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Title: ORZORA: Maintenance olaparib in patients with platinum-sensitive relapsed ovarian cancer: Outcomes by somatic and germline BRCA and other homologous recombination repair gene mutation status

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Objectives: The Phase III SOLO2 trial (NCT01874353) showed the significant benefit of maintenance olaparib for patients (pts) with platinum-sensitive relapsed ovarian cancer (PSROC) and a BRCA mutation (BRCAm), compared with placebo (median progression-free survival [PFS] 19.1 vs 5.5 months [m], respectively); however, no pts had a confirmed somatic (s) BRCAm and data prospectively evaluating efficacy of olaparib in this pt group were limited. ORZORA (NCT02476968), an open-label, single-arm, multicenter trial, was conducted to assess efficacy and safety of maintenance olaparib in PSROC pts with a BRCAm (s or germline [g]) who were in response to their most recent platinum-based chemotherapy after >=2 lines of treatment.

Methods: Pts underwent prospective central screening for tumor BRCAm status (myChoice CDx, Myriad Genetic Laboratories, Inc.), then s or g BRCAm status was determined by central g testing (BRACAnalysis CDx, Myriad Genetic Laboratories, Inc.). Pts received maintenance olaparib (400 mg bid; capsules) until disease progression. Co-primary endpoints were investigator-assessed PFS (RECIST v1.1) in BRCAm and s cohorts, conducted at 60% maturity. Secondary endpoints included time to second progression or death (PFS2), health-related quality of life (HRQoL; FACT-O trial outcome index) and tolerability. An additional exploratory cohort comprised pts with predefined homologous recombination repair gene mutations (HRRm) excluding BRCAm (FoundationOne CDx, Foundation Medicine, Inc.).

Results: A total of 181 pts were enrolled in ORZORA (BRCAm n = 145 [s n = 55; g n = 87; n = 3 s vs g status unknown]; HRRm n = 33; unassigned n = 3). Pt characteristics were similar between s and g cohorts: ≥3 prior lines of chemotherapy (38% vs 48%, respectively); partial response to prior platinum (45% vs 49%); tumor BRCA1-mutated (65% vs 64%). At the data cut-off (April 17, 2020), median follow-up for PFS was 22.3 months. Median PFS was similar in the BRCAm, s and g cohorts, and exploratory HRRm cohort (Figure). Median PFS2 for BRCAm pts was 30.9 m (95% confidence interval [CI] 24.7–40.0; s 24.7 [21.8–36.1]; g 32.5 [25.3–not calculable]). HRQoL was comparable in BRCAm and s cohorts (best overall change from baseline: improved 22 vs 21%; no change 69 vs 68%; worsened 11 vs 12%, respectively). Most common adverse events (AE; n = 177 treated pts) were nausea (54% pts), fatigue (43%), anemia (42%) and vomiting (28%). A total of 25% and 35% pts experienced serious and grade ≥3 (anemia 16% pts) AEs, respectively. 5% had an AE leading to treatment discontinuation. A total of 2 new primary malignancies, two acute myeloid leukemia and no myelodysplastic syndrome cases occurred.

Conclusions: PFS in pts with PSROC who received maintenance olaparib was similar irrespective of s or g BRCAm status. Activity of maintenance olaparib was also shown in pts with a non-BRCA HRRm. PFS, HRQoL and tolerability were consistent with previous olaparib studies in this population. Results highlight that PSROC pts beyond those with a gBRCAm can benefit from maintenance olaparib.