PARP Inhibition in Recurrent Ovarian Cancer

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Abstract: With the introduction of PARP inhibitors into frontline chemotherapy, with or without bevacizumab, the hope exists that more women may be spared a recurrence of their ovarian cancer. Whether or not this proves to be true, the fact remains that many or most women with ovarian cancer will experience a recurrence requiring the use of additional active chemotherapy and targeted options. This manuscript summarizes the known data to date regarding the use of PARP inhibitors in the recurrent setting.

Keywords
Recurrent ovarian cancer, PARP inhibition

Introduction

Despite a nearly ubiquitous response to frontline platinum-based chemotherapy and surgery, approximately 80% of women with advanced ovarian cancer experience a recurrence within 3 years of diagnosis.[1] For women whose disease recurs more than 6 months after completion of their last platinum-based chemotherapy cycle, repeat administration of a platinum-based doublet, such as carboplatin/gemcitabine, carboplatin/pegylated liposomal doxorubicin, or carboplatin/paclitaxel, is considered the standard of care.[2,3] Layered onto this standard is the inclusion of bevacizumab concurrently with and following completion of chemotherapy.[4,5] Poly(ADP-ribose) polymerase (PARP) inhibitors are also approved as switch maintenance treatment following a response to platinum-based therapy in the recurrent setting, irrespective of biomarker status.[6-8] Additionally, PARP inhibitors are approved as treatment in lieu of chemotherapy for patients with *BRCA*-associated cancers in the third line and beyond,[6,8] and for those with platinum-sensitive homologous recombination–deficient tumors in the fourth line and beyond,[7] and they are listed by the National Comprehensive Cancer Network in combination with bevacizumab as treatment for patients with platinum-sensitive recurrent disease.[9] Ongoing clinical trials in all lines of treatment are evaluating combinations of therapies to improve efficacy in the treatment of biomarker-negative tumors, as well as to overcome acquired PARP inhibitor resistance due to prior use.

The first big approvals for epithelial ovarian cancer (EOC) therapy came with phase 3 trials in platinum-sensitive disease. Starting with bevacizumab[10] and eventually including olaparib (Lynparza, AstraZeneca),[8] rucaparib (Rubraca, Clovis Oncology),[6] and niraparib (Zejula, GSK/Tesaro),[7] the incorporation of targeted therapies along with and/or following platinum-based chemotherapy was transformative for the treatment of platinum-sensitive recurrent disease. Despite the lack of a significant change in incidence or overall mortality, the percentage of women living with ovarian cancer is higher than ever. This suggests that increased access to and appropriate use of novel therapies have incrementally improved progression-free survival (PFS), with each line of therapy contributing to longer survival.[11,12] This review, which is the second part of a 2-part series, focuses on the current status of PARP inhibitor (PARPi) use and development in recurrent EOC. (The first part focused on PARP inhibition in frontline therapy.)

PARP Inhibitor Maintenance Following Response to Platinum in the Recurrent Setting

The initial approvals for PARPi maintenance therapy in EOC were based on randomized trials in the setting of platinum-sensitive recurrent disease and, with the exception of the initial European Medicines Agency (EMA) approval, are largely biomarker independent.

The first study to demonstrate benefit from PARPi maintenance therapy was Study 19. This was a randomized, double-blind phase 2 study of the use of olaparib capsules vs placebo following a response to platinum-based chemotherapy in the recurrent setting. Eligible patients were randomized in a 1:1 ratio to olaparib capsules at 400 mg twice a day vs placebo. The primary endpoint was PFS. *BRCA1/2* status was known for 96% and 95% of the patients in the olaparib and placebo groups, respectively, and of these, 54.4% and 48.1%, respectively, had *BRCA*-associated cancers. Among all patients, the hazard for progression or death was reduced by 65% (hazard ratio [HR], 0.35; 95% CI, 0.25-0.49; *P*<.001). The median PFS (mPFS) improved from 4.8 months to 8.4 months. Among those patients with *BRCA*-associated cancers, the benefit was even more profound, with a reduction in the hazard for progression or death of 82% (HR, 0.18; 95% CI, 0.10-0.31; *P*<.0001). The mPFS improved from 4.3 to 11.2 months. Even in the subgroup of patients with *BRCA* wild-type (*BRCA*wt) tumors, the HR was 0.54 (95% CI, 0.34-0.85; *P*=.0075).[13] These data led to the EMA approval of olaparib capsules on October 23, 2014, as maintenance following response to platinum-based chemotherapy for patients with *BRCA*-associated EOC.[14] Overall survival (OS) also was reported for Study 19, with an apparent advantage in median overall survival (mOS) of 27.8 vs 29.8 months (HR, 0.73; 95% CI, 0.55-0.95; nominal *P*=.021). Although it appears statistically significant, 3 analyses of this endpoint were conducted that required consideration of multiple comparisons. As such, the difference in OS was directionally interesting but hypothesis-generating only.[15]

In the United States, approval for the use of olaparib in this setting was based on the randomized, double-blind phase 3 SOLO2 study. SOLO2 used the tablet formulation of olaparib, which reduced the pill burden from 8 capsules twice a day to 2 tablets twice a day. Eligible patients were those with platinum-sensitive, recurrent *BRCA*-associated high-grade serous ovarian cancer (HGSOC) or high-grade endometrioid ovarian cancer (HGEOC) who had responded to platinum-based chemotherapy and had excellent performance status. They were randomized in a 2:1 ratio to olaparib tablets at 300 mg twice a day vs placebo, and the primary endpoint was investigator-assessed PFS. SOLO2 demonstrated significant benefit for the use of olaparib, with an improvement in mPFS from 5.5 to 19.1 months (HR, 0.30; 95% CI, 0.22- 0.41; *P*<.0001). Furthermore, at 24 months, 43% of the patients randomly assigned to olaparib remained disease-free, compared with 15% of those randomized to placebo.[16]

Subsequent subgroup analysis of the patients who entered SOLO2 with or without measurable disease has also provided interesting results. Among patients who entered the trial with measurable disease, the response rate was 41.1% for those randomized to olaparib, compared with 17.1% for those who received placebo. When patients with a complete response vs a partial response at study entry were assessed for magnitude of response to olaparib, the results were highly consistent. The mPFS among patients with a complete response who received olaparib was not reached, compared with 5.6 months for those who received placebo (HR, 0.26; 95% CI, 0.16-0.42). Among patients with a partial response who received olaparib, the mPFS was 13.8 months, compared with 5.5 months for those who received placebo (HR, 0.37; 95% CI, 0.25-0.54).[17]

SOLO2 led to US Food and Drug Administration (FDA) approval for olaparib as maintenance treatment in platinum-sensitive recurrent HGSOC on August 17, 2017.[8] Of note, this indication was biomarker-agnostic, as the benefit to patients from Study 19 with *BRCA*wt tumors was also considered. At the American Society of Clinical Oncology (ASCO) virtual meeting in 2020, the OS endpoint was presented. This demonstrated a nonadjusted OS improvement of 12.9 months (mOS of 51.7 in the olaparib group vs 38.8 months in the placebo group). The HR was 0.74 (95% CI, 0.54-1.00; *P*=.0537), although 38% of the patients who were randomized to placebo received a PARPi as a part of subsequent lines of therapy.[18]

The first PARPi to receive FDA approval for maintenance treatment of platinum-sensitive recurrent ovarian cancer was niraparib; approval was based on results of

the NOVA (ENGOT-OV16) trial. This study enrolled patients with platinum-sensitive recurrent HGSOC who had responded to platinum-based chemotherapy (no measurable disease >2 cm) and whose cancer antigen 125 (CA125) level was either normal or more than 90% reduced from baseline. NOVA comprised 2 cohorts; one evaluated patients with germline *BRCA*–associated cancers, and the other enrolled patients with germline *BRCA*wt HGSOC (but importantly, did include patients with somatic *BRCA*-mutated tumors). In both cohorts, patients were randomly assigned in a 2:1 ratio to either niraparib at 300 mg by mouth each day or placebo until progression or toxicity. The primary endpoint was PFS as assessed by independent radiographic review in 3 predefined analytic groups: germline *BRCA* (g*BRCA*), g*BRCA*wt/homologous recombination–deficient (HRD), and all-*BRCA*wt if significant in the g*BRCA*wt/HRD group. HRD was measured with the Myriad assay; a score of 42 or higher defined HRD. Use of niraparib maintenance resulted in improvement in PFS in all 3 predefined analytic groups. In the g*BRCA* group, mPFS was 21.0 months with niraparib vs 5.5 months with placebo (HR, 0.27; 95% CI, 0.173-0.410; *P*<.0001). In the g*BRCA*wt/HRD group, mPFS was 12.9 months with niraparib vs 3.8 months with placebo (HR, 0.38; 95% CI, 0.243-0.586; *P*<.0001). In the all-*BRCA*wt group, mPFS was 9.3 with niraparib vs 3.9 months with placebo (HR, 0.45; 95% CI, 0.338-0.607; *P*<.001).

In prespecified exploratory analyses, the benefit of niraparib was studied in patients whose tumors harbored somatic *BRCA* mutations (s*BRCA*). Overall, the mPFS in patients with these mutations was 20.9 months in the niraparib group vs 11 months in the placebo group (HR, 0.27; 95% CI, 0.081-0.903). Among patients with tumors that were s*BRCA*wt/HRD, the mPFS was 9.3 months in the niraparib group vs 3.7 months in the placebo group (HR, 0.38; 95% CI, 0.23-0.63). Among patients with HRp tumors, the mPFS was 6.9 months in the niraparib group vs 3.8 months in the placebo group (HR, 0.58; 95% CI, 0.361-0.922).[19] These findings led to FDA approval on March 27, 2017, for niraparib maintenance therapy following response to platinum-based therapy in the recurrent setting, irrespective of biomarker status.[7]

Use of a starting dose of niraparib of 300 mg by mouth daily resulted in dose reductions in more than 66% of patients and dose interruptions in nearly 70% of patients. The most common reason for dose modification was thrombocytopenia; grade 3 or higher thrombocytopenia occurred in 33.8% of patients.[19] Subsequent analysis with Rapid Adjustment of Dose to Reduce Adverse Reactions (RADAR) identified risk factors for severe thrombocytopenia: a starting body weight below 77 kg and/or a baseline platelet count below 150,000/μL. The risk for grade 3 or higher thrombocytopenia was 12% for patients without either of these findings vs 35% for patients with either risk factor.[20]

The final platinum-sensitive maintenance trial presented here is ARIEL3, which is a randomized, placebo-controlled phase 3 study of the PARPi rucaparib in patients with platinum-sensitive recurrent HGSOC or HGEOC that has responded to platinum-based therapy. Patients were randomized in a 2:1 fashion to rucaparib at 600 mg orally twice a day or placebo until progression or toxicity. The primary endpoint was investigator-assessed PFS in 3 populations analyzed in a hierarchical fashion: (1) tumor *BRCA* (germline or somatic; t*BRCA*); (2) HRD (as measured by loss of heterozygosity [LOH] with an assay from Foundation Medicine, Cambridge, Massachusetts); and (3) intention-to-treat (ITT). The use of rucaparib was effective in all analytical subgroups. In the t*BRCA* group, mPFS was 16.6 months with rucaparib vs 5.4 months with placebo (HR, 0.23; 95% CI, 0.16-0.34; *P*<.0001). In the HRD group (inclusive of t*BRCA*), mPFS was 13.6 months with rucaparib vs 5.4 months with placebo (HR, 0.32; 95% CI, 0.24-0.42; *P*<.0001). In the ITT group (inclusive of HRD and t*BRCA*), mPFS was 10.8 months with rucaparib vs 5.4 months with placebo (HR, 0.36; 95% CI, 0.30-0.45; *P*<.0001). In exploratory analyses, the benefit of rucaparib over placebo was maintained in the group of tumors that were *BRCA*wt but high in LOH, with mPFS values of 9.7 vs 5.4 months, respectively (HR, 0.44; 95% CI, 0.29-0.66; *P*<.0001). The benefit of rucaparib over placebo also was maintained in the group of tumors that were *BRCA*wt/LOH-low, with mPFS values of 6.7 vs 5.4 months, respectively (HR, 0.58; 95% CI, 0.4-0.85; *P*=.0049). In patients with measurable disease on enrollment, the overall response rates (ORRs) were 38%, 27%, and 18% in the 3 analytical groups.[21] These data led to FDA approval of rucaparib on April 16, 2018, as maintenance therapy in patients with platinum-sensitive recurrent disease.[6]

These 4 trials (summarized in Table 1) have established a new standard of care for women with a recurrence of platinum-sensitive ovarian cancer that has responded to platinum-based therapy. All of these trials were performed in patients who had no prior PARPi exposure. The challenge facing providers now and in the future is what to do for patients previously treated with a PARPi as frontline maintenance therapy. Efficacy data are not yet available for this "PARPi after PARPi" concept. Certainly, the biomarker status and history of response to and progression on prior PARPi treatment will be important determinants for re-response to PARPi monotherapy. Ongoing trials include OReO/ENGOT Ov-38 (NCT03106987), a phase 3 trial of olaparib maintenance re-treatment in patients with EOC, and DUETTE (NCT04239014), which is comparing olaparib vs olaparib/ceralasertib as maintenance in participants with EOC who previously received PARPi treatment. Another ongoing trial, ICON9 (NCT03278717), is a phase 3 randomized study to evaluate the efficacy of maintenance olaparib

Table 1. Randomized Phase 3 Studies of PARP Inhibitors in Recurrent Platinum-Sensitive Disease

Study	Study 19[13]	SOLO2[16] (g*BRCA*m)	NOVA[19] (g*BRCA*m)	NOVA[19] (non-g*BRCA*m)	ARIEL3[21] (t*BRCA*m)	ARIEL3[21] ITT
Agent	**Olaparib**	**Olaparib**	**Niraparib**	**Niraparib**	**Rucaparib**	**Rucaparib**
Difference in mPFS, mo	8.4 vs 4.8	19.1 vs 5.5	21.0 vs 5.5	9.3 vs 3.9	16.6 vs 5.4	10.8 vs 5.4
PFS HR, investigator assessed	**0.35** (95% CI, 0.25-0.49; *P*<.001)	**0.30** (95% CI, 0.22-0.41; *P*<.0001)	**0.27** (95% CI, 0.17-0.41)	**0.53** (95% CI, 0.41-0.68)	**0.23** (95% CI, 0.16-0.34; *P*<.0001)	**0.36** (95% CI, 0.30-0.45; *P*<.0001)
PFS HR, BICR	**0.39** (95% CI, 0.27-0.55; *P*<.001)	**0.25** (95% CI, 0.18-0.35; *P*<.0001)	**0.27** (95% CI, 0.17-0.41; *P*<.0001)	**0.45** (95% CI, 0.34-0.61; *P*<.0001)	**0.20** (95% CI, 0.13-0.32; *P*<.0001)	**0.35** (95% CI, 0.28-0.45; *P*<.0001)

BICR; blinded independent central radiographic review; g*BRCA*m, germline *BRCA*-mutated; HR, hazard ratio; ITT, intention-to-treat; mo, months; mPFS, median progression-free survival; t*BRCA*m, germline or somatic *BRCA*-mutated.

and cediranib vs olaparib monotherapy in PARPi-naive patients with relapsed platinum-sensitive EOC following a response to platinum-based chemotherapy. PARPi-naive patients may become less common now that PARP inhibitors have new frontline indications.[22]

Nonchemotherapy Options With PARP Inhibitors

Several nonchemotherapy approaches to treating recurrent ovarian cancer with PARP inhibitors are available. PARP inhibitors can be used as monotherapy, in combination with immunotherapy, or in combination with antiangiogenic agents (Table 2).

PARP Inhibitors As Monotherapy

The efficacy of PARP inhibitors as monotherapy in biomarker-selected populations has been demonstrated in 3 single-arm phase 2 trials. Study 42, the initial study of olaparib, led to accelerated FDA approval of this agent on December 19, 2014.[8] Study 42 was a basket trial that included patients with *BRCA*-associated EOC. In this population of patients, who were classified as either resistant to or inappropriate for further platinum treatment and who had at least 3 lines of chemotherapy, olaparib resulted in an ORR of 31% (95% CI, 24.6-38.1) and a duration of response of approximately 8 months.[8,23] Additional, similar data sets came from ARIEL2 and Study 10. These were both single-arm, phase 2 studies of rucaparib—ARIEL2 in recurrent ovarian cancer and Study 10 in *BRCA*-associated ovarian cancers. In a combined analysis that evaluated just those patients from each study who had either a germline or somatic *BRCA* mutation and had received at least 2 lines of chemotherapy, the ORR was 54% (95% CI, 44%-64%) and the median duration of response was 9.2 months (95% CI, 6.6-11.6). These findings resulted in FDA approval of rucaparib for patients who had germline or somatic *BRCA*-associated cancers with 2 or more prior lines of therapy.[6,24,25] Most recently, niraparib was approved for patients with platinum-sensitive recurrent HRD ovarian cancer who had received at least 3 prior lines of chemotherapy.[7] Approval was based on the QUADRA study, which was a phase 2, open-label, single-arm study evaluating niraparib in patients with relapsed EOC who had received at least 3 prior chemotherapy regimens. The primary endpoint for this study was ORR among patients with platinum-sensitive recurrent disease who were identified as having HRD tumors. ORR in the primary efficacy population was 27.7% (95% CI, 15.6-42.6), and mOS was 17.2 months.[26]

Although they definitely demonstrated the potential efficacy of PARPi monotherapy instead of chemotherapy, none of the aforementioned studies was randomized. Therefore, it was not understood whether a PARPi was equivalent or superior to chemotherapy. Surprisingly, an early randomized trial of 2 different dosing levels of olaparib vs pegylated liposomal doxorubicin (PLD) in women with recurrent *BRCA*-associated cancer demonstrated comparable efficacy of olaparib capsules at 200 mg twice daily vs olaparib capsules at 400 mg twice daily vs PLD at 50 mg/m^2 every 28 days, with mPFS values of 6.5, 8.8, and 7.1 months, respectively. The efficacy of PLD in *BRCA*-associated cancers in this study, and the fact that olaparib was at least as effective as chemotherapy, led to enthusiasm for continuing this line of research.[27]

As one example, NRG-GY004 (NCT02446600) is a phase 3 study comparing single-agent olaparib vs the combination of cediranib and olaparib vs standard platinum-based chemotherapy in patients with recurrent platinum-sensitive EOC. Eligible patients had received no more than 3 prior lines of chemotherapy, had measurable disease, and were PARPi-naive at the beginning of the study. The platinum-based chemotherapy regimen was at the discretion of the treating physician, and the study was

Table 2. Nonchemotherapy Clinical Trials Using PARP Inhibitors

	Agent	Study	Population	ORR	DOR	mPFS	mOS
Monotherapy	Olaparib	Study 42[23]	g*BRCA*m, >3 lines	31%	225 d	7.0 mo	16.6 mo
		Olaparib 200 mg vs olaparib 400 mg vs PLD 50 mg/m^2 [27]	g*BRCA*m	25% vs 31% vs 18%	6.0 vs 6.8 vs 5.5 mo	6.5 vs 8.8 vs 7.1 mo	NA
		SOLO3: olaparib vs IC chemotherapy[33]	g*BRCA*m, plat-sensitive, >2 lines	72% vs 51%	NA	13.4 vs 9.2 mo	NA
	Rucaparib	ARIEL2[25]	t*BRCA*m	54%	9.2 mo	11.1 mo	NA
		ARIEL4: rucaparib vs IC chemotherapy (NCT02855944)[31]	t*BRCA*m	Study ongoing			
	Niraparib	QUADRA[26]	t*BRCA*m or plat-sensitive and HRD+; >3 prior lines	27.7%	9.2 mo	NA	17.2 mo
Combination with immunotherapy	Olaparib	Olaparib + durvalumab[38]	Recurrent EOC; plat-resistant	15%	NA	NA	NA
	Niraparib	TOPACIO: niraparib + pembrolizumab[36]	Recurrent EOC; plat-resistant	18%	NR	3.4 mo	Immature
		MOONSTONE: niraparib + dostarlimab (NCT03955471)	Recurrent EOC; plat-resistant	Ongoing			
Combination with anti-angiogenesis	Olaparib	Olaparib vs olaparib + cediranib[40]	Recurrent EOC; plat-sensitive	47.8% vs 79.6%	NA	9 vs 17.7 mo	NA
		NRG-GY004: olaparib vs olaparib + cediranib vs IC chemotherapy[28]	Recurrent EOC; plat-sensitive	52.4% vs 69.4% vs 71.3%	NR	8.2 vs 10.4 vs 10 mo	31 vs 29 vs 30.1 mo
		NRG-GY005: olaparib vs cediranib vs olaparib + cediranib v IC chemotherapy (NCT02502266)	Recurrent EOC; plat-resistant	Ongoing			
	Niraparib	AVANOVA2: niraparib vs niraparib + bevacizumab[43]	Recurrent EOC; plat-sensitive	27% vs 60%	NA	5.5 vs 11.9 mo	Immature

d, days; DOR, duration of response; EOC, epithelial ovarian cancer; g*BRCA*m, germline *BRCA* mutation; HRD, homologous recombination–deficient; IC, investigator's choice; mo, months; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; NA, not applicable/not reported; NR, not reached; PLD, pegylated liposomal doxorubicin; plat, platinum; t*BRCA*m, germline or somatic *BRCA* mutation.

designed with PFS as its primary endpoint. The researchers found that results in the 2 olaparib-containing arms were not superior to those in the chemotherapy arm, with mPFS values of 10, 8.2, and 10.4 months in the chemotherapy, olaparib, and olaparib/cediranib arms, respectively. When the chemotherapy control was used as the reference, the HR for olaparib monotherapy was 1.2, but that for olaparib/cediranib was 0.856 (95% CI, 0.663-1.105; *P*=.077). In the prespecified *BRCA*-associated cancer subgroup, the mPFS results were 10.5, 12.7, and 18 months, respectively. This was not a hypothesis-tested subgroup, so no HR was given. Ongoing analysis based on HRD may be of interest.[28] The lack of maintenance therapy included in the control arm may bring the results and applicability of this

Table 3. Randomized Phase 2/3 Studies Currently Enrolling Patients With Recurrent, Platinum-Sensitive EOC

Study	Agents/Arms	Population	Primary Endpoints	Status
ICON9 (NCT03278717)[22]	(a) Olaparib 300 mg PO BID (b) Olaparib 300 mg PO BID + cediranib 20 mg PO QD (switch maintenance following response to reinduction chemotherapy)	Recurrent platinum-sensitive EOC with response to reinduction platinum-based chemotherapy	PFS and OS	Enrolling
ENGOT-OV41/ GEICO69-O/ANITA (NCT03598270)[45]	(a) Carboplatin + PC chemo and placebo followed by maintenance niraparib 200 or 300 mg (b) Carboplatin plus PC chemo and atezolizumab 1200 mg followed by niraparib 200 or 300 mg and atezolizumab 1200 mg IV every 3 weeks	Recurrent platinum-sensitive EOC	PFS	Enrolling
NSGO/AVANOVA Triplet (NCT03806049)[46]	(a) Niraparib + bevacizumab + dostarlimab (b) Niraparib + bevacizumab (c) Carboplatin + paclitaxel	Recurrent platinum-sensitive EOC (HGSOC or HGEOC)	PFS	Not yet enrolling
OReO (NCT03106987)[47]	(a) Olaparib 300 mg PO BID (b) Placebo 300 mg PO BID (switch maintenance after response to reinduction platinum-based chemotherapy)	Recurrent platinum-sensitive EOC with exposure to prior PARPi	PFS	Still enrolling
DUETTE (NCT04239014)[48]	(a) Ceralasertib 160 mg PO days 1-7 + olaparib 300 mg PO BID (b) Olaparib 300 mg PO BID (c) Placebo (switch maintenance following response to reinduction platinum-based chemotherapy)	Recurrent platinum-sensitive EOC with exposure to prior PARPi	PFS	Not yet enrolling

BID, twice a day; EOC, epithelial ovarian cancer; HGSOC, high-grade serous ovarian cancer; HGEOC, high-grade endometrioid ovarian cancer; IV, intravenously; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PC, physician's choice; PFS, progression-free survival; PO, orally; PC chemo, physician's choice platinum-based chemotherapy; QD, each day.

study's findings into question, especially given the rapid change in standard of care since this trial opened.[29]

NRG-GY005 (NCT02502266) is a randomized phase 2/3 study comparing the combination of cediranib and olaparib vs cediranib or olaparib monotherapy vs standard-of-care nonplatinum chemotherapy in patients with recurrent platinum-resistant EOC. After the phase 2 portion of the trial completed accrual, the independent data monitoring committee reviewed outcomes and elected to reopen the phase 3 portion of the trial without the option to randomize to single-agent olaparib. The phase 3 portion of the trial is currently open and continuing to accrue,

with an estimated completion in late 2020.[30]

ARIEL4 (NCT02855944) is a randomized phase 3 study of rucaparib vs chemotherapy in relapsed germline or somatic *BRCA*-associated EOC. The primary endpoint of the study is PFS. A notable difference between this trial and SOLO3 (discussed next) is that ARIEL4 does allow investigator's choice of platinum as an option for those enrolled patients with a platinum-free interval of 6 to 12 months. Trial accrual is ongoing.[31]

SOLO3 (NCT02282020) is a randomized phase 3 trial of olaparib vs chemotherapy in patients with platinum-sensitive relapsed *BRCA*-associated EOC. Patients had to have received at least 2 prior lines of platinum-based chemotherapy. Chemotherapy was investigator's choice and included weekly paclitaxel, topotecan, PLD, or gemcitabine. This study was originally designed with a PFS endpoint, but as PARP inhibitors became available for use, the population of patients who were PARPi-naive became smaller. As a result, the study was amended to stop early, and the endpoint was changed to ORR.[32] With ORR as an endpoint, SOLO3 did meet its primary endpoint; the ORR was 72% for olaparib vs 51% for investigator's choice (odds ratio, 2.53; 95% CI, 1.40-4.58; *P*=.002). When the patients were categorized according to number of prior lines of chemotherapy, those who had only 2 prior lines had an ORR of 85% with olaparib vs 62% with investigator's choice (odds ratio, 3.44; 95% CI, 1.42-8.54); those who had 3 or more prior lines had an ORR of 59% with olaparib vs 39% with investigator's choice (odds ratio, 2.21; 95% CI, 0.96-5.20). The study was able to present PFS data, reporting mPFS values of 13.4 vs 9.2 months (HR, 0.62; 95% CI, 0.43-0.91; *P*=.013).[33]

PARP Inhibitor Combinations: Immunotherapy

PARP inhibitors have been found to upregulate programmed death–ligand 1 (PD-L1), upregulate stimulator of interferon genes (STING),[34] and enhance immune cell infiltration into tumors, all of which provide a rationale for the combination of PARP inhibitors and immunotherapy agents.[35]

The phase 1/2 clinical trial TOPACIO evaluated the anti–PD-L1 monoclonal antibody pembrolizumab (Keytruda, Merck) along with niraparib in patients who had recurrent platinum-resistant EOC. Niraparib was given at 200 mg by mouth daily along with pembrolizumab at 200 mg intravenously every 21 days. Notably, 73% of the participants were *BRCA*wt. The confirmed ORR was 18% and did not vary by *BRCA* or HRD status. The median duration of response was not reached.[36,37] A phase 2 study of the anti–PD-L1 monoclonal antibody durvalumab (Imfinzi, AstraZeneca) along with olaparib was conducted in 35 patients. Of these 35 patients, 17% had *BRCA*-associated EOC. The ORR was 15%, with 2 of 5 partial responses occurring in patients who had a *BRCA*-associated cancer (NCT02484404).[38]

The randomized controlled ENGOT-Ov41/GEICO 69-0/ANITA (NCT03598270) trial is being conducted in patients with platinum-sensitive recurrent EOC. Patients receive platinum-based chemotherapy plus placebo for 6 cycles, then niraparib plus placebo maintenance vs platinum-based chemotherapy plus atezolizumab followed by niraparib plus atezolizumab maintenance. The primary endpoint is PFS, with a target HR of 0.70. This study is still accruing patients.[39]

PARP Inhibitor Combinations: Antiangiogenic Agents

Perhaps some of the most promising combinations are PARP inhibitors plus antiangiogenic agents; studies evaluating these are maturing. The first to report positive data was the study of Liu and colleagues, a randomized phase 2 trial that enrolled patients with platinum-sensitive recurrent EOC. Patients were randomized to olaparib monotherapy (400-mg capsules twice daily) vs olaparib/cediranib (200-mg capsules twice daily/30 mg once daily), with PFS as an endpoint. The results for mPFS were 9 months (95% CI, 5.7-16.5) vs 17.7 months (95% CI, 14.7 to not reached) in the monotherapy vs combination arms, respectively (HR, 0.42; 95% CI, 0.23-0.76).[40] This study provided the preliminary data for NRG-GY004, which was discussed previously. ENGOT-OV24-NSGO/AVANOVA1 (NCT02354131) sought to evaluate the safety and recommended phase 2 dose for the combination of niraparib and bevacizumab. In addition to this, it reported a promising ORR of 45%, and the mPFS was 49 weeks.[41,42] These results led to ENGOT-OV24-NSGO/AVANOVA2 (NCT02354131), a randomized phase 2 study of niraparib vs niraparib/bevacizumab in patients with platinum-sensitive recurrent EOC. Here, the mPFS was 11.9 vs 5.5 months (HR, 0.35; 95% CI, 0.21-0.57; *P*<.001) in the combination vs monotherapy arms, respectively. When patients were stratified by HRD status, the combination resulted in an HR of 0.38 (95% CI, 0.20-0.72; *P*=.0019) in the HRD subgroup and an HR of 0.40 (95% CI, 0.19-0.85; *P*=.0129 in the HRp subgroup. The ORRs among the ITT population were 60% vs 27% (odds ratio, 4.23; 95% CI, 1.79-9.97) for the combination of niraparib/bevacizumab vs niraparib.[43]

Conclusions

PARP inhibitors have dramatically changed the landscape and oncologic outcomes for an ever-increasing number of patients with a diagnosis of ovarian cancer. We can anticipate that the use of PARPi maintenance, with or without bevacizumab, will increase as a part of frontline management, and the data summarized in this review will be pertinent to the care of those patients without frontline PARPi exposure. The American Society of Clinical Oncology (ASCO) recently released a guideline for PARPi use in epithelial ovarian cancer that can be used to

Table 4. ASCO Guidelines on the Use of PARP Inhibitors in the Management of Ovarian Cancer

Maintenance therapy (1L) • Stage III-IV EOC • CR or PR to plat-based CT	• All patients *should be* offered PARPi maintenance therapy with niraparib • Patients with t*BRCA* mutations *should be* offered olaparib or niraparib • Olaparib + bevacizumab *may be* offered to patients with t*BRCA* mutations and/or genomic instability, as assessed by an FDA-approved test, who are in CR or PR to CT + bevacizumab
Maintenance therapy (≥2L) • Response to plat-based CT	• Single-agent PARPi *may be* offered to patients who have not received a PARPi, regardless of *BRCA* mutation status
Treatment of recurrent EOC	• PARPi *should be* offered to patients with recurrence >6 months after plat-based CT who – have not received a PARPi, and – have a t*BRCA* mutation or genomic instability as assessed by an FDA-approved test
Other recommendations	• PARPi are *not recommended* for use in combination with CT, other targeted agents, or immunotherapy agents in the recurrent setting outside clinical trials • PARPi are *not recommended* at this time for re-treatment; data to support reuse of PARP inhibitors in any setting are needed

1L, first-line; 2L, second-line; ASCO, American Society of Clinical Oncology; CR, complete response; CT, chemotherapy; EOC, epithelial ovarian, tubal, or primary peritoneal cancer; FDA, US Food and Drug Administration; t*BRCA*, germline or somatic breast cancer gene; PARPi, poly(ADP-ribose) polymerase inhibitor; PR, partial response; plat, platinum.

Source: Tew WP et al. *J Clin Oncol.* doi:10.1200/JCO.20.01924.[49]

guide treatment in PARPi-naive patients (Table 4).

However, for the care of patients who receive a PARPi during frontline therapy and then experience a recurrence, best practice is as yet unknown. We do not know if a PARPi still provides benefit for a patient who received a maintenance PARPi for 2 to 3 years but did not progress during treatment, or for a patient whose disease progressed during frontline maintenance PARPi treatment but then responded to re-treatment with platinum-based therapy. The response to platinum is suggestive of the continued loss of homologous recombination repair and possibly the efficacy of subsequent PARPi maintenance. We must also determine if we can convert PARPi-resistant tumors into sensitive ones with combinations with antiangiogenic agents, immunotherapy agents, or other assets that target different aspects of the DNA damage pathway, such as ATR/ATM, CHK1/2, WEE1, and phosphoinositide 3-kinase (PI3K), to name a few.[44] Fortunately, as described previously and in Table 3, studies of "PARP inhibition after PARP inhibition" are ongoing, and novel combination strategies in biomarker-directed subgroups are entering clinical trials. These studies will provide answers and new opportunities to continue to overcome resistance mechanisms, with the ultimate goal of prolonging our patients' survival.

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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