PARP Inhibition as Frontline Therapy in Ovarian Cancer

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Abstract: Poly(ADP-ribose) polymerase (PARP) inhibitors have been rapidly integrated into clinical practice for women with ovarian cancer. Currently, PARP inhibitors are approved as frontline maintenance treatment for patients with and without *BRCA*-associated cancers, and they are listed by the National Comprehensive Cancer Network (NCCN) as a treatment option for all high-grade serous and endometrioid cancers with or without bevacizumab. PARP inhibitors are also approved as maintenance treatment following a response to platinum-based therapy in the recurrent setting, irrespective of biomarker status. Additionally, PARP inhibitors are approved as third-line treatment and beyond in lieu of chemotherapy for patients with *BRCA*-associated cancers, and as fourth-line treatment and beyond for patients with platinum-sensitive homologous recombination–deficient tumors. They are also listed by the NCCN in combination with bevacizumab for the treatment of patients who have platinum-sensitive recurrent disease. The first part of this 2-part review focuses on the changing paradigm of frontline therapy options resulting from the recent approvals of PARP inhibitors; the second part considers the role of PARP inhibition in recurrent ovarian cancer.

Introduction

Treatment options for women with ovarian cancer have expanded immensely over the past 10 years. The first clinical trial evaluating the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (Lynparza, AstraZeneca), which was published in 2010, demonstrated its efficacy in *BRCA*-associated tubal, peritoneal, and epithelial ovarian cancers.[1] The year 2014 saw the first approvals of new targeted therapies for ovarian cancer. To date, the US Food and Drug Administration (FDA) has approved 12 targeted agents for use in ovarian cancer, including bevacizumab,[2] olaparib,[3] rucaparib

(Rubraca, Clovis Oncology),[4] niraparib (Zejula, Tesaro),[5] and pembrolizumab (Keytruda, Merck) for microsatellite instability–high tumors.[6] The continued development of and access to novel therapies, the enhanced identification of genetic biomarkers, and better supportive care have all contributed to the currently improved rates of ovarian cancer survivorship. Despite the lack of a significant change in incidence or overall mortality, the percentage of women living with ovarian cancer is higher than ever—suggesting that increased access to and the appropriate use of novel therapies have incrementally improved progression-free survival, with each line of therapy contributing to longer survival.[7,8] This review focuses specifically on the current status of poly(ADP-ribose) polymerase (PARP) inhibitor development and use in epithelial ovarian cancer. Part 1 addresses the use of PARP inhibitors as maintenance after primary therapy; part 2 considers their use as maintenance after chemotherapy for recurrent platinum-sensitive disease, as monotherapy, and in targeted therapy combinations.

Primary Therapy

The typical course of epithelial ovarian cancer (EOC) is well understood. The majority of women present with advanced-stage disease that is exquisitely sensitive to initial, frontline platinum-based therapy. In 75% of patients, however, disease recurs within 3 years after the completion of therapy. After EOC recurs, many treatment options are available that meaningfully prolong life. Cure is no longer expected after recurrence, however, because recurrence is generally the result of accelerating resistance to treatment.[9,10] The concept of maintenance therapy evolved owing to the high proportion of women who are not cured with frontline therapy despite an apparently complete response to treatment. The incorporation of bevacizumab both concurrently with and following the completion of 18 to 22 cycles of chemotherapy was evaluated in the Gynecologic Oncology Group GOG-0218 study and in the ICON7 trial. These 2 studies reported similar results, with improvements in progression-free survival (PFS) from 10.3 to 14.1 months (from 12 to 18.2 months when serologic progressions were censored) in GOG-0218 and from 17.3 to 19 months in ICON7. No effect on overall survival (OS) was noted.[11-13] Although this improvement in PFS was clinically meaningful, medications such as PARP inhibitors, which might prevent recurrence or at least result in a more substantial delay in recurrence, were needed.

PARP inhibitors are of interest in ovarian cancer treatment owing to the highly prevalent loss of some aspect of the DNA repair machinery in high-grade serous ovarian cancers (HGSOCs) and high-grade endometrioid EOCs, and the potential to exploit this deficiency to therapeutic advantage. The 2 main pathways for the repair of breaks in double-stranded DNA are homologous recombination and nonhomologous end joining (NHEJ). Homologous recombination uses sister chromatids as a template, occurs during the G2/M phase of the cell cycle, is high fidelity, and is greatly dependent on proteins encoded by *BRCA1* and *BRCA2* genes. Additional proteins encoded by *RAD51*, *MRN* complex, and *ATM* genes are recruited to the sites of DNA breaks. PARP1 acts to recruit MRE11 and NBS1, as well as ribosylating BRCA, to facilitate DNA repair via the high-fidelity homologous recombination pathway. In addition, PARP1 blocks access to the error-prone NHEJ pathway, thus facilitating repair through the high-fidelity homologous recombination pathway. In tumors with deficient BRCA1 or BRCA2 proteins, owing to either germline or somatic mutations or to epigenetic silencing, or in tumors with a loss of other key proteins in homologous recombination, PARP inhibition both accentuates tumor dependency on a compromised homologous recombination process and promotes alternative repair pathways such as NHEJ and alternative end joining (alt-EJ). Thus, impairment of the high-fidelity repair of DNA results in genomic instability and cell death.[14,15] Our increasing knowledge of the genomic and epigenetic landscape of HGSOC indicates that approximately 50% of tumors harbor some deficiency in their homologous recombination capabilities and are characterized as homologous recombination–deficient (HRD) to some degree.[16]

SOLO-1/GOG-3004 was the first clinical trial to incorporate the PARP inhibitor olaparib into the frontline treatment paradigm. SOLO-1 enrolled women with *BRCA1/2*-associated HGSOC or endometrioid cancer who had undergone some attempt at surgical debulking, either primary cytoreductive surgery (pCRS) or interval cytoreductive surgery (iCRS), and had exhibited a partial response (PR) or complete response (CR) to frontline platinum-based chemotherapy. The study patients were stratified according to PR or CR. Women were randomly assigned in a 2:1 ratio to receive olaparib tablets at 300 mg twice daily or placebo until disease progression or toxicity. At 2 years after randomization, if no progression was noted, the assigned therapy was discontinued unless a compelling clinical reason to continue existed. The primary endpoint was PFS as assessed by the investigator. Secondary endpoints included OS and health-related quality of life. Details about patient demographics are outlined in Table 1. The primary endpoint revealed an unprecedented reduction in the hazard for progression or death (70%) (hazard ratio [HR], 0.30; 95% CI, 0.23-0.41; $P<.0001$). The median PFS (mPFS) was 13.1 months for placebo vs not reached (NR) for olaparib. Sensitivity analyses esti-

Table 1. Summary of Results of Phase 3 Studies in the Frontline Treatment of Ovarian Cancer

Stage III/IV	*BRCA* Status	Surgical Status	CR/PR	Exp Arm	Control Arm	HR (95% CI) All Pts mPFS	HR (95% CI) for *BRCA*m mPFS	HR (95% CI) for *BRCA*wt, RD-Positive mPFS	HR (95% CI) for RD-Negative/Status Unknown mPFS
SOLO-1[17]									
O: 85%/15% P: 80%/20%	Mutated	pCRS/NGR O: 62%/76% P: 65%/73% iCRS/NGR O: 36%/81% P: 33%/84%	O: 82%/18% P: 82%/18%	Olaparib	Placebo	NT	HR: 0.30 (0.23-0.41) PFS: NR vs 13.8 mo	NT	NT
PRIMA[20]									
N: 65%/35% P: 64%/36%	All comers		N: 69%/31% P: 70%/30%	Niraparib	Placebo	HR: 0.62 (0.50-0.76) PFS: 13.8 vs 8.2 mo	HR: 0.40 (0.27-0.62) PFS: 21.9 vs 10.4 mo	HR: 0.50 (0.31-0.83) PFS: NR	HR: 0.68 (0.49-0.94) PFS: NR
VELIA[24]									
V: 77%/23% P: 78%/22%	All comers		NA	Veliparib	Placebo	HR: 0.68 (0.56-0.83) PFS: 23.5 vs 17.3 mo	HR: 0.44 (0.28-0.68) PFS: 34.7 vs 22.0 mo	HR: 0.74 (0.52-1.06) PFS: 22.9 vs 19.8	HR: 0.81 (0.60-1.09) PFS: 15.0 vs 11.5
PAOLA-1[21]									
	All comers	pCRS O: 50%/59% P: 51%/62% iCRS O: 42%/71% P: 41%/68%	O: 74%/26% P: 27%/28%	Olaparib/ bevacizumab	Placebo/ bevacizumab	HR: 0.59 (0.49-0.72) PFS: 22.1 vs 16.6 mo	HR: 0.33 (0.25-0.45) PFS: 37.2 vs 17.7 mo	HR: 0.43 (0.28-0.66) PFS: 28.1 vs 16.6	HR: 0.92 (0.72-1.17) PFS: 16.6 vs 16.2

*BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild-type; CR, complete response; exp arm, experimental arm; HR, hazard ratio; HRD, homologous recombination–deficient; iCRS, interval cytoreductive surgery; mo, months; mPFS, median progression-free survival; N, niraparib; NA, not applicable; NGR, no gross residual disease; NR, not reached; NT, not tested; O, olaparib; P, placebo; pCRS, primary cytoreductive surgery; pts, patients; PR, partial response; V, veliparib.

mated the mPFS to be between 47 and 49 months.[17]

Subsequent exploratory analyses evaluated the magnitude of benefit in women who underwent pCRS vs those who underwent iCRS. In a subset analysis, the HR for benefit was 0.31 (95% CI, 0.21-0.46) in women who underwent pCRS and 0.37 (95% CI, 0.24-0.58) in those who underwent iCRS. Similarly, the magnitude of benefit was maintained regardless of whether no gross residual disease (HR, 0.33; 95% CI, 0.23-0.46) or residual disease (HR, 0.44; 95% CI, 0.25-0.77) was present after surgery. Among women with stage III EOC who underwent pCRS to no gross residual disease, the mPFS was 21.9 months for placebo vs NR for olaparib (HR, 0.32; 95% CI, 0.20-0.51). Even those among this group of women with *BRCA*-associated cancers who had the most favorable surgical prognostic factors experienced recurrences without maintenance therapy. The percentage of women who were free of disease at 3 years was 35.4% in the placebo group vs 71.4% in the olaparib group.[18] This finding reinforces the importance of timely genetic and tumor (somatic) testing to identify those patients with *BRCA*-associated cancers for whom maintenance olaparib treatment is appropriate and establishes such treatment as the standard of care.

Approximately 1 year after the publication of SOLO-1, three additional studies were presented that evaluated the use of PARP inhibition in patients with *BRCA*-associated cancers and in those with *BRCA* wild-type (wt) and HGSOC with or without endometrioid tumors. The PRIMA/ENGOT-OV26/GOG-3012 trial led to a new indication from the FDA for niraparib as maintenance treatment in patients with advanced ovarian, fallopian tube, or primary peritoneal cancer and a CR or PR to first-line platinum-based therapy. Additionally, 2 of the 3 studies resulted in the addition of new options to the NCCN guidelines for the frontline treatment of EOC.[19]

PRIMA/ENGOT-OV26/GOG-3012 enrolled women with advanced HGSOC or stage III/IV endometrioid EOC, including those who had stage III disease and residual tumor after primary debulking surgery and those treated with neoadjuvant chemotherapy (NACT). As in SOLO-1, women had to have either a CR or PR following platinum- and taxane-based chemotherapy. Unlike in SOLO-1, a *BRCA* mutation was not required. The women were randomized in a 2:1 ratio to niraparib once daily or placebo and were treated until disease progression, toxicity, or 36 months. Stratification factors included tissue homologous recombination test status (either HRD or homologous recombination–proficient [HRp]/HRD status unknown), CR or PR, and NACT status (yes or no). Of note, the study was amended two-thirds of the way through enrollment to incorporate individualized dosing according to baseline weight and platelet count, with a starting dose of either 300 or 200 mg once daily. The primary endpoint as measured by blinded radiographic review was performed as a hierarchal analysis of PFS in the patients with HRD tumors first and, if significant, in the intention-to-treat (ITT) population. Among the women with HRD tumors, the reduction in the hazard for progression or death was 57% (HR, 0.43; 95% CI, 0.31-0.59; *P*<.001). The mPFS was 21.9 months for niraparib vs 10.4 months for placebo. In the ITT group, the reduction in the risk for progression or death was 38% (HR, 0.62; 95% CI, 0.50-0.76; *P*<.001). The mPFS in the ITT group was 13.8 months for niraparib vs 8.2 for placebo. In non–hypothesis-tested subgroups, the reductions in the hazard for progression or death were as follows. HRD/*BRCA*-positive: HR, 0.40 (95% CI, 0.27-0.62); HRD/*BRCA*wt: HR, 0.50 (95% CI, 0.31-0.83); and HRp/HRD status unknown: HR, 0.68 (95% CI, 0.49-0.94).[20] The results of the subset analyses for women with *BRCA*-associated tumors enrolled in PRIMA are consistent with those seen in SOLO-1. It is also important to note that the HRD tumor test performed in this analysis was based on an algorithmic measure of 3 tumor factors: loss of heterozygosity (LOH), telomeric allelic imbalance, and large-scale state transitions. In PRIMA, HRD was defined as a score of at least 42 on the HRD tumor test or the presence of a *BRCA*-associated cancer. Niraparib is currently listed in the NCCN guidelines as an option for maintenance following frontline therapy; it gained FDA approval for this use on April 29, 2020.[5,19]

PAOLA-1/ENGOT-ov25, a randomized phase 3 study built on prior studies, noted an increase in the efficacy of bevacizumab given during and following platinum and taxane chemotherapy when olaparib was added to the maintenance therapy. Women with stage III or IV HGSOC or endometrioid EOC who had received at least 3 cycles of bevacizumab as part of their frontline regimen and achieved a CR or PR were randomized in a 2:1 ratio to oral olaparib at 300 mg twice a day for 2 years plus bevacizumab at 15 mg/kg every 21 days for 15 cycles, or to placebo and bevacizumab. Stratification factors included tumor *BRCA* mutation (t*BRCA*m) status and PR or CR. The primary endpoint was investigator-assessed PFS in the ITT population. The addition of olaparib improved the mPFS from 16.6 to 22.1 months and led to a reduction in the hazard for progression or death of 41% (HR, 0.59; 95% CI, 0.49-0.72; *P*<.0001). In non–hypothesis-tested subgroups, the mPFS was 21.7 vs 37.2 months in the t*BRCA*m group (HR, 0.31; 95% CI, 0.20-0.47) and 16 vs 18.9 months in the non-t*BRCA* group (HR, 0.71; 95% CI, 0.58-0.88). Again, when non–hypothesis-tested subgroups were evaluated by the same HRD assay used in PRIMA, the mPFS was 17.7 vs 37.2 months when patients with HRD/*BRCA* were included (HR, 0.33; 95% CI, 0.25-0.45), 16.6 vs 28.1 for patients with HRD/*BRCA*wt (HR, 0.43; 95% CI, 0.28-0.66), and 16.2 vs 16.6 for patients with HRp/HRD status unknown (HR, 0.92; 95% CI, 0.72-1.17).[21] The combination of olaparib and bevacizumab is currently listed as a frontline treatment option in the NCCN guidelines, and it gained FDA approval on May 8, 2020, for patients with tumors characterized by HRD (the companion diagnostic is the myChoice CDx test from Myriad).[3,19]

The VELIA/GOG-3005 randomized phase 3 trial is the only study that incorporated a PARP inhibitor (veliparib) both during and after frontline chemotherapy. This study enrolled women at the beginning of chemotherapy (making it distinct from SOLO-1, PRIMA, and PAOLA-1, all of which enrolled women who had responded to chemotherapy at the time of completion). Eligible women with stage III or IV HGSOC and good performance status were randomized in a 1:1:1 ratio to veliparib throughout vs veliparib with chemotherapy followed by placebo vs placebo throughout. The dosing of veliparib given with chemotherapy was 150 mg by mouth twice a day. Once maintenance had been reached, the dosage was increased to 300 mg and then 400 mg by mouth twice a day by cycle 7. Maintenance cycles were 21 days long

Table 2. Maturing Randomized Phase 3 Studies in the Frontline Treatment of Ovarian Cancer That Are Currently Enrolling Patients

Study	Agents/Arms	Population	Primary Endpoints	Status
IMagyn050/ GOG 3015/ ENGOT-OV39 (NCT03038100)	(a) Paclitaxel/carboplatin/bevacizumab/placebo × 6 ➔ bevacizumab/placebo maintenance × 15 cycles vs (b) Paclitaxel/carboplatin/bevacizumab/atezolizumab × 6 ➔ bevacizumab/atezolizumab maintenance × 15 cycles	Stage III/IV EOC patients who have residual disease after pCRS or who underwent NACT	Co-primary endpoints of PFS and OS in PD-L1+ and ITT	Completed, awaiting results
DUO-O/GOG 3025/ENGOT (NCT03737643)	Non-t*BRCA* (a) Paclitaxel/carboplatin/bevacizumab/placebo × 6 ➔ bevacizumab/placebo (IV)/placebo (po) (15 mo) vs (b) Paclitaxel/carboplatin/bevacizumab/durvalumab × 6 ➔ bevacizumab/durvalumab/placebo (po) (15 mo) vs (c) Paclitaxel/carboplatin/bevacizumab/durvalumab × 6 ➔ bevacizumab/durvalumab/olaparib (15 mo) t*BRCA* (open-label) Paclitaxel/carboplatin (+/-) bevacizumab/durvalumab × 6 ➔ (+/-) bevacizumab/durvalumab/olaparib (15 mo)	Stage III/IV EOC; both pCRS and NACT allowed	PFS in non-t*BRCA*	Still enrolling
FIRST/ ENGOT-OV44 (NCT03602859)	Randomization at cycle 2 following cycle 1 with paclitaxel/carboplatin (a) Paclitaxel/carboplatin (+/-) bevacizumab/placebo (IV) × 5 ➔ (+/-) bevacizumab/placebo (IV)/placebo (po) (36 mo) (discontinued with amendment 4) vs (b) Paclitaxel/carboplatin (+/-) bevacizumab/placebo (IV) × 5 ➔ (+/-) bevacizumab/placebo (IV)/niraparib (36 mo) vs (c) Paclitaxel/carboplatin (+/-) bevacizumab/dostarlimab × 5 ➔ (+/-) bevacizumab/dostarlimab/niraparib (36 mo)	Stage IV or Stage III with - >5-cm upper abdominal disease - residual disease Any NACT	PFS in PD-L1+ and ITT	Still enrolling
KEYLYNK-001/ GOG-3036/ ENGOT-OV43/ MK-7339 (NCT03740165)	Randomization at cycle 2 following cycle 1 with paclitaxel/carboplatin (a) Paclitaxel/carboplatin (+/-) bevacizumab/placebo (IV) × 5 ➔ (+/-) bevacizumab/placebo (IV)/placebo (po) (35 infusions) vs (b) Paclitaxel/carboplatin (+/-) bevacizumab/pembrolizumab × 5 ➔ (+/-) bevacizumab/pembrolizumab/placebo (po) (35 infusions) vs (c) Paclitaxel/carboplatin (+/-) bevacizumab/pembrolizumab × 5 ➔ (+/-) bevacizumab/pembrolizumab/olaparib (35 infusions)	Stage III/IV EOC; pCRS and NACT allowed	PFS and OS	Still enrolling
ATHENA/ GOG-3020/ ENGOT-OV45 (NCT03522246)	Randomization occurs following chemotherapy and requires a complete or partial response. Randomization ratio is 4:4:1:1. (a) Rucaparib/nivolumab × 24 mo (b) Rucaparib/placebo (IV) × 24 mo (c) placebo (po)/nivolumab × 24 mo (d) placebo (po)/placebo (IV) × 24 mo	Stage III/IV EOC with complete or partial response to platinum-based chemotherapy	PFS in homologous recombination–defined subgroups (t*BRCA*, non-t*BRCA*/LOH-high, non-t*BRCA*/LOH-low, non-t*BRCA*/LOH unknown)	Still enrolling

EOC, epithelial ovarian cancer; ENGOT, European Network of Gynaecological Oncological Trial Groups; GOG, Gynecologic Oncology Group; ITT, intention-to-treat; IV, intravenous; LOH, loss of heterozygosity; mo, months; NACT, neoadjuvant chemotherapy; OS, overall survival; pCRS, primary cytoreductive surgery; PD-L1, programmed death ligand 1; PFS, progression-free survival; po, by mouth; t*BRCA*, tumor *BRCA*-positive.

Source: ClinicalTrials.gov. Accessed May 10, 2020.

and continued until disease progression, toxicity, or cycle 30. The primary endpoint was PFS as assessed by the investigator in the veliparib-throughout group compared with the placebo-throughout group. This was analyzed sequentially in women with *BRCA*-associated cancers, then in those with HRD, and finally in the ITT group. HRD was measured with the same assay that was used in PRIMA and PAOLA, but the cut-off score for HRD was 33 or greater. It is worth reinforcing the differences between VELIA and the other trials; the mPFS values for VELIA included the time spent on chemotherapy as well as the contribution of women who had either progressed on chemotherapy or had stable disease; these women were not eligible for enrollment in the previously discussed trials. Among the women with *BRCA*-associated cancers, the mPFS was 22.0 vs 34.7 months (HR, 0.44; 95% CI, 0.28-0.68; *P*<.001). In the HRD population, the mPFS was 20.5 vs 31.9 months (HR, 0.57; 95% CI, 0.43-0.76; *P*<.001), and in the ITT population, the mPFS was 17.3 vs 23.5 months (HR, 0.68; 95% CI, 0.56-0.83). In non–hypothesis-tested subgroups, the HRs were as follows: mPFS of 15.1 vs 18.2 for *BRCA*wt (HR, 0.80; 95% CI, 0.64-0.997); mPFS of 19.8 vs 22.9 for HRD/*BRCA*wt (HR, 0.74; 95% CI, 0.52-1.06); and mPFS of 11.5 vs 15.0 for HRp (HR, 0.81; 95% CI, 0.60-1.09). Veliparib currently has neither an FDA indication nor an NCCN guideline listing.

The results of these 4 randomized trials represent great advancements for women with a diagnosis of EOC and provide a clear indication for maintenance therapy in the frontline setting. However, many questions remain. One question, given the results of SOLO-1 and PAOLA-1, is whether women with *BRCA*-associated cancers should also receive bevacizumab, or whether olaparib is enough. The second question that arises on the basis of many of the non–hypothesis-tested subgroup analyses is whether an HRD assay should be used to identify the women for whom PARP inhibitor treatment is appropriate.

Neither of these questions can be definitively answered at this point. However, interesting hypothesis-generating data were presented at the 2020 Society of Gynecologic Oncology annual meeting regarding these 2 issues. First, Vergote and colleagues presented population-adjusted indirect treatment comparisons of olaparib monotherapy vs olaparib plus bevacizumab, olaparib monotherapy vs bevacizumab monotherapy, and finally bevacizumab vs placebo; these were unanchored population-adjusted indirect comparisons of women with *BRCA*-associated tumors enrolled in PAOLA-1 vs those in SOLO-1. Propensity weighting of the PAOLA-1 patients was done to balance the covariates. In the comparison of olaparib plus bevacizumab vs olaparib monotherapy, the percentages of women who were disease-free in the 2 arms at 12, 24, and 36 months were 96% vs 88%, 82% vs 73%, and 70% vs 61%, respectively (HR, 0.71; 95% CI, 0.45-1.09). These data would suggest that the addition of bevacizumab may increase benefit, but that the benefit is at most additive.[22]

As to the second question, regarding using the HRD assay as a biomarker for selection, Swisher and colleagues conducted an exploratory analysis of the HRD assay as a continuum (rather than selected cut points) in predicting benefit from the addition of veliparib among patients with *BRCA*wt tumors. In this analysis, they evaluated the HR for veliparib throughout vs placebo among women with tumors that were HRD/*BRCA*wt and those with tumors that were HRp/*BRCA*wt. The HR for the effect of veliparib was the same in both groups (HRs, 0.77 and 0.76, respectively). The mPFS was different for each group, however; it was 20 vs 23 months in the HRD group and 12 vs 15 months in the HRp group. Across the continuum of HRD scores, benefit was seen even in patients with very low HRD scores. The conclusion of this analysis is that HR status may be prognostic in patients with EOC but does not appear to be predictive for the benefit of veliparib.[23] Additional analyses will add more to this discussion.

Conclusions

PARP inhibitors have dramatically changed the treatment landscape and oncologic outcomes for an ever-increasing number of patients with a diagnosis of ovarian cancer. We can anticipate that the use of PARP inhibitor maintenance therapy, with or without bevacizumab, will become more frequent in frontline management. The role of immunotherapy with or without PARP inhibition is being evaluated in ongoing studies (Table 2) and may again change the paradigm for best practice in frontline therapy.

Although these developments are exciting, and of great benefit to our patients, the percentage of women who experience long-term disease-free survival with the addition of PARP inhibition remains unknown because the survival data are not yet mature. We can tell on the basis of PFS curves alone that disease is still recurring in these women despite new therapeutic options. We can therefore consider the results achieved with PARP inhibition to be the new "baseline" for oncology outcomes, which we must continue to strive to improve.

Disclosures

Dr Moore reports advisory board participation with AbbVie, AstraZeneca, Aravive, Eisai, GSK/Tesaro, Genentech/Roche, Immunogen, Merck, Mersana, Myriad, Tarveda, and VBL Therapeutics, and research funding from PTC Therapeutics, Lilly, Merck, and GSK/Tesaro. Dr Pothuri has received honoraria related to consulting for Eisai, Merck, AstraZeneca,

GSK, and Clovis. Dr Monk has received honoraria related to consulting and speaking for Genentech/Roche, Merck, AstraZeneca, GSK, and Clovis. Dr Coleman has received research support from Clovis, GSK, AbbVie, AstraZeneca, and Merck, and has received honoraria related to consulting for Clovis, GSK, AbbVie, AstraZeneca, Merck, Aravive, Agenus, and Janssen.

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