PARP inhibitors in ovarian cancer treatment: more than a hope

In 2014, olaparib (by AstraZeneca, London, UK) was the first poly-adenosine diphosphate (ADP) ribose polymerase (PARP) inhibitor to be approved by the European Medicines Agency as maintenance therapy for patients affected by BRCA1/2 mutated (BRCAm) ovarian cancer responding to platinum-based chemotherapy [1]. In the United States, olaparib also received accelerated approval by the Food and Drug Administration (FDA) as monotherapy in patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer and who have been treated with three or more prior lines of chemotherapy [2].

However, other PARP inhibitors have been investigated and, recently, results from maintenance trials with other potent PARP inhibitors, such as niraparib and rucaparib, have been presented, which have highlighted significant, potentially practice-changing developments in the treatment of ovarian cancer.

Rucaparib (AG 014699) has demonstrated clinical activity in BRCAm high-grade serous ovarian cancer (HGSOC) in two phase II studies [3, 4]. Data from these trials were pooled to examine the clinical activity and safety of rucaparib in BRCAm patients with HGSOC who have received ≥2 prior chemotherapy regimens. Results were recently presented at the European Society for Medical Oncology (ESMO) 2016 meeting, reporting that patient subgroups with mutant BRCA (germ line and somatic) had a 53.8% objective response rate and 10-months median progression-free survival (PFS) [5]. Overall response rate (ORR) was also assessed according to the various subgroups: patients with a germline BRCA mutation had a 53% response rate, compared with 46% in those with somatic mutations. Interestingly, most patients (61%) had received three or more prior therapies, and 39% had received two; the latter group achieved an ORR of 68%. Patients with a progression-free interval (PFI) of less than 6 months (27 patients) had an ORR of only 19%, while those with a PFI ranging between 6 and 12 months had an ORR of 63%, and those with a PFI above 12 months achieved an ORR of 74%.

Forty-seven percent of patients experienced at least one treatment-related grade 3 or higher adverse event. The most common adverse events related to dose reduction included anaemia (17%), asthenia/fatigue (14%), and nausea (11%). Treatment discontinuation was more commonly related to asthenia/fatigue (2%), small intestinal obstruction (2%), and nausea (1%). Overall, these results demonstrate that rucaparib may represent an important option for women with more than once-relapsed BRCA-mutated

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ovarian cancer, with an acceptable toxicity profile, especially in platinum-sensitive disease. Datasets from these trials were submitted to the US FDA earlier this year for a new drug application.

Niraparib (MK-4827) has been investigated in the NOVA trial, in which patients were categorised based on germline BRCA mutation status, forming the gBRCA cohort and non-gBRCA cohort, and randomised 2:1 to receive niraparib or placebo until disease progression [6]. Importantly, this trial included patients without a BRCA mutation, testing the hypothesis that PARP inhibitor therapy could be useful in a wider group of patients, which might harbour other less common germline and/or somatic mutations involved in homologous recombination disease (HRD). In order to identify this group of patients, a homologous recombination deficiency assay has been developed by Myriad Genetics [7] and applied in the NOVA trial; this test uses three combined measures to provide an HRD score: loss of heterozygosis (LOH), telomeric allelic imbalance, and large-scale state transitions in cancer cells. The study met its primary end point of significantly improving median PFS compared with placebo.

Median PFS with niraparib compared to placebo was 21.0 *versus* 5.5 months (hazard ratio [HR] 0.27; $p<0.001$) in the germline BRCA mutation group (n=203); 9.3 *versus* 3.9 months (HR 0.45; $p<0.001$) in the non-germline BRCA mutation group (n=350). The non-gBRCA-mutated patients were also categorised according to HRD status, using Myriad's myChoice® HRD test. Median PFS in the non-gBRCA cohort by HRD status was 12.9 *versus* 3.8 months (HR 0.38; $p<0.001$) in a subgroup of the non-mutation cohort who had homologous recombination DNA repair deficiencies, and 6.9 *versus* 3.8 months (HR 0.58; p=0.0226) in non-gBRCA, HRD-negative patients (n=134).

Compared to placebo, niraparib significantly prolonged the second progression-free survival, time to first subsequent treatment, and chemotherapy-free interval in the mutation and mutation-free groups, as well as in the HRD subgroup.

More than 10% of patients had grade 3/4 adverse events following treatment with niraparib, including 28% with thrombocytopenia, 25% with anaemia, and 11% with neutropenia. These were resolved with dose adjustments.

Importantly, in all subgroups analysed, niraparib improved median PFS compared with placebo and there was a clear separation of the PFS curves. These data indicate a benefit of niraparib in platinum-sensitive relapsed ovarian cancer patients regardless of BRCA mutation status or HRD status. The effect of niraparib on the non-gBRCA HRD-positive cohort could in part be attributed to the presence of somatic BRCA mutations in this group, however patients treated with niraparib whose tumours were BRCA wild-type (who were also non-gBRCA-mutated/HRD-negative) also experienced a delay in disease progression compared to those receiving placebo.

Overall, it could be stated the PARP inhibitors are becoming part of ovarian cancer management. Nevertheless, although benefits are clear, a number of unsolved questions still remain. Several strategies have already been explored to select patients who may benefit from PARP inhibitors, by focusing on the identification of predictive biomarkers for homologous recombination-deficient tumours but, having seen the widespread response

regardless of HRD status, it might be affirmed that a strong predictive biomarker of PARP inhibitor sensitivity beyond BRCA1/2 mutations has still not yet been identified. Further to BRCA status, which should be performed in each serous and endometrioid ovarian cancer, prior sensitivity to platinum remains a useful clinical and phenotypic predictor of HRD and, therefore, of potential PARP sensitivity.

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Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

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