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Frontline PARP inhibitor maintenance therapy in ovarian cancer: A Society of Gynecologic Oncology practice statement

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HIGHLIGHTS

- Data from four randomized phase 3 trials guides frontline PARP inhibitor maintenance therapy in ovarian cancer.
- There are now 3 FDA approvals for frontline PARP inhibitor maintenance in newly diagnosed advanced-stage ovarian cancer.
- The aim of this practice statement is to help clinicians make evidence-based decisions for utilization of frontline PARPi maintenance.

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ABSTRACT

PARP inhibitors (PARPi) have shown have activity in the treatment of ovarian cancer. Previous studies documented activity in patients with germline (gBRCA) and tumor (tBRCA) BRCA mutations (BRCAm) for treatment in lieu of chemotherapy as well as in recurrent ovarian cancer as maintenance therapy.

The recent data from four randomized phase 3 trials have established an important role for frontline PARPi maintenance therapy in ovarian cancer. While SOLO-1 only included BRCAm patients, PRIMA, VELIA, and PAOLA-1 enrolled broader patient populations. The magnitude of benefit of PARPi in these studies was consistently greatest in the BRCAm patients (germline or tumor). PARPi treatment also improved PFS in the HRD cohort but to a lesser degree than in patients with BRCAm. In secondary analyses, the overall impact of PARPi treatment in HR proficient patients, which comprise about 50% of ovarian cancers, was more limited than in the other subgroups. Data for overall survival, also a secondary endpoint, is currently immature for these four trials. Fatigue, hematologic, and GI toxicities are the most commonly noted adverse events with PARPi therapy. The recent FDA approvals of PARPi in the maintenance setting will enable clinicians to incorporate these into frontline armamentarium of ovarian cancer treatment.

1. Introduction

PARPs (poly[adenosine diphosphate–ribose] polymerases) are nuclear proteins that bind to damaged DNA and activate repair of single strand DNA breaks during base excision repair. When unrepaired single strand breaks reach DNA replication forks, they generate double strand breaks that require homologous recombination for high-fidelity repair [1]. Inhibitors of PARP (PARPi), through multiple mechanisms, enable genomic instability and cell death, predominantly in tumors that are deficient in homologous-recombination (HRD) such as those with *BRCA* mutations [2].

PARPi have activity in the treatment of ovarian cancer. Early studies documented activity in patients with germline (g*BRCA*) and tumor (t*BRCA*) *BRCA* 1/2 mutations (*BRCAm*). Lower levels of activity were seen in those without *BRCA* mutations, wildtype (*wtBRCA*) [3]. The next generation of trials documented activity of PARPi when used for maintenance therapy in treatment responsive, platinum sensitive recurrent disease [4–7].

Data are now available from four randomized phase III trials addressing the use of PARPi as maintenance after initial treatment of newly diagnosed ovarian cancer. The purpose of this practice statement is to review these studies and to help providers make evidence-based decisions about the use of PARPi maintenance therapy in the initial treatment of ovarian cancer.

1.1. SOLO-1/GOG-3004

Newly diagnosed ovarian cancer is the only setting in which treatment is administered with curative intent. SOLO-1, a randomized double blind, placebo-controlled study, addressed the impact of PARPi maintenance with olaparib on progression free survival (PFS) when

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utilized after primary platinum containing chemotherapy in patients with advanced ovarian cancer (Table 1). Patients with newly diagnosed, FIGO stage III-IV, high grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer with a germline or tumor *BRCAm*, status post primary or interval optimal cytoreduction, in complete response (CR) or partial response (PR) after platinum-based therapy were included. Three hundred and ninety-one patients were randomized 2:1 to olaparib 300 mg tablets BID versus placebo. Patients were stratified by response to platinum-based chemotherapy. Study treatment continued until disease progression, and patients with no evidence of disease stopped treatment at 2 years, while those with a PR could continue treatment. The primary endpoint was investigator-assessed PFS. The study demonstrated an unprecedented 70% reduction in the hazard for progression or death with an improvement in median PFS, 13.8 months in the placebo arm versus not reached in the olaparib arm (HR 0.30, 95% CI 0.23–0.41, $P < .001$). At 3 years, 60% of the olaparib treated patients compared to 27% in the placebo arm were still progression free, noting that the benefit appears to extend beyond 2 years of treatment [8]. Based on this data olaparib was FDA approved on 12/18/2018 as frontline maintenance therapy in *BRCAm* patients. [9]

A subsequent randomized, double blind, placebo-controlled phase III study, PRIMA/ENGOT-OV26/GOG-3012, evaluated the PARPi niraparib in the frontline maintenance setting in a broader population of advanced ovarian cancer patients at high risk of relapse following PR or CR to front-line platinum-based chemotherapy (Table 1). Key inclusion criteria included: high-grade serous or endometrioid histology; inoperable stage III and all stage IV disease; stage III with visible residual disease after PDS; any patient that received NACT; CR or PR following platinum treatment and HRD testing was required at screening (Myriad myChoice® HRD Test). Stratification factors included NACT, best response to platinum (CR or PR), and HRD status. HRD was defined by deleterious tumor *BRCAm* or HRD score ≥ 42. Patients were randomized 2:1 to niraparib versus placebo for a 3-year period; patients could not have received prior bevacizumab or PARPi. A dosing modification was made during the trial where starting dose was adjusted based on weight and platelet count. The primary endpoint was median PFS, with a hierarchal testing method for PFS, first in the HRD group, with subsequent intent to treat analysis if the HRD analysis was significant. Overall, 733 patients were randomized, 67% of the patients had NACT, 35% had stage IV disease, and 51% were HRD. A median PFS of 21.9 vs 10.4 months was noted for niraparib versus placebo, respectively (HR 0.43, 95% CI 0.31 to 0.59, $P < .001$) in the HRD cohort. Given the significant improvement in median PFS in the HRD group, the overall population was analyzed and also demonstrated an improvement in PFS of 13.8 mos vs 8.2 mos in the niraparib vs placebo groups (HR 0.62, 95% CI 0.50–0.76, $P < .001$) [10]. In the HR proficient group the PFS was 8.1 vs. 5.4 months, HR 0.68, 95% CI 0.49–0.94. It should be noted that patients who had optimal debulking with no visible residual disease were not eligible, but all NACT regardless of residual at interval debulking were eligible for this trial. Niraparib is currently listed as a maintenance option following front line therapy on NCCN guidelines and gained FDA approval as maintenance treatment in patients with advanced ovarian, fallopian tube or primary peritoneal cancer who are in CR or PR to first-line platinum based therapy on April 29, 2020. [11,12]

1.2. VELIA/GOG-3005

Although PARPi have proven effective in the management of ovarian cancer, combination with chemotherapy has been difficult due to overlapping toxicities. The PARPi veliparib previously demonstrated a 26% response rate (90% CI: 16%–38%, CR: 2, PR: 11) in recurrent *BRCAm* ovarian carcinoma [13]. Additional studies have suggested that veliparib was tolerable and safe to give with chemotherapy [14].

In the VELIA/GOG-3005 study, investigators evaluated veliparib in combination with platinum-based chemotherapy, and then continued as maintenance for stage III or IV newly diagnosed high-grade serous ovarian carcinoma (Table 1). Both primary and interval cytoreduction were permitted on trial, and weekly versus every3-week paclitaxel dosing was at the discretion of the treating physician. Central assessment of g*BRCA*, t*BRCA*, and HR status was required. Importantly, g*BRCA* status was added as a stratification factor after 655 patients (57%) were enrolled in order to address an observed imbalance regarding *BRCA*-mutation status [14,15]. In an effort to mitigate toxicity, veliparib was dosed at 150 mg orally twice daily concurrent with chemotherapy, increasing to 400 mg twice daily in the maintenance phase as permitted. The primary end point was investigator-assessed PFS in the veliparib throughout group as compared with the control group, with a sequential step-wise analysis in the *BRCAm* cohort, the HRD cohort, and lastly the intention-to-treat population. A total of 1140 patients underwent randomization over a 2-year period. The primary efficacy end-point, PFS, was significantly prolonged in all cohorts when comparing veliparib-throughout and control groups (Table 1). In the ITT population, the median PFS was longer with veliparib maintenance therapy than with placebo (23.5 vs. 17.3 months; HR 0.68; 95% CI 0.56–0.83; $P < .001$), and this benefit was additionally seen in the HRD cohort (31.9 vs 20.5 months; HR 0.57; 95% CI 0.43–0.76). In the *BRCA*m cohort, the median PFS was 34.7 months in the veliparib-throughout group and 22.0 months in the control group (HR 0.44; 95% CI, 0.28 to 0.68; $P < .001$). Despite the potential for overlapping toxicity, the relative dose intensity of carboplatin and paclitaxel were similar across cohorts and study arms.

The design of the VELIA/GOG-3005 trial is unique when compared to contemporary front-line PARPi studies in that patients were not required to have had a response to front-line cytotoxic chemotherapy, potentially permitting enrollment of platinum resistant patient populations impacting the magnitude of benefit seen in the intention-to-treat population. Furthermore, PFS was measured from start of cytotoxic chemotherapy (initial randomization) and there was no maintenance PARPi alone arm, in contrast to PRIMA, PAOLA-1 and SOLO-1.

1.3. PAOLA-1

In an effort to augment response to PARPi therapy, PAOLA-1/ENGOT-ov25, the only investigator-initiated front-line phase 3 clinical trial, examined the use of olaparib maintenance after chemotherapy with bevacizumab in patients with advanced stage ovarian cancer, regardless of *BRCA* mutation status (Table 1) [16]. The rationale was based on preclinical work suggesting that hypoxia might decrease HR compliance inducing the potential for PARPi to work in HR-proficient states and prior data suggesting an improved PFS when PARPi are combined with antiangiogenic therapy in patients with recurrent platinum sensitive ovarian cancer [17,18]. Eligible patients were required to have stage III-IV high grade serous or endometrioid ovarian carcinoma. Alternate nonmucinous epithelial ovarian cancer histologies were permitted to enroll if they had a documented *BRCA*m. Importantly, patients were required to have had a CR or PR to their front-line platinum-taxane based chemotherapy plus bevacizumab regimen irrespective of surgical outcome. The primary endpoint was investigator-assessed PFS in the ITT, a non-biomarker restricted population. A total of 806 patients underwent randomization; 30% had stage IV disease and 30% harbored a *BRCA*m (germline or tumor). Combination bevacizumab plus olaparib resulted in a significant improvement in PFS compared to placebo (median, 22.1 months vs. 16.6 months; HR 0.59; 95% CI, 0.49 to 0.72; $P < .001$) [3]. In patients harboring a *BRCA*m, the median PFS was 37.2 months in the olaparib group and 21.7 months in the placebo group (HR 0.31; 95% CI, 0.20 to 0.47). There was no benefit of adding olaparib to bevacizumab in the biomarker negative cohort ($n = 419$), defined as "HRD-negative" ($n = 277$)or "HRD unknown" ($n = 142$); the median PFS was 16.9 months in the olaparib group and 16.0 months in the placebo group (HR 0.92; 95% CI, 0.72 to 1.17); however, this was not a pre-specified sub-group analysis. When examining adverse events, only fatigue, nausea and anemia were significantly more

Table 1
Frontline PARPi maintenance trials.

Study	PARPi	Patient population	Study arms	Primary endpoint	Outcome	Special considerations
SOLO1 ($N = 391$)	Olaparib	HGS/endometrioid *BRCA*m (germline or tumor), s/p primary or interval optimal cytoreduction, in CR or PR after platinum-based therapy	1. Olaparib 2. Placebo	PFS (investigator)	HR 0.30; 95% confidence interval, 0.23 to 0.41; P < .001) (13.8 months vs NR)	Only 2 patients w/ centrally confirmed t mutation
PRIMA/ENGOT-OV26/GOG-3012 (N = 733)	Niraparib	HGS/endometrioid, inoperable stage III and all stage IV disease, stage III with visible residual disease after PDS, any patient that received NACT, CR or PR following platinum treatment	1. Niraparib 2. Placebo	PFS (Blinded Independent Central Review) Hierarchical: HRD⇨ITT	HRD+: HR, 0.43; 95% confidence interval [CI], 0.31 to 0.59; P < .001) (21.9 months vs. 10.4 months) ITT: HR, 0.62; 95% CI, 0.50 to 0.76; *P* < .001) (13.8 months and 8.2 months)	PRIMA/ENGOT-OV26/GOG-3012 ($N = 733$)
VELIA/GOG-3005 ($N = 1140$)	Veliparib	HGS, in combination with platinum-based chemotherapy, and as maintenance in stage III or IV primary or with interval cytoreduction	1. Chemo/placebo⇨placebo 2. Chemo/veliparib⇨placebo 3. Chemo/veliparib⇨veliparib	PFS (investigator) Hierarchical: *BRCA*m⇨HRD⇨ITT	HR 0.68 (Arm 1 vs 3) (17.3 vs 23.5 months)	Randomization prior to start of chemotherapy Enrollment irrespective of response to platinum
PAOLA-1/ENGO-ev25 ($N = 806$)	Olaparib	HGS/endometrioid or nonmucinous *BRCA*mt, CR or PR to their front-line platinum-taxane based chemotherapy plus bevacizumab	1. Bevacizumab/olaparib 2. Bevacizumab/placebo	PFS (investigator) Predefined subgroups: t*BRCA* status and HRD	HR 0.59 (16.6 vs 22.1 months)	"active" placebo arm containing bevacizumab

HGS = high grade serous; mt = mutation; PFS = progression free survival; HRD = homologous recombination deficient; ITT = intention to treat; t*BRCA* = tumor *BRCA* mutation.

common in the olaparib arm. Approximately 20% of the olaparib arm discontinued therapy due to treatment related adverse events, compared to 5% in the placebo arm.

Interestingly, the magnitude of benefit identified in the *BRCA*m population of PAOLA-1, was consistent with that seen in SOLO1, HR 0.31 versus HR 0.30, respectively. However, the incorporation of an "active" placebo arm containing bevacizumab in PAOLA-1 distinguishes the studies. Additionally, absence of an olaparib alone arm makes interpretation of the relative contribution of bevaciuamb in the combination arm difficult. Furthermore, differences in the patient populations at the time of enrollment make direct comparisons regarding outcomes difficult. Olaparib in combination with bevacizumab is currently listed as a front line option in the NCCN guidelines and gained FDA approval on May 8, 2020 for the "maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to 1st-line platinum-based chemotherapy and whose cancer is associated with HRD positive status, defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability". FDA also approved the Myriad myChoice® CDx (Myriad Genetic Laboratories, Inc.) as a companion diagnostic for olaparib [11,19].

1.4. Toxicity

Although the clinical benefit of PARPi therapy in the front-line setting is evident, and oral formulations are attractive to patients, daily dosing means that even low-grade side-effects can significantly impact quality of life. (Table 2) Dose interruptions and initiation of prophylactic supportive medications may permit resumption at the same dose level and help ensure that patients deriving clinical benefit remain on therapy. (Table 3) However, more severe toxicities may necessitate a dose reduction, as well as alternate supportive measures. Rarely, PARPi may need to be discontinued due to toxicity (Table 2). [2,4–7,15,20–23] It is important to proactively counsel patients on side-effect management. Simple interventions such as taking prophylactic antiemetics 30 to 60 min prior to the PARPi, taking smaller meals with more frequent snacks, avoidance of trigger foods, taking the drug with food or at bedtime, may all help mitigate the gastrointestinal side effects [23]. An additional dose should not be taken if missed or vomited [23]. It is important to consider potential interactions of PARPi with concomitant medications and certain foods (Table 3) [2,4,15,20]. Patients should be counseled to review any supplements with the clinical team.

Fatigue is a common side effect of PARPi [2,4–7,15,20–23]. Other contributing factors, such as disease-related fatigue, depression, insomnia, and anemia, or sedation from concomitant medications should be ruled out. Patients are encouraged to exercise as tolerated and consultation with a physical therapist may help maintain activity. Psychosocial interventions, including counseling, mind-body therapies, massage and education on good sleep hygiene can also help. Pharmacologic interventions, including treatment of underlying pain, depression, or insomnia may improve energy levels [21]. Brief interruptions in dosing may allow resumption of the PARPi at the same dose level.

Myelotoxicity, in particular anemia and leukopenia are common with PARPi and profound thrombocytopenia can be seen with niraparib. [2,4–7,15,20–23] It is important to ensure that patients have adequately recovered from any hematologic toxicity related to prior chemotherapy before PARPi initiation. Veliparib is the least myelosuppressive and was

Table 2
≥3 Grade toxicity during maintenance therapy post platinum-based chemotherapy.

≥3 Grade Toxicity	Olaparib [9]	Niraparib [10]	Veliparib [15]
	Olaparib/Placebo	Niraparib/Placebo	Veliparib/Placebo
Anemia	19%/2%	25%/0%	3%/1%
Thrombocytopenia	1%/1%	34%/1%	1%/<1%
Neutropenia	5%/4%	20%/2%	2%/4%
Elevated transaminases	0%/1%	4%/2%	NR/NR
Elevated creatinine	0%/0%	NR/NR	NR/NR
Fatigue	4%/2%	8%/1%	2%/1%
Nausea	3%/0%	3%/1%	1%/<1%
Hypertension	0%/0%	8%/2%	NR/NR

NR = not reported.

Table 3
Dosing, interactions, and dose reductions.

	Olaparib	Niraparib	Veliparib
Formulations	100 mg and 150 mg tablets	100 mg capsules	100 mg and 50 mg capsules
Interaction with cytochrome (CYP) enzymes	Inhibits CYP3A4 and induces CYP2B6 Avoid Seville oranges and grapefruits	Not significantly metabolized by CYP enzymes	Not significantly metabolized by CYP enzymes
Initial dose	300 mg BID (two 150 mg tablets BID)	300 mg daily (three 100 mg capsules)	400 mg BID (four 100 mg capsules BID)
1st dose reduction	250 mg BID (one 150 mg and one 100 mg tablet BID)	200 mg daily (two 100 mg capsules)	300 mg (three 100 mg capsules BID)
2nd dose reduction	200 mg BID (two 100 mg tablets BID)	100 mg daily (one 100 mg capsule)	250 mg (two 100 mg and one 50 mg capsules BID)

started during upfront therapy in the VELIA study [15]. Complete blood cell counts (CBCs) should be checked monthly, with consideration for every 2 weeks during the initial 4–6 weeks of therapy of olaparib. Niraparib requires more frequent monitoring (weekly CBCs during the first 4 to 6 weeks of therapy and after any dose reduction) due to risk of significant thrombocytopenia. Patients with baseline myelosuppression (platelets <150 K) and/or who weigh less than 77 kg may start niraparib at 200 mg daily without impact on efficacy. Transfusion may be required for symptomatic anemia, after treating any underlying vitamin and/or iron deficiencies. Erythropoiesis-stimulating agents are not advised.

Olaparib can be associated with increases in serum creatinine due to their effect on the multidrug and toxin extrusion transporters [2,5,7,20–22]. This frequently occurs early but other causes, including hydronephrosis or nephrotoxins, should be considered. Dose reduction is recommended for olaparib for creatinine clearance <50 mL/min [2,6,7,21,22]. All PARPi, especially olaparib, can cause nasopharyngitis [2,4–7,20–23]. Use of a humidifier at night and a decongestant or throat lozenges can help. Olaparib can cause rash in up to 20% of patients. [2,4–7,20–22]. Niraparib can cause hypertension and palpitations so blood pressure should be checked at home and in the clinic [4]. Pneumonitis, although rare, should be considered in a patient with worsening dyspnea and cough [2,4–7,20–22]. Myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurs in 0.5–2% of patients and necessitates long-term follow-up [2,4–7,19–23]. The rates of AML/MDS in the frontline maintenance trials were similar to the recurrence maintenance/treatment trials. The prognosis of therapy-related MDS/AML is particularly poor. Patients with prior exposure to platinum, alkylating agents (cyclophosphamide), topoisomerase II inhibitor (etoposide) and anthracycline (doxorubicin) may be at higher risk. Patients with prolonged pancytopenia, should be referred to a hematologist for further evaluation.

1.5. Testing

The four front-line studies, excluding SOLO-1, presented results of the test groups as a whole and in pre-defined subgroups based on HR pathway markers including *BRCAm* and HRD. In all four trials, subjects with a known or suspected germline or tumor mutation in *BRCA1* or *BRCA2* were reported independently. g*BRCA* are identified using normal tissue (blood, saliva or buccal swabs). t*BRCA* are identified as damaging mutations in a tumor specimen not present in germline testing. Information from germline and tumor testing may overlap. For example, an individual with an inherited *BRCAm* should also have the same mutation in their tumor. The SOLO1 trial was limited to subjects with a g*BRCA* or t*BRCA* mutation [6]. The trial included tumor genomic testing in most patients. Of the 341 patients with a tumor *BRCA* result, 17 (5%) did not confirm the germline *BRCA* status: 12 had a tumor *wtBRCA* and 5 had a tumor *BRCA* variant of uncertain significance (VUS). The discordances between germline and tumor *BRCA* mutation results were felt to be explained by differences in test coverage, variant classification, and detection of large rearrangements.

While about 25% of ovarian cancers have HRD due to germline or tumor *BRCAm*, an additional 25% have HRD due to other alterations that inactivate this pathway. In view of this, in the three trials that included wt*BRCA* patients, testing was done to attempt to define tumors with HRD using the myChoice® HRD Plus assay from Myriad Genetic Laboratories. This measures loss of heterozygosity, (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST). The numeric score used as the cutoff to define HRD varied across studies.

2. Summary

The recent data from four randomized phase 3 trials have established an important role for frontline PARPi maintenance therapy, and highlight the importance of universal germline and tumor *BRCAm* testing in ovarian cancer. While SOLO-1 only included *BRCA*m patients, PRIMA, VELIA, and PAOLA-1 enrolled broader patient populations. The magnitude of benefit of PARPi in these studies was consistently greatest in the *BRCAm* patients (germline or tumor). PARPi treatment also improved PFS in the HRD cohort but to a lesser degree than in patients with *BRCA*m. In secondary analyses, the overall impact of PARPi treatment in HR proficient patients, which comprise about 50% of ovarian cancers, was more limited than in the other subgroups and when seen was modest. Data for overall survival, also a secondary endpoint, is currently immature for these four trials. Fatigue, hematologic, and GI toxicities are the most commonly noted adverse events with PARPi therapy. These and other toxicities should be considered and discussed with patients; shared decision making should be utilized for PARPi maintenance therapy in the frontline setting. It is clear from these studies that select patients (i.e. *BRCA*m) derive significant clinical benefit with PARPi maintenance therapy in the front-line setting. The recent FDA approvals of PARPi in the frontline setting will enable clinicians to incorporate these into frontline armamentarium of ovarian cancer treatment. Many important questions such as choice of PARP inhibitor, when to utlize combination therapy with bevacizumab, role of HRD testing, optimal treatment of the HR proficient patient and cost/benefit remain unanswered and/or controversial and areas of needed future investigation.

Author contributions

- Bhavana Pothuri: conceptualization, methodology, writing-original draft, writing- review and editing, supervision, project administration.
- Deborah K Armstrong: conceptualization, writing-original draft, writing- review and editing.
- Ramez Eskander: conceptualization, writing-original draft, writing-review and editing.
- Roisin E. O'Cearbhaill: conceptualization, writing-original draft, writing- review and editing.

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