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GYNAECOLOGICAL CANCER

PARP inhibition — moving beyond *BRCA*-mutated disease

Poly[ADP-ribose] polymerase (PARP) inhibition results in synthetic lethality in cells with homologous-recombination deficiency (HRD), and PARP inhibitors have proven therapeutic activity in women with *BRCA*-mutated ovarian cancer. This group, however, accounts for only ~20% of patients with ovarian cancer. Importantly, approximately 30% of women with this disease have HRD of a different aetiology, and might also benefit from PARP inhibition. New data now confirm that women with *BRCA*-wild-type (*BRCA*-WT) tumours can benefit from such treatment, and provide insights into how these patients can be identified.

The ARIEL2 study was designed to investigate HRD, defined based on the extent of genomic loss of heterozygosity (LOH), as a biomarker of responsiveness to the PARP inhibitor rucaparib. The Cancer Genome Atlas data were used to predetermine a LOH cutoff to define HRD, enabling 192 of 204 enrolled women with recurrent, platinum-sensitive, high-grade ovarian cancer to be classified into three disease subgroups: *BRCA*-mutated; *BRCA*-WT, LOH-high (≥14%; HRD); and *BRCA*-WT, LOH-low (<14%).

The median progression-free survival (PFS) was 12.8 months, 5.7 months, and 5.2 months in the *BRCA*-mutated, LOH-high, and LOH-low groups, respectively. Although these data suggest limited activity of rucaparib in the *BRCA*-WT setting, a PFS benefit was observed in the LOH-high group versus the LOH-low group. As lead author Elizabeth Swisher explains, "the median PFS occurred at a time point when the PFS curves are closest together, but this is just one arbitrary time point to compare outcomes. The hazard ratio is a better measure for comparing the entire curves and was both statistically and clinically significant at 0.62."

A difference in response rates was also observed between the LOH-high and LOH-low subgroups: 29% versus 10%; however, the response rate in the *BRCA*-mutated group was 80%. Moreover, although broadly in line with the ARIEL2 results, recent data from the NOVA trial of niraparib maintenance treatment for platinum-sensitive, recurrent ovarian cancer, suggested that even patients with *BRCA*-WT, LOH-low tumours can derived a PFS benefit from PARP inhibition. Together, these findings indicate that refinement of the use of LOH and HRD as predictive biomarkers is required.

"We have used data from ARIEL2 to refine the LOH cutoff, in order to better separate patients with *BRCA*-WT ovarian cancer into responders and nonresponders," states Swisher. "This revised LOH cutoff is being tested in ARIEL3, which has completed enrolment. Similar to NOVA, ARIEL3 is a placebo-controlled, phase III trial of PARP-inhibitor maintenance therapy."

Swisher adds, "testing for germ-line *BRCA* mutations is recommended for all women with ovarian cancer. In the future, it may be more efficient and cost-effective to perform broader sequencing in order to identify both germ-line and somatic mutations in *BRCA1/2* and other genes, and also to get LOH information for HRD categorization." She concludes, however, that "the current HRD tests are not ready for clinical use; ongoing clinical trials will define the utility of various HRD tests."

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ORIGINAL ARTICLES Swisher, E. M. *et al.* Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol.* http://dx.doi.org/10.1016/S1470-2045(16)30559-9 (2016) | Mirza, M. R. *et al.* Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N. Engl. J. Med.* **375**, 2154–2164 (2016).