Update on PARP Inhibitors for the Treatment of Ovarian Cancer

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Abstract: Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors (PARPis) were first granted US Food and Drug Administration (FDA) approval for ovarian cancer. Trials have focused on high-grade serous histology, in which *BRCA* mutations and homologous recombination deficiency (HRD) are most common. The initial clinical trials of PARPis were performed in patients with heavily pretreated recurrent *BRCA*-mutated (*BRCA*m) ovarian cancer. Since then, concerns over possible reductions in overall survival with long-term PARPi treatment in recurrent disease have led to the withdrawal of most FDA approvals in this setting, and the use of PARPis has moved to the maintenance setting in newly diagnosed advanced ovarian cancer, in which trials have demonstrated significant progression-free survival benefits and trends for overall survival benefit with certain PARPis in patients who have *BRCA* mutations. Additionally, the risks of secondary acute myeloid leukemia and myelodysplastic syndrome are lower in the newly diagnosed setting than in the recurrent setting, potentially because of a predefined duration of PARPi treatment and/or less prior exposure to chemotherapy. Currently, several PARPis are FDA-approved in ovarian cancer: (1) olaparib (*BRCA*m), niraparib (*BRCA*m and *BRCA* wild-type [*BRCA*wt]), and olaparib/bevacizumab (*BRCA*m and *BRCA*wt/HRD) as maintenance therapy after platinum in newly diagnosed advanced disease; and (2) olaparib, niraparib, and rucaparib for recurrent *BRCA*m platinum-sensitive disease. This review discusses PARPi data in the newly diagnosed and recurrent settings, how current FDA approvals have evolved, and PARPi combination data.

Keywords
BRCA mutations, homologous recombination deficiency, ovarian cancer, PARP inhibitors

Introduction

High-grade serous ovarian cancer (HGSC) has been ideal for studying the use of poly(adenosine diphosphate-ribose) polymerase inhibitors (PARPis) in ovarian cancer because of the frequent presence of underlying homologous recombination deficiency (HRD),

which occurs in approximately 50% of these tumors. Notably, approximately 22% of the tumors harbor *BRCA* mutations, either germline or somatic.[1] PARPis were initially tested as single agents in relapsed *BRCA*-mutated (*BRCA*m) ovarian cancer, leading to the first US Food and Drug Administration (FDA) approval of a PARPi, olaparib, in December 2014 for heavily treated *BRCA*m ovarian cancer. Approvals followed for PARPis in the recurrent platinum-sensitive maintenance setting on the basis of 3 phase 3 studies and, finally, in the upfront maintenance setting for platinum-sensitive high-grade cancers, in which these agents are now used predominantly. However, beginning in 2022, several FDA approvals of PARPis were voluntarily withdrawn in the recurrent setting, including those for (1) heavily treated recurrent *BRCA*m or HRD ovarian cancer and (2) non-*BRCA*m or *BRCA* wild-type (*BRCA*wt) platinum-sensitive disease as maintenance. PARPis have been associated with certain described toxicities, including the risk of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), which is highest in the setting of relapsed, heavily pretreated *BRCA*m disease and appears to be lowest when PARPis are used upfront as maintenance treatment in patients with newly diagnosed disease. In this review, the development and use of single-agent PARPis are discussed chronologically by different settings in the course of the diagnosis and treatment of disease, starting with newly diagnosed advanced ovarian cancer, moving on to platinum-sensitive recurrent ovarian cancer, and then to heavily pretreated *BRCA*m ovarian cancer. Additionally, data on PARPi combinations are discussed.

PARPi Maintenance in Newly Diagnosed Ovarian Cancer

Four phase 3 studies have tested PARPi maintenance in newly diagnosed advanced ovarian cancer. Three of these studies, SOLO1 (olaparib; Lynparza, AstraZeneca),[2-4] PRIMA (niraparib; Zejula, GSK),[5,6] and ATHENA (rucaparib; Rubraca, Clovis Oncology),[7-9] have tested PARPis vs placebo as maintenance therapy following response to upfront platinum and taxane chemotherapy and prescribed for a defined period. The fourth study, PAOLA-1, tested bevacizumab maintenance vs bevacizumab/olaparib maintenance after platinum/taxane chemotherapy.[10-12] These trials and their results are described in Table 1. In all of them, the primary endpoint was progression-free survival (PFS), randomization was 2:1 in the experimental vs the control arm, all patients enrolled had either stage III or IV cancer, and patients needed to be in a complete or partial response following completion of chemotherapy. Secondary endpoints included overall survival (OS), time to progression on second-line therapy (PFS2), time to first and second subsequent therapies, toxicities, and quality of life.

SOLO1 enrolled patients with *BRCA*m (either somatic or germline) stage III or IV HGSC or high-grade endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (moving forward, the term *ovarian cancer* will encompass all 3 of these diagnoses).[2] Most patients in SOLO1 had stage III cancer; 15.4% of the patients randomized to olaparib and 19.8% of the patients randomized to placebo had stage IV disease. Of the patients who received olaparib, 61.9% had upfront surgery, 36.2% had interval surgery, and 1.5% had no surgery. Of the patients who received placebo, 64.9% had upfront surgery, 32.8% had interval surgery, and 2.3% did not have surgery.

In the primary analysis, the PFS rate at 3 years (the absence of disease progression and death) was 60% in the olaparib group vs 27% in the placebo group (hazard ratio [HR], 0.30; 95% CI, 0.23-0.41; $P<.001$).[2] In an updated PFS analysis conducted after a 5-year follow-up,[3] the median PFS (mPFS) was 56.0 months in the olaparib group vs 13.8 months in the placebo group (HR, 0.33; 95% CI, 0.25-0.43). Median OS (mOS) was assessed at 7 years[4] and was not reached in the olaparib arm vs 75.2 months in the placebo arm (HR, 0.55; 95% CI, 0.40-0.76; $P=.0004$.). Significance was not met for OS. A total of 44.3% of patients who received placebo eventually crossed over to a PARPi for future treatment. The incidence of MDS/AML was 1.5% in the olaparib group and 0.8% in the placebo group.[4] On December 19, 2018, the FDA approved olaparib for maintenance treatment in patients with newly diagnosed advanced *BRCA*m ovarian cancer in complete or partial response to first-line platinum-based chemotherapy, and this became a new standard of care for this group of patients. The approval is noteworthy not only because the mPFS was improved for olaparib vs placebo but also because a meaningful trend toward OS improvement was observed even though 44.3% of the placebo patients later crossed over to a PARPi. Additionally, the proportion of patients who had not initiated a subsequent line of therapy—a measure that can serve as a proxy estimate of evidence of disease recurrence—was 45.3% at 7 years in those receiving olaparib vs 20.6% in those receiving placebo, suggesting the possibility that 2 years of maintenance olaparib could result in long-term PFS.

The PRIMA study tested niraparib vs placebo in patients who had advanced HGSC or high-grade endometrioid histology; patients in this study received study treatment for 36 months or until disease progression.[5] Niraparib dosing started at 300 mg once daily, but the trial was later amended to use an individualized dosing regimen of 200 mg per day if the patient had a baseline

Table 1. Phase 3 studies of Maintenance PARPis for Newly Diagnosed Advanced Ovarian Cancer

Trial	Active Arm	Control Arm	Primary Endpoint	PFS, Active vs Control Arm	OS, Active vs Control Arm	AML/MDS, Active vs Control Arm	FDA Approval?
SOLO1[2-4]	Olaparib (2 y)	Placebo	PFS (by investigator)	At 5 y: 56.0 vs 13.8 mo	At 7 y: NR vs 75.2 mo	1.5% vs 0.8%	Yes
PRIMA[5-6]	Niraparib (3 y)	Placebo	PFS (by BICR)	Overall: 13.8 vs 8.2 mo HRD: 24.5 vs 11.2 mo HRP: 8.4 vs 5.4 mo	ITT (62.5% maturity): 46.6 vs 48.8 mo HRD: 71.9 vs 69.8 mo HRP: 36.6 vs 32.2 mo	2.3% vs 1.6%	Yes
ATHENA, mono and combo[7-9]	Rucaparib (2 y)	Placebo	PFS (by investigator)	**MONO:** ITT: 20.2 vs 9.2 mo HRD: 28.7 vs 11.3 mo HRP: 12.1 vs 9.1 mo **COMBO:** ITT: 15.0 mo rucaparib + nivolumab, 20.2 mo rucaparib + placebo HRD: 28.9 mo rucaparib + nivolumab, 31.4 mo rucaparib + placebo HRP: 12 mo mono, 11 mo combo	**MONO:** ITT (25% maturity): NR for both arms HRD (35% maturity): NR rucaparib, 46.2 mo placebo **COMBO:** (46.5% maturity): 49.4 mo rucaparib + nivolumab, 58.0 mo rucaparib + placebo	0.98% rucaparib + nivolumab, 0.89% rucaparib alone	No
PAOLA-1[10-12]	Olaparib (2 y) + bev	Bev	PFS (by investigator)	ITT: 22.1 mo combo, 16.6 mo bev only HRD: 37.2 mo combo, 17.7 mo bev only t*BRCA*m: 37.2 mo combo, 21.7 mo bev only HRP: 16.6 mo combo, 16.2 mo bev only	ITT: 56.5 mo combo, 51.6 mo bev only HRD: 75.2 mo combo, 57.3 mo bev only t*BRCA*m: 75.2 mo combo, 66.9 mo bev only HRP: 36.8 mo combo, 40.4 mo bev only	1.7% olaparib + bev, 2.2% bev only	Yes, for *BRCA*m and HRD. No approval for HRP cancers

AML, acute myeloid lymphoma; bev, bevacizumab; BICR, blinded independent central review; *BRCA*m, *BRCA*-mutated; FDA, US Food and Drug Administration; HRD, homologous recombination deficient; HRP, homologous recombination–proficient; ITT, intention-to-treat; MDS, myelodysplastic syndrome; mo, month(s); NR, not reached; OS, overall survival; PARPis, poly(adenosine diphosphate-ribose) polymerase inhibitors; PFS, progression-free survival; t*BRCA*m, tumor *BRCA*-mutated; y, year(s).

weight of less than 77 kg, a platelet count of less than 150,000/mm^3, or both.[13] Otherwise, patients received 300 mg once per day. In both the niraparib group and the placebo group, nearly two-thirds of the patients had stage III cancer, and the remainder had stage IV. Neoadjuvant chemotherapy was administered to 66.1% of the overall population randomized to niraparib and to 67.9% of the overall population randomized to placebo. PFS was assessed by blinded independent central review (BICR) for patients with HRD cancer and for the overall population, as determined on hierarchical testing. The mPFS in the patients who had HRD cancer was 21.9 months with niraparib and 10.4 months with placebo (HR, 0.43; 95% CI, 0.31-0.59; *P*<.001), and in the overall population, mPFS was 13.8 months with niraparib and 8.2 months with placebo (HR, 0.62; 95% CI, 0.50-0.76; *P*<.001). These results were stable in a recent update,[6] in which mPFS was 24.5 months (niraparib) vs 11.2 months (placebo) for the HRD group, 13.8 months (niraparib) vs 8.2 months (placebo) for the overall population, and 8.4 months (niraparib) vs 5.4 months (placebo) for the homologous recombination–proficient (HRP) group. On the basis of the initial PFS results in PRIMA, niraparib received FDA approval on April 29, 2020, for use as

maintenance treatment for patients with advanced ovarian cancer in a complete or partial response to first-line platinum-based chemotherapy. OS results were recently reported[6]; in the overall population, mOS was 46.6 months for the niraparib group and 48.8 months for the placebo group (HR, 1.01; 95% CI, 0.84-1.23; *P*=.8834). Because this was not a significant difference, formal testing of the HRD group was not done. However, mOS results were provided per group: 71.9 months (niraparib) vs 69.8 months (placebo) (HR, 0.95, CI, 0.71-1.29) in the HRD group and 36.6 months (niraparib) vs 32.2 months (placebo) (HR, 0.93; 95% CI, 0.69-1.26) in the HRP group. The specific results for the patients with HRD/*BRCA*m disease were not reported, but the OS curves were provided in the supplementary section of the manuscript,[6] and the HR was 0.94 (95% CI, 0.63-1.41). Patients in the placebo arm had a 57.7% rate of crossover to PARPi use. The updated AML/MDS risks were 2.3% in the niraparib arm and 1.6% in the placebo arm.[6]

ATHENA[7-9] is a phase 3 trial that is testing 4 maintenance arms after upfront platinum and taxane chemotherapy for advanced ovarian cancer. Patients are being randomized in a 4:4:1:1 ratio to rucaparib/nivolumab, rucaparib, nivolumab (Opdivo, Bristol Myers Squibb), and placebo. Tumor HRD status was determined by FoundationOne Liquid CDx testing, whereas the previous 3 trials all used the Myriad MyChoice CDx test. ATHENA-MONO compared rucaparib alone vs placebo, and ATHENA-COMBO compared rucaparib/nivolumab vs rucaparib alone. The primary endpoint was investigator-assessed PFS in the intention-to-treat (ITT) population. In the ITT population of ATHENA-MONO,[7] mPFS was 20.2 months for rucaparib vs 9.2 months for placebo (HR, 0.52; 95% CI, 0.40-0.68; *P*<.0001). In the HRD group, mPFS was 28.7 months for rucaparib vs 11.3 months for placebo (HR, 0.47; 95% CI, 0.31-0.72; *P*=.0004); in the HRD-negative group, mPFS was 12.1 months for rucaparib vs 9.1 months for placebo (HR, 0.65; 95% CI, 0.45-0.95). Interim OS showed that in the HRD population,[8] both the rucaparib mOS and the placebo mOS were not reached (HR, 0.84; 95% CI, 0.44-1.58). For the ITT group, mOS was not reached for rucaparib and was 46.2 months for placebo (HR, 0.83; 95% 0.58-1.17). For the exploratory subgroup of non-tumor *BRCA*m (non-t*BRCA*m)/loss of heterozygosity (LOH) low, OS was 42.9 months for rucaparib and 32.4 months for placebo (HR, 0.75; 95% CI, 0.48-1.17).

The ATHENA-COMBO PFS and interim OS results were presented at the 2024 European Society for Medical Oncology (ESMO) Congress.[9] For the ITT overall group, mPFS was 15.0 months in the rucaparib/nivolumab arm and 20.2 months in the rucaparib-alone arm (HR, 1.29; 95% CI, 1.08-1.53). For placebo alone, mPFS was 9.2 months. Interim OS results at 46.5% maturity showed a mOS of 49.4 months for rucaparib/nivolumab vs 58.0 months for rucaparib alone (HR, 1.13; HR, 0.93-1.38). Rates of crossover of placebo patients to a future PARPi have not been reported for ATHENA. The AML/MDS risk was 0.98% for rucaparib/nivolumab vs 0.89% for rucaparib alone. Although the ATHENA-MONO results were consistent with those from other trials of PARPi monotherapy maintenance, rucaparib is currently not FDA-approved in the upfront maintenance setting. Furthermore, the results of ATHENA-COMBO suggest that no benefit is derived from the addition of nivolumab to rucaparib in the maintenance setting.

PAOLA-1 tested maintenance bevacizumab vs bevacizumab/olaparib in patients with newly diagnosed advanced ovarian cancer who had received at least 3 cycles of bevacizumab with their upfront platinum and taxane chemotherapy.[10] In the overall group, the mPFS was significantly longer in the olaparib/bevacizumab group than in the bevacizumab-alone group, at 22.1 vs 16.6 months (HR, 0.59; 95% CI, 0.49-0.72; *P*<.001). For patients whose cancers were HRD (tumor score of ≥42 on the Myriad HRD assay or tumor harboring *BRCA* mutations), mPFS was 37.2 months in the olaparib/bevacizumab group vs 17.7 months in the bevacizumab-alone group (HR, 0.33; 95% CI, 0.25-0.45). In patients with a t*BRCA* mutation, mPFS was 37.2 months in the olaparib/bevacizumab group and 21.7 months in the bevacizumab-alone group (HR, 0.31; 95% CI, 0.20-0.47). In patients with HRD-negative or HRP cancers, no benefit was seen; the mPFS was 16.6 months in the olaparib/bevacizumab group and 16.2 months in the bevacizumab-alone group (HR, 1.00; 95% CI, 0.75-1.35). Future crossover to a PARPi occurred in 19.6% of the olaparib patients and 45.7% of the placebo patients. Olaparib and bevacizumab combination therapy received FDA approval on May 8, 2020, as upfront maintenance for advanced-stage HRD ovarian cancer defined by *BRCA*m status and/or HRD disease defined by the FDA-approved Myriad HRD companion diagnostic test.

In the PAOLA-1 study, mOS was 56.5 months for the olaparib/bevacizumab group vs 51.6 months for the bevacizumab-only group in the ITT population (HR, 0.92; 95% CI, 0.76-1.12; *P*=.4118), a difference that was not statistically significant.[11,12] In the t*BRCA*m population, mOS was 75.2 months for the combination vs 66.9 months for bevacizumab only (HR, 0.60; 95% CI, 0.39-0.93). In the HRD population, mOS was 75.2 for olaparib/bevacizumab vs 57.3 months for bevacizumab only (HR, 0.62; 95% CI, 0.45-0.85). In patients with HRD-negative or HRP cancers, however, mOS was 36.8 for the combination vs 40.4 months for bevacizumab alone (HR, 1.19; 95% CI, 0.88-1.63), confirming that

no clinical benefit is seen with olaparib/bevacizumab maintenance in this patient population. Long-term safety data demonstrated that the risk of AML/MDS was 1.7% in the olaparib group vs 2.2% in the placebo group.[11]

PARPi Maintenance in Recurrent Platinum-Sensitive Ovarian Cancer

Four randomized trials, including 3 phase 3 trials (SOLO2, NOVA, ARIEL3) and 1 randomized phase 2 trial (Study 19), led to the initial FDA approvals of PARPis as maintenance therapy for recurrent platinum-sensitive ovarian cancer and are described below. PFS was the primary endpoint of all these trials.[14-25] The 3 phase 3 studies enrolled patients who had HGSC or high-grade endometrioid histology and whose cancers were sensitive to their most recent platinum regimen and their penultimate platinum regimen. Maintenance therapy with the PARPi or placebo continued until cancer progression and/or toxicities, with no defined upper limit to the duration of treatment even if the patient remained in remission, and patients were randomized 2:1 to the PARPi vs placebo. Each of these studies led to both FDA and European Medicines Agency (EMA) approvals for PARPis as maintenance therapy in the setting of recurrent platinum-sensitive disease, regardless of *BRCA* or HRD status. However, as described below, the FDA approvals for niraparib and rucaparib were voluntarily withdrawn by the manufacturers in 2022 after discussion with the FDA regarding the platinum-sensitive non-*BRCA*m or *BRCA*wt maintenance setting, followed by voluntary withdrawal of olaparib for the same indication in 2023. At this time, therefore, no PARPis are approved for maintenance therapy following a response to platinum-based chemotherapy in recurrent platinum-sensitive *BRCA*wt ovarian cancer.

The phase 2 Study 19 randomized patients with recurrent platinum-sensitive HGSC 1:1 to maintenance olaparib or placebo after response to platinum-based chemotherapy.[14] In the overall ITT population, mPFS was 8.4 months for olaparib vs 4.8 months for placebo (HR, 0.35; 95% CI, 0.25-0.49; *P*<.001). In a prespecified retrospective analysis, outcomes were analyzed on the basis of *BRCA*m status. Among patients with *BRCA*m disease, mPFS was significantly longer in the olaparib group than in the placebo group (11.2 vs 4.3 months; HR, 0.18; 95% CI, 0.10-0.31; *P*<.001). Among the patients with *BRCA*wt cancers, mPFS was 7.4 months for olaparib vs 5.5 months for placebo (HR, 0.54; 95% CI, 0.34-0.85; *P*=.0075).[15,16] Long-term results[17] showed that in the overall population, mOS was 29.8 months for olaparib and 27.8 months for placebo (HR, 0.73; 95% CI, 0.55-0.95). In the *BRCA*m subgroup, mOS was 34.9 for olaparib and 30.2 months for placebo (HR, 0.62; 95% CI, 0.42-0.93). In the *BRCA*wt population, mOS was 24.5 months for olaparib and 26.6 months for placebo (HR, 0.84; 95% CI, 0.57-1.25). In June 2014, the FDA Oncology Drugs Advisory Committee reviewed the Study 19 results and voted 11 to 2 that the available evidence did not support an accelerated approval for olaparib as maintenance treatment for patients with recurrent platinum-sensitive *BRCA*m ovarian cancer.

Table 2 summarizes the results of randomized phase 2 and 3 studies in recurrent ovarian cancer that led to initial FDA approval of maintenance PARP inhibitors. In SOLO2, 291 patients with relapsed platinum-sensitive *BRCA*m ovarian cancer were randomized to either olaparib or placebo maintenance following a response to platinum-based chemotherapy.[18,19] The mPFS as assessed by the investigator was 19.1 months for olaparib vs 5.5 months for placebo (HR, 0.30; 95% CI, 0.22-0.410; *P*<.001). The mOS was 51.7 months for olaparib and 38.8 months for placebo (HR, 0.74; 95% CI, 0.54-1.00), although statistical significance was not met.[19] Long-term results also identified the increased risks of AML/MDS in this population of patients with *BRCA*m cancer; the incidence of AML/MDS was 8.2% in the patients who received olaparib vs 4% in those who received placebo.[19] On August 17, 2017, on the basis of data from SOLO2 and Study 19, the FDA granted approval to olaparib as maintenance treatment for patients who had recurrent platinum-sensitive ovarian cancer in a complete or partial response to platinum-based chemotherapy.

NOVA was a study that tested niraparib vs placebo for maintenance in recurrent platinum-sensitive disease.[13,21] Two groups of patients were studied, those with germline *BRCA*-mutated (g*BRCA*m) cancer and those with non-g*BRCA*m cancer; these groups were enrolled simultaneously and studied independently. In the most updated mPFS results, the g*BRCA*m patients who received niraparib had a mPFS of 21.0 months, and those who received placebo had a mPFS of 5.5 months (HR, 0.27). In the non-g*BRCA*m group, those who received niraparib had a mPFS of 9.3 months, and those who received placebo had a mPFS of 3.9 months (HR, 0.45).[21,22] Exploratory group analysis showed that in the non-g*BRCA*m/HRD group, PFS was 12.9 months for niraparib and 3.8 months for placebo. In the non-g*BRCA*m/HRP group, mPFS was 6.9 months for niraparib and 3.8 months for placebo (HR, 0.58). These results led to the FDA approval of niraparib on March 27, 2017, for the maintenance treatment of adult patients with recurrent ovarian cancer in complete or partial response to platinum-based chemotherapy. In final OS results for NOVA,[22] the mOS for the g*BRCA*m group was 40.9 months with niraparib and 38.1 months with placebo (HR, 0.85; 95% CI, 0.61-1.2). The mOS

Table 2. Randomized Phase 2/3 Studies of Maintenance PARPis for Recurrent Ovarian Cancer Leading to FDA *BRCA*m Maintenance Approval Only

Trial	Active Arm	Control Arm	Primary Endpoint	PFS, Active vs Control Arm	OS, Active vs Control Arm	AML/MDS, Active vs Control Arm
SOLO2	Olaparib	Placebo	PFS	19.1 vs 5.5 mo	51.7 vs 38.8 mo	8.2% vs 4%
NOVA	Niraparib	Placebo	PFS	g*BRCA*m: 21.0 vs 5.5 mo Non-g*BRCA*m: 9.3 vs 3.9 mo g*BRCA*wt/HRD: 12.9 vs 3.8 mo g*BRCA*wt/HRP: 6.9 vs 3.8 mo	g*BRCA*m: 40.9 vs 38.1 mo Non-g*BRCA*m: 31.0 vs 34.8 mo g*BRCA*wt/HRD: 35.6 vs 41.4 mo g*BRCA*wt/HRP: 27.9 vs 27.9 mo	g*BRCA*m: 7.4% vs 3.1%
ARIEL3	Rucaparib	Placebo	PFS	ITT: 10.8 vs 5.4 mo *BRCA*m: 16.6 vs 5.4 mo HRD: 13.6 vs 5.4 mo	ITT: 36.0 vs 43.2 mo *BRCA*m: 45.9 vs 47.8 mo HRD: 40.5 vs 47.8 mo *BRCA*wt/LOH low (ie, HRP): 28.6 vs 32.6 mo	3.7% vs 3.2%; exceptional responders (defined as having PFS on rucaparib for ≥2 y): 11.4% vs 0%

AML, acute myeloid lymphoma; *BRCA*m, *BRCA*-mutated; FDA, US Food and Drug Administration; g*BRCA*m, germline *BRCA*-mutated; g*BRCA*wt, germline *BRCA* wild-type; HRD, homologous recombination deficient; HRP, homologous recombination proficient; ITT, intention-to-treat; LOH, loss of heterozygosity; MDS, myelodysplastic syndrome; mo, month(s); OS, overall survival; PARPis, poly(adenosine diphosphate-ribose) polymerase inhibitors; PFS, progression-free survival; y, year(s).

for the non-g*BRCA*m group was 31.0 months for niraparib and 34.8 months for placebo (HR, 1.06; 95% CI, 0.81-1.37).[22] In subgroup analyses,[22] mOS in the non-g*BRCA*m/HRD group was 35.6 months for niraparib and 41.4 months for placebo (HR, 1.29; 95% CI, 0.85-1.95). In the non-g*BRCA*m/HRP group, mOS was 27.9 months with niraparib and 27.9 months with placebo (HR, 0.93; 95% CI, 0.61-1.41). The incidence of AML/MDS was 3.8% in patients who received niraparib and 1.7% in patients who received placebo. The risk of AML/MDS was 7.4% in the g*BRCA*m carriers who received niraparib and 3.1% in the g*BRCA*m patients who did not receive niraparib.[22]

ARIEL3 randomized patients in the platinum-sensitive maintenance setting to rucaparib or placebo. Initial PFS results[23] demonstrated that mPFS in the *BRCA*m patients was 16.6 months for rucaparib vs 5.4 months for placebo maintenance (HR, 0.23; 95% CI, 0.16-0.34; *P*<.001). In the patients with HRD cancers, mPFS was 13.6 months for rucaparib vs 5.4 months for placebo (HR, 0.32; 95% CI, 0.24-0.42; *P*<.001), and in the ITT population, mPFS was 10.8 months vs 5.4 months (HR, 0.36; 95% CI, 0.30-0.45; *P*<.001). On the basis of these results, on April 6, 2018, the FDA approved rucaparib as a maintenance treatment for adults with recurrent ovarian cancer in response to platinum-based chemotherapy. However, the ARIEL3 OS results presented in 2022 showed trends of poorer OS for rucaparib vs placebo in all groups studied.[24] In the ITT population, median OS was 36.0 months for rucaparib vs 43.2 months for placebo (HR, 0.995; 95% CI, 0.809-1.223).[24] In the *BRCA*m cohort, mOS was 45.9 months for rucaparib and 47.8 months for placebo (HR, 0.832; 95% CI, 0.581-1.192). In the HRD cohort, mOS was 40.5 months for rucaparib and 47.8 months for placebo (HR, 1.005; 95% CI, 0.766-1.320). For patients with *BRCA*wt/LOH-low (ie, HRP) tumors, OS was 28.6 months for rucaparib and 32.6 months for placebo (HR, 1.153; 95% CI, 0.784-1.695).[24]

Like SOLO2 and NOVA, ARIEL3 reported a higher incidence of MDS/AML in the patients with *BRCA*m ovarian cancer who received the PARPi vs placebo and also in the patients with non-*BRCA*m ovarian cancer.[24,25] The total frequency of MDS/AML in ARIEL3 has been reported as 3.7% (14/375) in the patients in the rucaparib arm and 3.2% (6/189) in the patients in the placebo arm.[24] However, when the risk of MDS/AML was examined among "exceptional responders," defined as those progression-free for at least 2 years on rucaparib (21.1% of patients [79/375]),[25] 9 of the 14 cases of MDS/AML in the rucaparib group occurred in the 79 exceptional responders, resulting in an 11.4% risk of MDS/AML in this population.[25] No cases of MDS/AML were seen in the exceptional responders who received placebo. Interestingly, in a response to a letter to the editor, the authors reported that of the 9 cases, 2 occurred in g*BRCA*m patients and 5 in somatic *BRCA*m patients, with 2 additional cases in *BRCA*wt patients,[26,27] suggesting that the risk for MDS/AML may

be increased in patients with *BRCA*m ovarian cancer regardless of whether the mutation is germline or somatic.

Withdrawals of PARPi Maintenance Treatment in Recurrent Platinum-Sensitive Ovarian Cancer

The OS data from NOVA and ARIEL3 for the patients with non-g*BRCA*m disease, as well as the data from Study 19, led to the withdrawals of niraparib (in September 2022), rucaparib (in December 2022) and olaparib (in September 2023) as maintenance treatment for platinum-sensitive recurrent *BRCA*wt ovarian cancer. The FDA indication for *BRCA*m maintenance remains for all 3 drugs (germline or somatic for rucaparib and olaparib and germline for niraparib). Additionally, the EMA has not withdrawn any of the PARPi approvals in the recurrent maintenance setting; thus, the available standards of care differ between the United States and Europe. The effect of PARPi use on OS has been challenging to quantify because of the crossover of patients on placebo to eventual PARPi use after progression, continued missing data in some studies, lack of uniform anticancer treatment after the study treatment, and lack of understanding regarding the effect of PARPis on creating mechanisms of resistance to future treatments. Notably, in a post hoc analysis of a subset of 147 patients in SOLO2 done to determine the outcomes of different treatment regimens after cancer progression,[20] the time to second treatment was significantly longer in the placebo-treated patients than in those who received olaparib (12.1 vs 6.9 months; HR, 2.17; 95% CI, 1.47-3.19); this was particularly notable in the patients who received platinum chemotherapy vs those who received nonplatinum drugs. These data suggest that PARPi use may affect response to and efficacy of future treatments and may help explain why PFS improvements with PARPis have not translated into OS gains, especially in the recurrent maintenance setting. However, prospective data in this setting remain limited.

PARPis as Single-Agent Treatments for Recurrent Ovarian Cancer

Olaparib as a single agent for heavily pretreated recurrent g*BRCA*m ovarian cancer received accelerated FDA approval on December 19, 2014, on the basis of an objective response rate (ORR) of 34% and a median duration of response of 7.9 months for olaparib in 137 patients with advanced *BRCA*m ovarian cancer who had received at least 3 lines of chemotherapy.[28] Rucaparib was granted FDA accelerated approval in December 2016 for the treatment of patients with advanced *BRCA*m ovarian cancer (both germline and somatic) who had received at least 2 forms of chemotherapy on the basis of an ORR of 54% and a median duration of response of 9.2 months.[29,30] In 2019, niraparib also received indications for the single-agent treatment of recurrent *BRCA*m and/or HRD ovarian cancer in patients who had received at least 3 prior lines of treatment, on the basis of QUADRA data.[31]

However, 2 subsequent randomized phase 3 trials—SOLO3 and ARIEL4—that tested single-agent PARPis vs chemotherapy as treatment for relapsed ovarian cancer led to withdrawals of the treatment approvals of all 3 drugs.[32-35] SOLO3 was an open-label phase 3 trial that tested olaparib vs nonplatinum chemotherapy in patients who had g*BRCA*m recurrent platinum-sensitive ovarian cancer and had received at least 2 prior lines of platinum-based chemotherapy.[32] Choices of chemotherapy included pegylated liposomal doxorubicin, paclitaxel, gemcitabine, and topotecan. The primary endpoint, ORR as assessed by BICR, was higher in the patients treated with olaparib than in those receiving chemotherapy (72.2% vs 51.4%). However, in a post hoc OS analysis based on the number of prior lines of chemotherapy, OS was better with chemotherapy than with olaparib in those patients who had been treated with at least 3 lines of chemotherapy. In these patients, median OS was 28.9 months for olaparib vs 39.4 months for chemotherapy (HR, 1.33; 95% CI, 0.84-2.18).[33] Given these findings, the indication for olaparib in the treatment of heavily pretreated recurrent *BRCA*m ovarian cancer was withdrawn in August 2022.

ARIEL4 enrolled patients who had recurrent ovarian cancer with g*BRCA* or t*BRCA* mutations and had received at least 2 prior chemotherapy regimens, including at least one prior platinum-based regimen.[34] The primary endpoint was investigator-assessed PFS. Patients with platinum-resistant or partially platinum-sensitive (6- to 12-month platinum-free interval [PFI]) were randomized 2:1 to either rucaparib or weekly paclitaxel, whereas patients who were "fully" platinum sensitive (>12-month PFI) were randomized 2:1 to rucaparib or platinum-based chemotherapy (either single-agent platinum or platinum doublet). ARIEL4 met its primary endpoint, with an improvement in median PFS to 7.4 months in patients receiving olaparib vs 5.7 months in those receiving chemotherapy (HR, 0.64; 95% CI, 0.49-0.84; *P*=.0010).[34] However, in the ITT overall population, mOS was 19.4 months with rucaparib and 25.4 with chemotherapy (HR, 1.313; 95% CI, 0.999-1.725).[35] Among the patients with platinum-resistant ovarian cancer, mOS was 14.2 months in those treated with rucaparib and 22.2 months in those treated with chemotherapy (HR, 1.511; 95% CI, 1.052-2.170). Among patients who had partially platinum-sensitive cancer, mOS was 21.1 months for rucaparib vs 23.2 months for chemotherapy (HR, 0.972; 95% CI, 0.583-1.621), and among those who had fully platinum-sensitive cancer, OS was 36.3 months for rucaparib

vs 47.2 months for chemotherapy (HR, 1.243; 95% CI, 0.619-2.498).[35] Although the ARIEL4 OS analyses were secondary and it is unclear why the PFS and OS findings in the study are so discrepant, these findings nonetheless raised concerns that PARPi therapy for recurrent ovarian cancer could pose an OS detriment. Accordingly, in June 2022, Clovis withdrew the FDA indication for rucaparib as a treatment for recurrent *BRCA*m ovarian cancer in patients who had received at least 2 chemotherapies, and the EMA recommended that patients not receive rucaparib for this indication.

Other Important Trials Affecting PARPi Development

Two other phase 2 studies besides Study 19 helped to shape the development of PARPis as treatments for ovarian cancer. Study 12 was a randomized phase 2 (RP2) study of 97 patients that had 3 arms: lower-dose olaparib, standard-dose olaparib, and pegylated liposomal doxorubicin at a dose of 40 mg/m^2 for patients with recurrent platinum-sensitive *BRCA*m ovarian cancer.[36] The mPFS was 6.5 months with lower-dose olaparib, 8.8 months with standard-dose olaparib, and 7.1 months with pegylated liposomal doxorubicin, with no significant differences in mPFS noted among the 3 arms. A second, open-label RP2 study, by Oza and colleagues, tested carboplatin/paclitaxel vs carboplatin/paclitaxel + olaparib followed by olaparib maintenance in patients with recurrent platinum-sensitive ovarian cancer.[37] The olaparib-throughout group received a lowered dose of carboplatin at an area under the curve (AUC) of 4. The mPFS was 12.2 months in the olaparib-throughout group and 9.6 months in the chemotherapy group.[37] Neither of these strategies was taken forward for PARPi development; instead, the Study 19 strategy of using olaparib as maintenance after chemotherapy was pursued in phase 3 studies.

The OREO study asked the question of PARPi efficacy following previous receipt of a PARPi. Enrolled patients had previously received PARPi therapy following first-line chemotherapy for advanced cancer for at least 18 months and for at least 12 months in the *BRCA*m and *BRCA*wt cohorts, respectively[38]; patients were also eligible if they had received a prior PARPi after a second or subsequent line of chemotherapy. In the *BRCA*m patients, mPFS was 4.3 months for olaparib vs 2.8 months for placebo (HR, 0.57; 95% CI, 0.37-0.87; *P*=.022). In the *BRCA*wt cohort, mPFS was 5.3 months for olaparib vs 2.8 months for placebo (HR, 0.43; 95% CI, 0.26-0.71; *P*=.0023).[38] Given the minimal PFS benefit, the lack of OS data, and the risk of AML/MDS with PARPi treatment, reuse of a PARPi following prior receipt of a PARPi is not the standard of care.

PARP Inhibitor Combination Studies

Multiple studies of PARPi combinations have been performed, and the rationale for these studies is detailed in the review of Veneris and colleagues on this subject.[39] Because a discussion of the various PARPi trials is beyond the scope of this review, only noteworthy RP2 or phase 3 trials will be mentioned here; these include PARPi combinations with anti-angiogenic agents, immunotherapy, and phosphoinositide 3-kinase (PI3K) inhibitors.[40-57]

Bevacizumab

The PAOLA-1 study of bevacizumab and olaparib was previously discussed in the upfront newly diagnosed maintenance setting. To date, this has been the most successful combination of a PARPi with an anti-angiogenic agent. A previously reported RP2 study (AVANOVA2) tested the addition of bevacizumab to niraparib maintenance in the platinum-sensitive recurrence setting.[40] This was a randomized 1:1 phase 2 study of 97 patients who received either niraparib plus bevacizumab or niraparib alone. The mPFS was 11.9 months for the combination vs 5.5 months for niraparib alone (HR, 0.35; 95% CI, 0.21-0.57; *P*<.001). However, the bevacizumab-plus-PARPi combination in the recurrent setting, unlike in the upfront maintenance setting, is not approved by the FDA.

Cediranib

Cediranib is an oral multi-tyrosine kinase inhibitor, and data from a randomized phase 2 study reported improvement in mPFS with the combination of olaparib and cediranib vs olaparib alone for the treatment of platinum-sensitive recurrent ovarian cancer.[41] In this study, the mPFS was 17.7 months for patients treated with olaparib/cediranib vs 9.0 months for those treated with olaparib monotherapy (HR, 0.42; 95% CI, 0.23-0.76; *P*=.005). These findings led to NRG-GY004,[42] an open-label, randomized phase 3 trial conducted in the United States and Canada. Eligible patients had high-grade serous or endometrioid platinum-sensitive ovarian cancer and were randomized 1:1:1 to platinum-based chemotherapy, olaparib, or olaparib/cediranib. PFS was the primary endpoint, and olaparib/cediranib was found not to be superior to platinum-based chemotherapy (HR, 0.86; 95% CI, 0.66-1.10; *P*=.077). The mPFS was 10.3 months for chemotherapy, 8.2 months for olaparib, and 10.4 months for olaparib/cediranib.[42] In patients with a g*BRCA* mutation, the PFS HR vs chemotherapy was 0.55 for olaparib/cediranib and 0.63 for olaparib. Of note, mOS results were as follows: 32.7 months for platinum-based chemotherapy, 33.5 months for olaparib/cediranib, and 31 months for olaparib (HR for olaparib/cediranib vs chemotherapy, 1.12; 95% CI, 0.874-1.43).[43]

NRG-GY005 tested the combination of olaparib/

cediranib vs single-agent cediranib vs single-agent nonplatinum chemotherapy in patients with platinum-resistant recurrent ovarian cancer.[44] Co-primary endpoints were PFS and OS. The mPFS was 5.2 months with the combination vs 3.4 months with chemotherapy (HR, 0.796; 95% CI, 0.597-1.060; *P*=.145) and 4.0 months with cediranib alone (HR vs chemotherapy, 0.972; 95% CI, 0.726-1.300; *P*=1.00). Combination olaparib/cediranib did not meet the primary endpoints of improved PFS and OS vs chemotherapy in platinum-resistant recurrent ovarian cancer.

Immunotherapy

Several phase 2 and 3 studies have tested PARPi and immune checkpoint inhibitor combinations. Notable phase 2 trials in the platinum-resistant setting include the MOONSTONE study (niraparib and dostarlimab [Jemperli, GSK])[45] and the OPAL trial (bevacizumab, dostarlimab, and niraparib).[46] MOONSTONE tested the combination of dostarlimab and niraparib in patients with platinum-resistant ovarian cancer and demonstrated a 7.3% ORR; the study was terminated early because the prespecified interim futility criterion was met.(45) OPAL tested the triplet of niraparib, bevacizumab, and dostarlimab in platinum-resistant recurrent disease and reported an ORR of 17.1%.[46] The relative lack of activity of the triplet combination of a PARPi, an anti-angiogenic agent, and an immune checkpoint inhibitor is in contrast to the observations from the MEDIOLA study,[47] in which significant activity was observed with a doublet of olaparib and durvalumab (Imfinzi, AstraZeneca) in patients with g*BRCA*m platinum-sensitive ovarian cancer and a triplet of olaparib, durvalumab, and bevacizumab in patients with non-g*BRCA*m platinum-sensitive ovarian cancer. This difference in activity may have been due to the clinical setting; OPAL was conducted in patients with platinum-resistant ovarian cancer, whereas MEDIOLA was conducted in a platinum-sensitive setting. For example, the recently reported NRG-GY023 study testing immunotherapy combinations of cediranib plus durvalumab, cediranib plus olaparib, or the triplet of cediranib, olaparib, and durvalumab[48] in recurrent platinum-resistant ovarian cancer was stopped early at the interim futility analysis, with none of the arms demonstrating activity superior to that of single-agent chemotherapy.[48]

Two phase 3 studies have tested the addition of a PARPi to an immune checkpoint inhibitor for both upfront therapy of newly diagnosed disease and maintenance therapy of platinum-sensitive disease. The first was the ATHENA-COMBO study, discussed earlier in the newly diagnosed setting, in which the addition of nivolumab to rucaparib maintenance did not improve PFS. The phase 3 ENGOT-Ov41/GEICO 69-O/ANITA trial[49] tested the addition of atezolizumab (Tecentriq, Genentech) to chemotherapy and then to PARPi maintenance with niraparib vs standard PARPi maintenance in the platinum-sensitive recurrent setting. When added to niraparib maintenance, atezolizumab did not significantly improve PFS (11.2 months for the combination and 10.1 months for standard therapy; HR, 0.89; 95% CI, 0.71-1.10; *P*=.28).

PI3K Inhibitors

A study of olaparib and alpelisib conducted on the basis of preclinical work[50,51] showed that PARPis combined with PI3K inhibitors could inhibit the homologous recombination repair (HRR) pathway and induce a more HRD state, leading to a recommended phase 2 dose of alpelisib at 200 mg once a day plus olaparib at 200 mg twice a day; additionally, it was observed that the combination produced encouraging responses in platinum-resistant *BRCA*wt HGSC, for which the expected rate of response to PARPis is less than 5%.[52] These findings led to the subsequent randomized phase 3 EPIK-O study, in which patients with platinum-resistant ovarian cancer were randomized to either the combination of alpelisib and olaparib at the RP2 dose or the investigator's choice chemotherapy.[53] The study did not meet the primary endpoint of improved PFS for the PARPi combination vs chemotherapy. The mPFS via BICR was 3.6 months for olaparib/alpelisib vs 3.9 months for chemotherapy (HR, 1.14; 95% CI, 0.88-1.48; one-sided *P*=0.84).[53]

Other combinations that are currently in clinical trials include PARP/ATR inhibition,[54] PARP/MEK inhibition,[55] PARP/USP1 inhibitors,[56] and other HRD-inducing agents.[57]

Conclusions

The use of PARPis as maintenance therapy after response to platinum-based chemotherapy has improved the outcomes of patients with newly diagnosed ovarian cancer, specifically HGSC and high-grade cancers with endometrioid histologies. The greatest benefit has been observed in *BRCA*m tumors, either g*BRCA* or t*BRCA*. Patients with ovarian cancers that do not harbor a *BRCA* mutation but still have genomic features suggesting HRD also derive PFS benefit, whereas the least benefit has been observed in patients with tumors that are *BRCA*wt and HRP. Currently, no data suggest substantial differences in efficacy between the 3 PARPis available in ovarian cancer. The choice of PARPi can be guided by considerations of schedule (twice-daily vs once-daily dosing) and duration of treatment (2 vs 3 years), concerns for toxicity or drug-drug interactions, availability, and formulary. When used for a defined duration in the upfront setting, PARPis can extend PFS significantly, and olaparib has achieved clinically meaningful extensions of OS for patients with

*BRCA*m tumors. Similar OS improvement was not seen with niraparib despite marked PFS improvement for numerous reasons, including the percentage of patients with subsequent crossover to a PARPi, the effect of subsequent lines of therapy, and differing characteristics in the trial populations. Nevertheless, the current data suggest that PARPi maintenance, either as monotherapy or in conjunction with bevacizumab for patients who received bevacizumab with their initial chemotherapy, should be offered to patients with *BRCA*m cancers and discussed with patients whose cancers are *BRCA*wt, test positive for HRD, and have responded to initial chemotherapy and surgery. Although PFS benefit has been observed in patients whose cancers are *BRCA*wt and test negative for HRD (ie, HRP), the benefits are modest, and a discussion of PARPi monotherapy with patients who have these tumors should include a careful consideration of the relative risks and benefits. Notably, the combination of bevacizumab and olaparib did not demonstrate clinical benefit and should not be offered to patients whose cancers are *BRCA*wt and test negative for HRD (HRP).

Indications for PARPi use as maintenance in the *BRCA*wt setting and as treatment for recurrent *BRCA*m and/or platinum-sensitive HRD disease have been withdrawn by the FDA because of concerns regarding decreased OS vs OS in control arms in phase 3 studies. To date, PARPi combinations, with the exception of olaparib and bevacizumab in the upfront *BRCA*m and HRD settings, have not demonstrated favorable results vs controls in phase 3 studies, although combinations remain an area of active investigation.

Disclosures

Dr Liu reports advisory board participation for Clovis Oncology, Genentech/Roche, GSK, Regeneron, AstraZeneca, Eisai, Daiichi Sankyo, Zentalis, Loxo/Lilly, and Revolution Medicine; consulting for AstraZeneca and BMS; and funding to institution for clinical trials from Genentech/Roche, AstraZeneca, BMS, CytomX Therapeutics, Regeneron, Clovis Oncology, 2X Oncology, Vigeo Therapeutics, Aravive, Arch Oncology, Zentalis, GSK, Impact Therapeutics, Pfizer, Seagen, SystImmune, Volastra, and Pheon Therapeutics. Dr Matulonis declares participation in scientific advisory boards for Allarity, NextCure, AbbVie, Immunogen, Profound Bio, Eisai, the Ovarian Cancer Research Alliance, Tango Therapeutics, Novartis, and GSK; and participation in data safety monitoring boards for Mural Oncology and Symphogen.

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