μL at screening) QD until discontinuation. The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST v1.1. Secondary objectives were progression-free survival (PFS), safety, and disease control rate (DCR). A posthoc analysis by biomarker (BRCA mutation [BRCAm] status, homologous recombination repair mutation [HRRm], and combined positive score [CPS; a measure of intratumoral and immune infiltrate PD-L1 expression], prior lines of therapy, and prior bev use) was performed.

Results: A total of 41 pts were enrolled and dosed. Median age was 66 years old. A total of 2 pts did not have a postbaseline scan and were not included in the response-evaluable population (n = 39). Tumor BRCA status: 4 (10%) pts had BRCAm, 32 (82%) pts had BRCA wild-type (wt), and 3 (8%) pts were unknown (unk). A total of 7 (18%) pts had HRRm, 29 (74%) pts wt, and 3 (8%) pts unk. ORR was 17.9% (95% CI 8.7–31.1; 0 confirmed complete responses [CR], 7 confirmed partial responses [PR]); DCR was 76.9% (23 stable disease, 7 PR, 0 CR). Median PFS was 7.6 mo (95% CI 4.2–10.6). Best percentage change in target lesion size by biomarker status is shown in the figure. ORR was similar across subgroups based on prior lines of therapy, tumor BRCA, or HRR status. However, ORR was lower in pts who had received prior bev (prior bev ORR 6% [95% CI 0.3–25.0]; no prior bev ORR 27% [95% CI 12.6–46.8]).The most common grade ≥ 3 treatment-emergent adverse events (TEAEs) were hypertension (22.0%), fatigue (17.1%), and anemia (17.1%). A total of 6 pts (14.6%) developed grade ≥ 3 small intestinal obstruction, all assessed as not related to study drug; 1 pt developed a grade 4 bowel perforation that was assessed as related to bev. The most common serious treatment-emergent adverse effects (TEAE) were thrombocytopenia (7.3%), anemia (4.9%), and hypertension (4.9%). A total of 34.1% of pts discontinued 1 of the 3 study drugs due to a TEAE. No TEAE resulted in death.

Conclusions: Conclusion: Triplet therapy with niraparib, dostarlimab, and bev is tolerable and demonstrated clinical activity in pts with PROC, most of which were BRCA or HRR wt. AEs were as expected.Clinical trial identification: NCT03574779Funding: GlaxoSmithKline