Pursuing biomarkers research for a more efficient use of PARP inhibitors

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The use of poly-adenosine diphosphate-ribose polymerase (PARP) inhibitors as maintenance therapy following response to platinum-based chemotherapy in frontline treatment and recurrent disease has dramatically changed the treatment for advanced ovarian cancer. In frontline treatment, olaparib for patients with BRCA-mutated tumors, olaparib plus bevacizumab for patients with homologous recombination deficiency, and niraparib for any patient regardless of homologous recombination status have received regulatory approval in the United States, the European Union, and many other countries around the world.[1] When the disease recurs, maintenance treatment with olaparib, niraparib, or rucaparib has been approved after response to platinum-therapy rechallenge. This treatment option is considered a standard of care for patients who have not received PARP inhibitors in the front line,[2] in view of the significant increment in progression-free survival and the improvement in secondary endpoints considered as surrogates of overall survival (as progression-free survival 2 or time to second subsequent therapy), which have been observed in different trials (SOLO-2, NOVA, and ARIEL-3).

One of the challenges to the use of PARP inhibitors as maintenance is the identification of, and research on, predictive factors for response (sensitivity) or progression (resistance) with these inhibitors. The most important predictive factor, both in frontline treatment and in recurrent disease is the presence of a BRCA mutation, as was demonstrated by all the trials that included patients with BRCA-mutant and BRCA wild-type tumors. In addition, homologous recombination status has been shown to have more predictive value in the frontline than in recurrence, where the possibility of a benefit with a PARP inhibitor cannot be excluded in patients with homologous recombination proficient tumors as demonstrated by the NOVA and ARIEL-3 trials. However, in frontline treatment, the PRIMA study showed a discrete benefit with niraparib in the population with homologous recombination proficient tumors, which was not demonstrated with the combination of olaparib and bevacizumab in comparison with bevacizumab. So, research into the biological and clinical factors predicting sensitivity or resistance to maintenance with PARP inhibitors is clearly needed for clinical practice to enable better selection of patients for this therapeutic intervention.

Drs Andrew Clamp and Domenica Lorusso[3] have presented, on behalf of ARIEL-3 investigators, the outcome of maintenance treatment of patients with rucaparib after platinum-based chemotherapy response in recurrent disease according to the platinum-free interval following penultimate platinum (6–12 months versus >12 months), the number of prior chemotherapy lines (two versus three or more), and prior use of bevacizumab. The first was a pre-planned analysis, as a platinum-free interval was one of the stratification factors, and the other two analyses were exploratory. The ARIEL-3 study demonstrated that rucaparib significantly improved progression-free survival in comparison with placebo in all primary analysis groups, in those with BRCA-mutant tumors, in those with homologous recombination deficiency (BRCA mutant + BRCA wild-type and high loss of heterozygosity), and in the intention-to-treat population. The new information provided here by the investigators confirms the benefit of rucaparib, regardless of the platinum-free interval, with a HR of 0.33 (95% CI 0.24 to 0.46) for patients with a progression-free interval of 6–≤12 months, and 0.39 (95% CI 0.30 to 0.52) for those with a progression-free interval >12 months; number of prior chemotherapies two versus three or more (HR 0.42, 95% CI 0.32 to 0.54 vs HR 0.28, 95% CI 0.19 to 0.41, respectively); and prior use of bevacizumab (HR 0.42, 95% CI 0.26 to 0.68) versus those without prior use (HR 0.35, 95% CI 0.28 to 0.45). Importantly, this benefit was observed across biomarker subgroups. This new evidence adds to the concept that there is no clinical factor associated with a clear absence of benefit with rucaparib maintenance in recurrent disease and is consistent with the results from other trials with niraparib or olaparib in the same setting (NOVA, SOLO-2, or Study-19).

One interesting observation of the sub-analysis presented by the ARIEL-3 investigators is that the median progression-free survival achieved with rucaparib is influenced by the penultimate platinum-free interval. Thus for a progression-free

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interval of 6–12 and >12 months, progression-free survival was 11.4 versus 18 months for BRCA-mutant tumors, 8.3 versus 18.4 months for the homologous recombination deficient population, and 8.2 versus 13.6 for the intention-to-treat population, respectively. In addition, the median progression-free survival for the intention-to-treat patients with a progression-free interval >24 months progression-free survival was 23.6 months. A similar trend was observed according to number of prior lines but only in the BRCA mutant population (21.9 months in patients with two prior lines vs 13.7 months for patients with three or more lines).

This clinical correlation between the penultimate progression-free interval and the median progression-free survival obtained with rucaparib might be explained by the presence of cross-resistance and cross-sensitivity mechanisms between PARP inhibitors and platinum-based therapy. For instance, BRCA reversion mutations and BRCA promoter methylation loss have been identified as cross-resistance mechanisms for platinum and PARP inhibitor therapy.[4 5] In addition, there is a great interest in obtaining knowledge about the clinical behavior and outcome of patients already treated with PARP inhibitors who subsequently receive platinum-based therapy, and this analysis should be highly encouraged for the ARIEL-3 study.

The analysis presented by Drs Cramp and Lorusso, confirms that there is no clinical factor precluding a potential benefit from rucaparib as maintenance after response to platinum in recurrent disease. Nevertheless, information on the magnitude of the benefit according to the penultimate platinum-free interval should be an additional incentive to continue research into biologic predictive biomarkers of PARP inhibitor resistance.

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