Use of PARP Inhibitors for Ovarian Cancer

Presented by Deborah K. Armstrong, MD

ABSTRACT

PARP inhibitors have been used to treat numerous diseases, but these agents have been approved the longest for use in ovarian cancer. All trials of PARP inhibitor maintenance in newly diagnosed ovarian cancer are positive for prolonged progression-free survival (PFS), but patients with *BRCA* mutations consistently derive the most benefit. Testing for homologous recombination deficiency may provide information regarding the degree of PFS benefit. In individuals without a *BRCA* mutation, PARP inhibition also prolongs PFS after chemotherapy for platinum-sensitive, PARP-naïve disease. As in the up-front setting, patients with *BRCA* mutations derive the most benefit in these trials. Finally, PARP inhibitors are active as monotherapy in PARP-naïve, *BRCA*-mutated relapsed disease, with increased activity observed in platinum-sensitive versus platinum-resistant disease.

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Although PARP inhibitors have been developed for multiple diseases, they have been approved the longest for treatment of ovarian cancer, and thus offer the most useful data in that indication, according to Deborah K. Armstrong, MD, Director, Breast and Ovarian Surveillance Service, and Professor of Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. During the NCCN 2021 Virtual Annual Conference, Dr. Armstrong described data from PARP inhibitor trials in patients with newly diagnosed advanced ovarian cancer, reviewed factors that may affect the extent of clinical benefit from PARP inhibitor therapy, and discussed considerations for selecting recurrence therapy in patients whose disease has progressed on or after PARP inhibitor maintenance.

Frontline Maintenance

The SOLO-1 study enrolled patients with a germline or somatic *BRCA* mutation and stage III–IV disease who had completed initial therapy.¹ Patients were also required to be in complete or partial response after platinum-based therapy. Study participants were randomized to receive either the PARP inhibitor olaparib or placebo, and were continued on treatment for 2 years if there was no evidence of disease progression. Results showed a striking difference in median progression-free survival (PFS), which improved from 13.8 months in the placebo group to 56 months in the olaparib group (hazard ratio [HR], 0.33).

“One of the most interesting parts of this study is that after discontinuing olaparib, the survival curves stay separate and maintain benefit out to >5 years of follow-up,” said Dr. Armstrong. “Other trials have used longer

duration therapy, but our hope is that [olaparib] is nipping disease in the bud early on.”

The PAOLA-1 study enrolled patients with newly diagnosed, stage III–IV, high-grade serous/endometrioid ovarian, fallopian tube, or primary peritoneal cancer.² All subjects had to have undergone ≥ 3 cycles of bevacizumab with their initial chemotherapy. At the end of that initial treatment, patients were randomized to either continue bevacizumab + placebo or bevacizumab + olaparib. Unlike SOLO-1, which selected for patients with a *BRCA* mutation, PAOLA-1 had broad eligibility. Results demonstrated an improvement in PFS in the intent-to-treat population. Patients treated with bevacizumab alone had a median PFS of 16.6 months, and those treated with bevacizumab + olaparib had a median PFS of 22.1 months (HR, 0.5).

The PRIMA study looked at the PARP inhibitor niraparib in patients with stage III–IV high-grade serous or endometrioid cancer with visible residual disease postsurgery.³ All patients had to have experienced a complete or partial response to platinum-based chemotherapy. The primary endpoint showed a median PFS of 8.2 months in the placebo group versus 13.8 months in the niraparib group.

Finally, the VELIA study examined arms combining chemotherapy with a PARP inhibitor in addition to the use of a PARP inhibitor as maintenance therapy.⁴ The study’s first arm was placebo + carboplatin/paclitaxel followed by placebo as maintenance. Arm 2 was veliparib + carboplatin/paclitaxel followed by placebo. Arm 3 was veliparib + carboplatin/paclitaxel followed by veliparib maintenance. An improvement in PFS was again observed in patients receiving a PARP inhibitor throughout. Median PFS was 23.5 months for veliparib throughout versus 17.3 months with carboplatin/paclitaxel followed by placebo.

However, relatively little difference in survival was observed in patients receiving veliparib + chemotherapy.

Unlike prior studies, which had to document a response to initial therapy, patients in the VELIA study were started on the treatment de novo and thus probably included some who would not have responded to therapy, noted Dr. Armstrong. “Because this study may have included a poor prognosis group of patients, the findings may be a little more real-world, and the benefit that is still seen in this group of patients is not just selectively in patients who had responded to initial chemotherapy.”

BRCA Mutation Status

Aside from the SOLO-1 trial, which selected patients based on *BRCA* mutation status, a similar HR was observed in the other 3 studies,²⁻⁴ said Dr. Armstrong. Subgroup analysis of *BRCA* mutation carriers across all 4 studies also showed similarly favorable HRs. “We see the greatest survival benefit in those patients with a *BRCA* mutation, either somatic or germline,” she said.

Although not the same degree of benefit, PARP inhibition also led to improved PFS in patients with *BRCA* wild-type, according to analysis of the PAOLA-1 and VELIA trials. Furthermore, patients with *BRCA* wild-type with some measure of homologous recombination deficiency (HRD) had a greater benefit in PFS from PARP inhibitor maintenance than the overall group (18.2 vs 19.6 months in PRIMA³; 16.6 vs 28.1 months in PAOLA-1²).

Conversely, patients with *BRCA* wild-type and are homologous recombination proficient are the least likely to benefit from a PARP inhibitor. “There was still some benefit for this population of patients in PRIMA,” said Dr. Armstrong, who noted that median PFS went from

5.4 to 8.1 months,³ “but the magnitude is different. Also note that patients who are homologous recombination proficient and with *BRCA* wild-type do worse overall,” she added. “Their PFS just with chemotherapy in the placebo arm is worse.”

The FDA has approved olaparib for frontline maintenance in patients with germline or somatic *BRCA* mutations. Niraparib has been approved for use in patients who have experienced a complete or partial response after initial therapy. Olaparib has been approved in combination with bevacizumab for maintenance therapy in those whose cancer is HRD-positive based on the PAOLO-1 study.

Maintenance Post-Recurrence

For platinum-sensitive, PARP-naïve patients responding to platinum, PARP inhibitor maintenance has also been shown to prolong PFS (Table 1). As in the up-front setting, patients with *BRCA* mutations also consistently derive the most PFS benefit in these trials.

In the NOVA study, for example, which was enriched for patients with *BRCA* mutations, median PFS was 5.5 months for placebo versus 21 months for niraparib.⁵ For patients with germline *BRCA* wild-type, median PFS was 3.9 versus 9.3 months, respectively. Niraparib was the first PARP inhibitor that was FDA approved for the maintenance setting after treatment of recurrent platinum-sensitive disease. “Even without documented *BRCA* mutation, platinum-sensitive recurrent disease does select for patients who experience benefit from PARP inhibitors,” said Dr. Armstrong. “In fact, the benefit in the *BRCA* wild type is actually a bit more significant than it is in the up-front setting because patients who would develop platinum-resistant recurrence are not included here.”

Table 1. Platinum-Sensitive Maintenance

	Study 19 ¹⁰	SOLO2 ⁶	NOVA ⁵	ARIEL3 ¹¹
Patients, N	265	295	553 (203 gBRCA, 350 non-gBRCA)	564
PARP inhibitor	Olaparib	Olaparib	Niraparib	Rucaparib
Arms	1. Olaparib 2. Placebo	1. Olaparib 2. Placebo	1. Niraparib 2. Placebo	1. Rucaparib 2. Placebo
Population	HGS	HGS/Endometrioid and BRCAmt	HGS	HGS/Endometrioid
Primary endpoint	PFS (investigator)	PFS (investigator)	PFS (BICR) Independent cohorts: gBRCAmt gBRCAwt Hierarchical HRD→ITT	PFS (investigator) Hierarchical BRCAmt→HRD→ITT
Outcome	HR, 0.35 (mPFS, 4.8 vs 8.4 mo)	HR, 0.30 (mPFS, 5.5 vs 19.1 mo)	gBRCAmt: HR, 0.27 (mPFS, 5.5 vs 21.0 mo) gBRCAwt: HR, 0.45 (mPFS, 3.9 vs 9.3 mo)	HR, 0.36 (mPFS, 5.4 vs 10.8 mo)

Abbreviations: BICR, blinded, independent, central review; BRCAmt, *BRCA* mutant; gBRCA, germline *BRCA*; gBRCAmt, germline *BRCA* mutation; gBRCAwt, germline *BRCA* wild-type; HGS, high-grade serous; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention to treat; mPFS, median progression-free survival; PFS, progression-free survival.

Similar to the up-front setting, testing for HRD does not identify a patient subpopulation who would experience a PFS benefit from PARP inhibitor maintenance, although it may provide information regarding degree of PFS benefit, Dr. Armstrong added.

SOLO2 was the first trial to show a survival benefit of PARP inhibitor maintenance in *BRCA*-mutated ovarian cancer.⁶ Median overall survival improved from 38.8 months in the placebo group to 51.7 months in the olaparib group (HR, 0.74). Patients in this trial could not have been previously treated with a PARP inhibitor, so there is no information on whether these benefits would be seen in patients who had previously received PARP inhibitors.

Recurrent Disease

Active treatment of relapsed disease with PARP inhibitors has also been well tested in *BRCA*-positive disease, with ARIEL2 and QUADRA studying rucaparib and niraparib, respectively.^{7,8} Although the trials had different criteria regarding prior lines of therapy, objective response rates in this heavily pretreated population were 54% and 40%, respectively.

In ARIEL2,⁷ which enrolled a patients who were platinum-sensitive, the overall response rate was 80% for those with *BRCA* mutations and 29% for *BRCA* wild-type with some measure of HRD. The overall response rate was only 10% in *BRCA* wild-type with homologous recombination proficiency. In the QUADRA study,⁸ which was platinum agnostic, the overall response rate was 29% in *BRCA*-positive disease, 9% for *BRCA* wild-type with HRD, and only 3% for *BRCA* wild-type.

“Once again, *BRCA* mutation carriers experience the greatest benefit across the line,” said Dr. Armstrong. “The

second greatest benefit is seen in patients with *BRCA* wild-type and some measure of HRD.” Furthermore, “these drugs are clearly more active in the platinum-sensitive setting,” she added.

Future Directions in PARP Inhibitor Therapy

Investigators are now currently exploring various combinations of 4 treatment approaches: chemotherapy, bevacizumab, immune checkpoint inhibition, and PARP inhibition.

The triplet combination of olaparib/durvalumab/bevacizumab, for example, has shown promising efficacy as treatment in the absence of chemotherapy for women with germline *BRCA* wild-type, platinum-sensitive, relapsed advanced ovarian cancer, with a median PFS of 15 months.⁹ Of note, said Dr. Armstrong, exploratory analysis suggests that the high overall response rate was not driven by differences in genomic instability status. The triple combination is now being tested as part of first-line maintenance treatment in the phase III study.

“The field is getting very complicated,” said Dr. Armstrong. “There are a large number of ongoing trials looking at PARP inhibitors with other molecularly targeted agents to overcome resistance to PARP inhibition, either de novo or acquired resistance. It’s a very active field of investigation in ovarian cancer.”

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