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TARGETED THERAPY

ARIEL3 — broad benefit of PARP inhibitors in ovarian cancer

In 2017, the FDA approved two PARP inhibitors, olaparib and niraparib, as maintenance treatments for women with ovarian cancers who respond to induction platinum-based chemotherapy, regardless of their *BRCA*-mutation status. Now, findings of the phase III ARIEL3 trial of rucaparib corroborate the genotype-agnostic benefit of PARP inhibition.

In ARIEL3, 564 women with high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma and an objective response to second-line or later-line platinum-based chemotherapy were randomly assigned 2:1 to receive rucaparib or placebo. In addition to the overall efficacy and safety of treatment, a test of genome-wide loss of heterozygosity (LOH) — a marker of homologous recombination deficiency (HRD) — was prospectively evaluated as a predictive biomarker. "While patients with any genotype were enrolled, the analysis was designed to assess efficacy in a 'step-down' fashion including sequentially larger cohorts of patients," explains lead author Robert Coleman.

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In the smallest of three nested cohorts, comprising only women with germ-line or somatic *BRCA* mutations, the median progression-free survival (PFS) duration was 16.6 months with rucaparib, compared with 13.6 months in the larger LOH-high (HRD) disease cohort, and 10.8 months in the intention-to-treat population (versus 5.4 months with placebo in each cohort). Coleman adds: "the most compelling finding is that rucaparib delayed disease progression across prespecified subgroups — those we expected to benefit (women with somatic *BRCA* alterations or *BRCA*-wild-type, LOH-high disease), as well as those we didn't (patients with LOH-low tumours)." Notably, 12-month PFS in women with *BRCA*-wild-type, LOH-low tumours was <5% with placebo, but >30% with rucaparib.

These findings are consistent with those for olaparib and niraparib in Study 19 and NOVA, respectively. An interesting difference between these three trials is that women with 'bulky' residual disease (>2 cm) were included in ARIEL3. Importantly, objective responses (including complete responses) were observed during rucaparib treatment in some patients with measurable disease (38% with *BRCA* mutations and 27% with HRD, versus 9% and 7% with placebo). "While we expected to see responses in patients with residual disease based on previous observations with rucaparib and other PARP inhibitors, documenting these effects in a placebo-controlled trial was nicely confirmatory," says Coleman.

The findings of ARIEL3 confirm that PARP inhibitors have activity extending beyond synthetic lethality with *BRCA* mutations or other HRDs, thus affirming maintenance therapy with these agents as standard care for patients with platinum-sensitive ovarian cancer. Nevertheless, better predictive biomarkers might eventually improve patient selection.

Coleman concludes: "we strive to do better because even patients with the best outcomes eventually need additional treatment and, thus, rely on us to improve their care by developing better combinations and therapeutic strategies. That's the future: better combinations, overcoming resistance, and learning how to identify patients that will still benefit from PARP inhibitors despite having previously received this class of treatment."

David Killock

ORIGINAL ARTICLE Coleman, R. L. *et al.* Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* http://dx.doi.org/10.1016/S0140-6736(17)32440-6 **(2017)**