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Title: Rucaparib versus chemotherapy in patients with advanced, relapsed ovarian cancer and a deleterious BRCA mutation: Efficacy and safety from ARIEL4, a randomized phase III study

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Objectives: Prospective studies comparing poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors with standard-of-care (SOC) chemotherapy (CT) in patients (pts) with relapsed ovarian cancer (OC) are currently limited. ARIEL4 (NCT02855944) is a phase III, randomized, open-label, international, multicenter study of the efficacy and safety of rucaparib vs SOC CT as treatment for PARP-inhibitor naïve pts with relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, who had a deleterious BRCA1/2 (BRCA) mutation and had received ≥ 2 prior CT regimens.

Methods: Pts were randomized 2:1 to oral rucaparib 600 mg twice daily or SOC CT and stratified based on progression-free interval (>=1 to <6 months = platinum resistant; >=6 to <12 months = partially platinum sensitive; >=12 months = fully platinum sensitive). Pts in the CT arm with platinum-resistant or partially platinum-sensitive disease received weekly paclitaxel 60-80 mg/m2; pts with fully platinum-sensitive disease received investigator's choice of platinum-based CT (single-agent carboplatin or cisplatin, or platinum doublet [carboplatin + paclitaxel, carboplatin + gemcitabine, or cisplatin + gemcitabine]). Pre-study-treatment plasma samples were assessed for BRCA reversion mutations. The primary endpoint was investigator-assessed progression-free survival (PFS). Secondary endpoints included objective response rate (ORR) per RECIST and safety. Each efficacy endpoint was first evaluated in the efficacy population (randomized pts with deleterious BRCA mutations excluding those with BRCA reversion mutations), stepping down to the intent-to-treat (ITT) population (all randomized pts).

Results: A total of 233 pts were randomized to rucaparib and 116 to CT (visit cutoff Sep 30, 2020); 179 (51.3%) had platinum-resistant, 96 (27.5%) had partially platinum-sensitive, and 74 (21.2%) had fully platinum-sensitive disease. A total of 23 pts (6.6%) with BRCA reversion mutations and 1 pt without a BRCA mutation were excluded from the efficacy population. Median PFS was significantly longer with rucaparib vs CT in both the efficacy and ITT populations (Table). In an exploratory analysis of pts with BRCA reversion mutations, median PFS was shorter with rucaparib (n = 13) vs CT (n = 10); 2.9 vs 5.5 months, hazard ratio 2.769 (95% CI, 0.989–7.755). ORR was not significantly different between the rucaparib and CT arms in both populations (Table). Adverse events were consistent with the known safety profiles of rucaparib and CT.

Conclusions: Patients with BRCA-mutated advanced, relapsed OC who received rucaparib had a significant improvement in PFS vs SOC CT. No new safety signals were identified. This is the first prospective report from a randomized trial demonstrating that the presence of a BRCA reversion mutation predicts for primary resistance to rucaparib.