Which poly(ADP-ribose) polymerase (PARP) inhibitors are approved for use as maintenance therapy in ovarian cancer?

Two PARP inhibitors are approved for use as frontline maintenance therapy in advanced ovarian cancer in patients who have responded to their antecedent platinum-based chemotherapy: olaparib (Lynparza, AstraZeneca) and niraparib (Zejula, GSK). Olaparib is approved for use in combination with bevacizumab based on the results of the PAOLA-1 trial that was led by Dr. Isabelle Ray-Coquard and colleagues, whereas niraparib is approved for use as monotherapy based on the results of the PRIMA trial led by Dr. Antonio González-Martín and colleagues. Olaparib was initially approved for use as a single-agent maintenance strategy in patients with a germline or somatic BRCA mutation, based upon the results of SOLO-1. This frontline approval was expanded to include olaparib in combination with bevacizumab for patients with homologous recombination deficiency (HRD). Niraparib is approved for use in patients irrespective of their HRD status.

Three PARP inhibitors—olaparib, niraparib, and rucaparib (Rubraca, Clovis Oncology)—are approved for maintenance therapy in patients with recurrent, platinum-sensitive disease.

Could you discuss the design and the results of the ATHENA-MONO trial?

ATHENA-MONO is a randomized, double-blind phase 3 trial that is looking at rucaparib monotherapy vs placebo as maintenance treatment following response to first-line platinum-based chemotherapy and surgery in patients with stage III or IV, high-grade ovarian cancer. The other component of the ATHENA trial, called ATHENA-COMBO, is comparing rucaparib/nivolumab vs rucaparib alone as maintenance. All patients must have achieved a complete or partial response to the chemotherapy and have an Eastern Cooperative Oncology Group performance status of 0 or 1 in order to be eligible.

Dr. Bradley Monk presented results from ATHENA-MONO at the 2022 annual meeting of the American Society of Clinical Oncology; these results were simultaneously published online in the Journal of Clinical Oncology. The researchers randomly assigned 538 patients in a 4:1 ratio to receive either rucaparib or placebo, with investigator-assessed progression-free survival (PFS) as the primary endpoint. After a median follow-up of 26 months, the median investigator-assessed PFS in the HRD population was 28.7 months in the rucaparib group vs 11.3 months in the placebo group. This represented an impressive difference between the arms, with a hazard ratio (HR) of 0.47 (P < .001). The median investigator-assessed PFS in the intent-to-treat population was 20.2 months in the rucaparib group vs 9.2 months in the placebo group. This finding was equally impressive, with an HR of 0.52 (P < .001).

Exploratory analysis revealed better investigator-assessed PFS with rucaparib than placebo in other subgroups, including the BRCA-mutant group (not reached vs 14.7 months; HR, 0.4) and the BRCA–wild-type/
loss of heterozygosity (LOH)-low subgroup (12.1 vs 9.1 months; HR, 0.65). There was a trend toward better investigator-assessed PFS with rucaparib than placebo in the BRCA–wild-type/LOH-high subgroup (20.2 vs 9.2 months; HR, 0.58), but the difference was not statistically significant. I was especially impressed to see the improvement in PFS with rucaparib in the BRCA–wild-type/LOH-low subgroup. This subgroup also did better with rucaparib treatment than with placebo in the evaluation of PFS by blinded independent central review (BICR), at 12.0 vs 6.4 months, respectively (HR, 0.60). This improvement in PFS of nearly 6 months is more impressive than what we have seen with other PARP inhibitors.

The most common grade 3 or higher treatment-emergent adverse events were anemia, which occurred in 28.7% of rucaparib patients vs no placebo patients, and neutropenia, which occurred in 14.6% of rucaparib patients vs 0.9% of placebo patients. The toxicity profile of rucaparib was consistent with what we expect with PARP inhibitors, with most toxicities being manageable. These data are impressive thus far, although it remains to be seen whether the US Food and Drug Administration (FDA) approves the use of rucaparib as maintenance therapy soon in ovarian cancer.

H&O Could you discuss the studies that established the use of PARP inhibitors as maintenance in platinum-sensitive, relapsed or recurrent ovarian cancer?

TH A total of three phase 3 studies have looked at this indication: ENGOT-OV16/NOVA, SOLO2, and ARIEL3. ENGOT-OV16/NOVA showed that maintenance therapy with niraparib significantly prolonged PFS by BICR in patients with platinum-sensitive recurrent ovarian cancer regardless of germline BRCA mutation or HRD status. SOLO2 showed that maintenance therapy with olaparib significantly improved PFS in patients with platinum-sensitive relapsed ovarian cancer who also have a BRCA1/2 mutation. ARIEL3 showed that maintenance therapy with rucaparib significantly improved PFS in patients with platinum-sensitive ovarian cancer who had achieved a response to their most recent platinum-based chemotherapy.

H&O Could you discuss the “Dear Health Care Provider” letters that were issued earlier this year regarding PARP inhibitors?

TH Several “Dear Health Care Provider” letters were issued this spring to address concerns over the use of PARP inhibitors in ovarian cancer. The first letter, which was issued in May 2022 and updated in June, cited results from the open-label phase 3 ARIEL4 trial that showed a trend towards inferior OS with the use of rucaparib vs chemotherapy in patients with relapsed, BRCA1/2-mutated ovarian cancer. The median OS was 19.6 months for those who received rucaparib vs 27.1 months for those who received chemotherapy, for an HR of 1.55 (95% CI, 1.085-2.214). The second letter, also dated May 2022, cited results from the phase 3 ENGOT-OV16/NOVA study of niraparib maintenance in patients with platinum-sensitive, recurrent ovarian cancer. Based on a data cutoff of October 1, 2020, the median OS was 31.1 months for those treated with niraparib vs 36.5 months for those treated with placebo, for an HR of 1.10 (95% CI, 0.83-1.46). In addition, the median OS in a subgroup of patients without the germline BRCA mutation who were HRD-positive was 37.3 months for patients treated with niraparib vs 41.4 months for those treated with placebo (HR, 1.32; 95% CI, 0.84-2.06).

Following the release of these letters, the European Medicines Agency issued a recommendation in July that doctors not begin using rucaparib in the third-line and later settings in new patients until further review is completed. In addition, the company voluntarily pulled this FDA indication for use in the third line and beyond.

Most recently, AstraZeneca has stated plans to pull olaparib’s indication for use in the fourth line and beyond based on similar data trends regarding OS from the SOLO3 trial.

H&O What are the implications of these letters?

TH I believe that these letters certainly will lead to less use of PARP inhibitors in later lines of treatment. This change will continue a trend that had already begun, based on the impressive results with these agents in frontline disease. Because of this trend, patients are likely to have received a PARP inhibitor long before they need third-line or later treatment, especially if they have HRD.

My concern with the OS data is that these trials were not fully powered to assess OS. Furthermore, the results do not account for the significant crossover to
PARP inhibitors among the non-PARP cohorts. Finally, the fact that the confidence intervals cross unity may be statistical noise, pointing to a false conclusion that has the potential to lead to less PARP use in patients who could benefit from these novel agents. Another concern is that clinicians may reduce the length of maintenance therapy from the current recommendations, despite limited data to support this approach.

**H&O** What could potentially cause reductions in OS to occur despite improvements in PFS?

**TH** A potential explanation might be that exposure to PARP inhibitors could induce subsequent resistance to platinum and other DNA-damaging drugs. The challenge is how to determine whether this is occurring when we lose so many patients to follow-up as soon as a study’s primary endpoint is reached. It takes a tremendous amount of time and resources to follow patients for the sufficient length of time needed to better understand this dynamic, and to either prove or refute this hypothesis. Nonetheless, although I believe that this theory is plausible, the data presented thus far are insufficient to prove it. Further data are needed.

**H&O** What questions remain to be answered regarding PARP inhibition?

**TH** First, we would like to learn the relative value of PARP inhibition in the 50% of patients who test negative for HRD. If PARP inhibitors benefit these patients, how great is the benefit, and what are the costs in terms of quality of life and toxicity? Second, we would like to answer the question raised by the health care provider letters: can these agents lead to worse OS outcomes? Third, we need to accrue more data regarding long-term toxicities, such as myelodysplastic syndrome and acute myelogenous leukemia (MDS/AML). The rate of MDS/AML was 8% with olaparib in mature results from the SOLO2 trial, and 6.6% with niraparib among patients in ENGOT-OV16/NOVA with germline *BRCA* mutations. Are there certain patients who are more likely to develop MDS or AML, and can we identify these patients a priori? Finally, and relatedly, we need to determine the optimal length of maintenance therapy with PARP inhibitors.

**Disclosure**

Dr Herzog has served on the scientific advisory board of AstraZeneca, Caris, Clovis, Epsilogen, Genelux, Genentech, GSK, J&J, Merck, and Seagen.

**Suggested Readings**


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