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The Current Landscape of PARP Inhibitors in Ovarian Cancer

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Abstract

Purpose of Review The aim of this study is to discuss the background of PARP inhibitors and to provide an overview of the utility of these drugs for treatment of epithelial ovarian cancer.

Recent Findings Numerous phase I–III trials are presented within the manuscript that outline the safety and efficacy of several PARP inhibitors in women with primary and recurrent ovarian cancer. There are now three FDA-approved PARP inhibitors for use in ovarian cancer patients in the USA: olaparib, niraparib, and rucaparib. These drugs have activity both alone and in combination with other agents, including chemotherapy and targeted anti-cancer drugs. Although PARP inhibitor toxicities often overlap with chemotherapy including myelosuppression, fatigue, and gastrointestinal distress, there are idiosyncratic differences in adverse event profiles and peculiar aspects of each drug. Additionally, the indications for use differ with respect to line of chemotherapy, whether a germline or somatic *BRCA* mutation is required, and maintenance versus active treatment intention. Although these were initially thought to be only applicable to patients with germline *BRCA* mutations, we now know that other patients benefit from these agents alone and in combination.

Summary The first PARP inhibitor was approved for use in the USA less than 3 years ago, but we are rapidly gaining knowledge about when and in which settings to use these drugs. Continued focused study with clinical trials will enable us to identify the optimal patient populations for prescription of these agents.

Keywords PARP inhibitors · Ovarian cancer · Epithelial ovarian cancer · Olaparib · Niraparib · Rucaparib

Introduction

Poly-ADP ribose polymerase (PARP) inhibitors are cytotoxic agents which interfere with the repair of single-stranded breaks in DNA. If single-stranded breaks remain unrepaired, they replicate and become double-stranded breaks, ultimately leading to cell death. Synthetic lethality is a process first recognized nearly a century ago wherein a defect in either one of two genes has little effect, but when two deficits are present concomitantly, cell death ensues. The use of PARP inhibitors (PARPi) in the presence of *BRCA* mutations exploits synthetic lethality due to loss of homologous recombination (HR) repair, a high fidelity process wherein the normal BRCA1 and BRCA2 proteins repair double-stranded breaks on DNA [1]. Consequently, low fidelity methods of DNA repair are triggered, such as non-homologous end joining (NHEJ), often leading to further DNA alterations. Such changes can lead to cancer initiation or progression. Although initially it was believed that the mechanism responsible for the anti-cancer effect of PARPi was loss of HR repair, it is now known that additional mechanisms contribute such as PARP trapping (which interferes with the normal catalytic cycle of PARP1) and activity beyond DNA repair such as apoptosis, transcription, and immune function [1–4].

The optimal setting for prescription of PARPi for epithelial ovarian cancer (EOC) is controversial and not yet determined. After completion of front-line chemotherapy, one may defer further treatment until there is evidence of disease recurrence, which unfortunately will manifest in the majority (75–85%) of patients. This enables patients to have a treatment-free interval. Alternatively, continuation of further treatment after

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completion of planned chemotherapy is sometimes elected. This entails maintenance therapy, wherein the goal is prolonging the interval until disease recurrence. The debate with maintenance therapy is what degree of clinical benefit justifies its use given the additional toxicities incurred, since the alternative is a treatment holiday and the prospect of recovery from detrimental effects of upfront treatment. Establishing meaningful endpoints for the use of maintenance therapy requires a thorough understanding of disease- and treatment-related symptoms and also overall prognosis. Herein we aim to outline the currently available data on PARPi use for active treatment, PARPi for maintenance therapy, and the toxicities associated with various PARPi.

Timing of PARPi Use

With three PARPi now approved by the Food and Drug Administration (FDA) in the USA and one in the European Union (EU), the treatment paradigm for recurrent EOC has become more complex. There are questions of who should receive a PARPi and in what line of therapy. Olaparib was approved by the US FDA December 19, 2014 for use in patients who harbor a germline BRCA mutation (gBRCA) and who have received ≥ 3 lines of prior chemotherapy [5]. It was approved by the EU in October 10, 2014 for use as monotherapy maintenance in women with relapsed, platinum-sensitive EOC who have responded to platinum-based chemotherapy and also harbor gBRCA [6]. On August 17, 2017, the FDA approved olaparib for maintenance therapy after complete or partial response to chemotherapy for platinum sensitive disease.

The PARPi rucaparib was granted US FDA approval in December 2016 for treatment of women with relapsed EOC who harbor a gBRCA or somatic BRCA (sBRCA) mutation and have received > =2 lines of prior chemotherapy. The randomized phase 3 trial (ARIEL3; NCT01968213) evaluating rucaparib in women with relapsed, platinum-sensitive EOC led to the US FDA approval.

The PARPi niraparib was granted US FDA approval in March 2017 for use as monotherapy maintenance in women with relapsed, platinum-sensitive EOC who have responded to platinum-based chemotherapy *irrespective* of BRCA mutation status. This approval was based on the NOVA study (NCT01847274), which evaluated response to maintenance niraparib in gBRCA and wild-type BRCA patients with designated subgroups with and without homologous recombination deficiency (HRD) [7••]. Benefit with niraparib was noted in all subgroups, leading to the approval. Single-agent niraparib efficacy in the treatment setting awaits the completion of the QUADRA trial (NCT 02354586).

With these approved and pending indications, providers may elect to use a PARPi for patients irrespective of BRCA status in the maintenance setting (niraparib or olaparib) or reserve use of PARPi for a treatment line with gBRCA or sBRCA (olaparib or rucaparib). This section of the review will summarize the outcomes data for PARPi used as a line of active treatment in relapsed EOC as well as summarize completed and ongoing combination studies including PARPi.

Single-Agent PARPi for Active Treatment

Olaparib (Astra Zeneca) was the first PARPi to be approved in the USA and the EU in 2014 (Table 1). In the USA, it is indicated with ≥ 3 prior therapies in women who harbor a gBRCA mutation. This approval was based on a pooled analysis of data but was primarily drawn from Study 42, which was a basket trial of olaparib 400 mg capsules BID across several solid tumors in which patients had a gBRCA mutation. Of the 193 EOC patients, the overall response rate (ORR) was 31.3% (95% CI 24.6–38.1). The overall median duration of response (DOR) was 225 days [8]. A pooled analysis from both phase I and II trials of olaparib was performed to look at tumor outcomes among patients 300 patients with EOC. When restricted to patients who had both measurable disease and received > 3 lines of chemotherapy, the analysis included 205 patients. ORR was 36%, and the median DOR was 7.4 months. Importantly, this analysis also evaluated ORR by lines of prior therapy among the entire cohort. They reported that the ORR decreases from 50% with only 1 prior line, 31% with > 3 prior lines, and 24% for > 6 prior lines of therapy [12]. This suggests that PARPi should not be reserved until later lines of therapy if efficacy is to be preserved. Based on the results of SOLO-2 (NCT01874353) and Study 19 (NCT00753545), the FDA approved olaparib for maintenance therapy after response to chemotherapy for platinum sensitive disease in 2017.

Rucaparib (Clovis) was the second PARPi to gain approval by the US FDA in December 2016. This approval is for treatment of women with relapsed EOC, gBRCA or sBRCA, and ≥ 2 lines of chemotherapy. This approval was based on the pooled analysis of Study 10 (NCT01482715) and ARIEL 2 (NCT01891344) and included 106 patients who all received 600 mg po BID. The ORR was 54% (95% CI 44, 64), and the median DOR was 9.2 months (95% CI 6.6, 11.6) [10, 11••] (Table 1).

Niraparib (Tesaro) was the third PARPi to gain approval by the US FDA in March 2017 for use as monotherapy maintenance following platinum-based therapy in patients with relapsed EOC irrespective of BRCA status at a dose of 300 mg once daily. Single-agent efficacy for treatment is pending the results of the QUADRA study (NCT02354586), which is still accruing. In the phase I study, Sandhu et al. reported an ORR of 40% (inclusive of both RECIST and CA-125 responses),

Table 1 Single-agent PARP inhibitor therapy for active treatment

	Agent	Population	ORR	Median PFS/DOR
NCT01078662 (Study 42) [9••]	Olaparib 400 mg capsule BID	gBRCA, ≥ 3 lines of prior therapy measurable disease	34% (95% CI 26, 42)	DOR 7.9 (95% CI 5.6, 9.6)
NCT010482715 (Study 10) NCT01891344 (ARIEL2) [10, 11••]	Rucaparib 600 mg tablets BID	gBRCA and sBRCA, ≥ 2 lines of prior therapy, measurable disease	54% (95% CI 44, 64) PS: 66% (95% CI 54, 76) PR 25% (95% CI 9, 49) PRef 0%	DOR 9.2 (95% CI 6.6,11.6)
NCT02354586 QUADRA	Niraparib 300 mg tablets qd	Unselected but enriched for HRD+ patients, 3–4 prior therapies, measurable disease	Study is still accruing	Study is still accruing
NCT01540565 GOG 280(13)	Veliparib 400 mg tablets po BID	gBRCA, 1–3 prior therapies, measurable disease	26% (95% CI 16–38) PS 35% (95% CI 18–56) PR 20% (95% CI 9–36%)	Median PFS 8.18 months

ORR overall response rate, *PFS* progression-free survival, *DOR* duration of response, *PS* platinum sensitive, *PR* platinum resistant, *PRef* platinum refractory

and a median DOR of 387 days at doses that ranged from 80 to 400 mg/day [13].

Veliparib (AbbVie) has not yet gained an FDA indication. It has been studied as a single agent in a treatment trial that included both platinum-sensitive and platinum-resistant recurrent EOC patients with a gBRCA mutation. ORR was 26%; however, when separated out into platinum-sensitive and platinum-resistant, it was 35 and 20% respectively [14].

Single-agent PARPi has demonstrated a strong signal among patients with gBRCA or sBRCA with high ORR and reasonable DOR, especially given the line of therapy in which these patients were often treated. The next question is how these results compare in terms of ORR and DOR and, importantly, quality of life to chemotherapy. There are several ongoing studies which will attempt to answer this important question. ARIEL4 (NCT02855944) compares rucaparib to chemotherapy among patients with relapsed EOC, gBRCA mutations, and ≥ 2 lines of prior therapy. This study includes platinum-based therapy as a physician's choice option. SOLO3 (NCT02282020) compares olaparib to physician's choice chemotherapy among patients with relapsed EOC, gBRCA mutations, and ≥ 2 lines of prior therapy. Platinum-based regimens are not an option here. These studies will aid the discussion of whether or not PARPi should replace chemotherapy as a line of therapy or is best used in the maintenance setting.

PARPi Combinations for Active Treatment

While none are yet approved for use outside clinical trials, there is growing excitement about the ability to expand the population for whom PARPi may be a beneficial therapy through novel combinations. One of the more promising areas is combination of PARPi with anti-angiogenic agents. The rationale for this combination comes from evidence that tumor hypoxia (which may be induced by anti-angiogenic agents) regulates DNA repair gene expression. Depending on the degree and chronicity of induced hypoxia, proteins involved in base excision repair, mismatch repair, homologous recombination, etc. can undergo transcriptional, translational, or epigenetic modifications. This results in down-regulation of DNA damage repair pathway proteins, which may induce a BRCA-like phenotype, which is more responsive to PARPi [15]. This theory has been borne out by Liu et al. in a randomized phase 2 trial including patients with relapsed, platinum-sensitive EOC. Patients were not required to have a gBRCA mutation to participate. They were randomized to olaparib 400 mg capsules BID or to olaparib 200 mg BID plus cediranib 30 mg po qd. Among the 90 patients enrolled, approximately 52% were known gBRCA, 13% had never seen an anti-angiogenic agent, and > 50% had a progression-free interval (PFI) from their penultimate platinum of 6–12 months. Twenty-one percent of patients had ≥ 3 prior lines of therapy. Among the entire study group, the median PFS was 8.2 vs. 16.5 months in the olaparib vs. olaparib/cediranib group, respectively (HR 0.50; 95% CI 0.3–0.83; $p = 0.007$). In a subset analysis however, those patients with a known gBRCA had a median PFS of 16.5 and 16.4 months, respectively (HR 0.75; 95% CI 0.38–1.49; $p = 0.42$), but those who were BRCA unknown or wild type had a median PFS of 5.7 vs. 23.7 months, respectively (HR 0.32; 95% CI 0.16–0.66; $p = 0.002$) [16, 17]. This study suggests that the greatest benefit of combination therapy is in those patients who do not harbor a gBRCA mutation. While promising, this combination was not without adverse events which included hypertension (80% G1–4; 41% G3–4), diarrhea (93% G1–4; 23% G3), fatigue (86% G1–4; 27% G3), nausea (73% G1–4, 5% G3), headache (44% G1–4, 5% G3), and hypothyroidism (16% G1–2) [16, 17].

As previously mentioned, while promising, this regimen needs to compare favorably to chemotherapy in outcomes and

QOL in order to consider it a replacement for standard platinum-based chemotherapy. Currently ongoing studies include NCT02446600 (NRGY004) which compares olaparib alone, olaparib + cediranib, and standard platinum-based chemotherapy in patients with platinum-sensitive recurrent EOC. A second trial, NCT02502266 (NRGY005), is comparing cediranib + olaparib, cediranib alone, olaparib alone, or standard chemotherapy for patients with recurrent platinum-resistant EOC.

Given the promise of anti-angiogenic/PARPi combinations and the toxicity of cediranib, another anxiously awaiting ongoing trial is NCT02354131 (AVANOVA) which is comparing niraparib to niraparib + bevacizumab to bevacizumab alone in patients with relapsed platinum-sensitive ovarian cancer who harbor HRD.

Combinations of PARPi and monoclonal antibodies targeting cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death protein 1 (PD-1 or PD-L1) are also of interest. Targeting these inhibitory proteins with monoclonal antibodies allows for a more immune stimulatory environment. Targeting CTLA4 attempts to restore T cell priming and activation (ipilimumab or tremilimumab), and targeting PD-1/PD-L1 aims to restore T cell function through a number of mechanisms within the tumor microenvironment, including preventing tumor-infiltrating lymphocyte (TIL)-induced PD-L1 expression, increased effector T cell signaling and cytokine production, and decreased susceptibility to T cell apoptosis [18]. With these combinations, the rationale is that patients with EOC who have gBRCA (and perhaps HRD) harbor higher neo-antigen loads, which should make them more susceptible to immune checkpoint blockade, which is supported by pre-clinical data. Higuchi et al. reported that the combination of anti-CTLA4 antibodies and PARPi but not combination of anti-PD-1/PD-L1 plus PARPi resulted in immune-mediated tumor clearance and long-term survival of BRCA-deficient mice [19]. The same group then moved on to a phase I clinical trial in women with relapsed EOC and gBRCA mutation who received olaparib 300 mg tablets BID plus tremelimumab 10 mg/kg monthly [20]. This phase I trial demonstrated feasibility for the combination and has led to an ongoing phase 2 trial (NCT02571725).

The anti PD-L1 inhibitor durvalumab has been evaluated in a phase I trial in combination with olaparib or cediranib (NCT02484404). Eighty-three percent of the patients enrolled had relapsed EOC; none of them were gBRCA in the durvalumab/olaparib cohort. The recommended phase 2 dose was durvalumab 1500 mg every 4 weeks with olaparib 300 mg po bid. ORR for this combination was 17%, and clinical benefit rate of 83%. There were no dose-limiting toxicities noted for this combination, and the most common treatment-related adverse events were anemia (42% G1–4; 8% G3), thrombocytopenia (25% G1), nausea (58% G1–4, 0% G3–4), diarrhea (30% G1–4, 0% G3–4), and fatigue (75% G1–4, 0% G3–4). The phase 2 component of this study is still enrolling [21].

In addition, NCT02734004 (MEDIOLA) which is a phase 1–2 study of durvalumab and olaparib in recurrent, platinum-sensitive EOC for gBRCA patients and NCT02953457, a phase 1–2 study of combination durvalumab, tremelimumab, and olaparib in the same population (inclusive of somatic BRCA mutation carriers) are currently enrolling. NCT02657889 (TOPACIO) is a phase 1–2 study of niraparib and the anti-PD-1 antibody pembrolizumab in patients with recurrent triple negative breast cancer and platinum-resistant EOC (≤ 4 lines of therapy). This study has not been reported but at a press briefing at ASCO 2017, the company reported a disease control rate of 69% in the EOC cohort. Because of the risk of thrombocytopenia at the 300 mg qd dose of niraparib, the phase 2 portion of the study was enrolled using 200 mg qd. Results of this study are anticipated later in 2017 [6].

Combination studies extend beyond those being performed with anti-angiogenic agents and immune-oncology agents. Promising pre-clinical data supporting the combination of PI3K inhibition and PARPi led to the phase I trial exploring the pan PI3K inhibitor BKM120 in combination with olaparib. Of the 70 patients enrolled, 46 had EOC, and 70% of these had a gBRCA mutation. The maximum tolerated dose was BKM120 50 mg qd and olaparib 300 mg po bid. ORR was 29% irrespective of platinum sensitivity, which is not much different than what would be seen with olaparib monotherapy in this population of mostly gBRCA patients [22]. While somewhat disappointing, this combination may be most effective in BRCA wild-type patients just as was seen in the olaparib + cediranib study, and further exploration of this combination in that molecular subgroup may be warranted.

PARP for Maintenance Therapy

Given the high recurrence rates of EOC, multiple trials have assessed the role of maintenance therapy after surgery and adjuvant platinum-based chemotherapy (see Table 2). To date, no trial has demonstrated a survival advantage with this strategy [23–26]. Moreover, maintenance therapy adds cumulative toxicity and negatively impacts quality of life and has therefore not been adopted in upfront treatment strategies. PARPi are orally administered and better tolerated than chemotherapy, so their use in the maintenance setting has appeal.

Maintenance Therapy After Treatment for Recurrent Disease

The first trial to show promise of PARPi for maintenance was Study 19 [27]. Women were eligible for this phase II trial if they had high-grade serous ovarian, primary peritoneal, or fallopian tube cancer and had received ≥ 2 platinum-based

Table 2 PARP inhibitor use for maintenance therapy

	Trial name	Treatment	Design	Study population	BRCA status	Primary outcome	HR with PARP therapy
PARP after primary therapy	SOLO 1	Olaparib 300 mg tablets BID vs placebo	RPh3	CR or PR after upfront platinum-based therapy	gBRCA mutant	PFS	Ongoing
	PRIMA	Niraparib 300 mg daily vs placebo	RPh3	CR or PR after upfront platinum-based therapy	Any	PFS	Ongoing
	GOG 3005	T/C + - concurrent and maintenance veliparib	RPh3	Adjuvant or planned neoadjuvant chemotherapy	Any	PFS	Ongoing
	PAOLA	Olaparib 300 mg tablets BID vs placebo	RPh3	CR or PR after upfront platinum-based therapy. Received upfront bev with plan to continue bev maintenance	Any	PFS	Ongoing
PARP after recurrence treatment	Study 19	Olaparib 400 mg capsule BID vs placebo	RPh2	Recurrent with ≥ 2 platinum regimens with CR or PR	Any	PFS	All: 0.35 ($p < 0.001$) gBRCA: 0.18 ($p < 0.001$)
	SOLO2	Olaparib 300 mg tablets BID vs placebo	RPh3	Recurrent with ≥ 2 platinum regimens with CR or PR	gBRCA mutant	PFS	0.30**
	NOVA	Niraparib 300 mg daily vs placebo	RPh3	Recurrent with ≥ 2 platinum regimens with CR or PR	Any	PFS	gBRCA: 0.27 ($p < 0.001$); HRD: 0.38 ($p < 0.001$)
	ARIEL3	Rucaparib 600 mg BID vs placebo	RPh3	Recurrent with ≥ 2 platinum regimens with CR or PR	Any	PFS	All: 0.35** BRCA mut: 0.23** HRD: 0.32**

HR hazard ratio, *RPh3* randomized phase 3 trial, *RPh2* randomized phase 2 trial, *CR* complete response, *PR* partial response, *PFS* progression-free survival, *T/C* paclitaxel and carboplatin, *bev* bevacizumab, *gBRCA* germline BRCA mutation, *HRD* homologous recombination deficiency

**Signifies all HR with $p < 0.0001$

regimens with a partial or complete response to therapy. Women were randomized to olaparib 400 mg twice daily or placebo. *BRCA* mutation status was not considered for enrollment or treatment allocation. PFS was improved in the olaparib arm (8.4 vs 4.8 months, hazard ratio (HR) 0.35, 95% CI 0.25–0.49, $p < 0.001$). Interim analysis did not show a difference in OS (HR 0.94, 95% CI 0.63–1.39, $p = 0.75$). In a pre-planned analysis of survival by *BRCA* mutation status, patients with a deleterious mutation who were randomized to olaparib therapy had a remarkably low hazard ratio for recurrence (HR 0.18, 95% CI 0.10–0.31, $p < 0.001$), but wild-type patients still derived substantial benefit from therapy (HR 0.54, 95% CI 0.34–0.85, $p = 0.0075$).

Olaparib maintenance in the platinum-sensitive recurrent setting was further explored in the SOLO2 trial (NCT01874353). Eligibility included recurrent high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer with a deleterious germline *BRCA* mutation. Similar to Study 19, patients completed ≥ 2 lines of platinum-based therapy with a complete or partial response. Preliminary results were presented at the Society of Gynecologic Oncology in March of 2017 [28]. A significant improvement in PFS (primary endpoint) was noted in the olaparib arm, 19.1 versus 5.5 months, translating into a HR for progression of 0.30 (95% CI 0.22 to 0.41, $p < 0.0001$). When measured by a blinded independent central review, PFS was 30.2 versus 5.5 months (HR 0.25, 95% CI 0.18–0.35, $p < 0.0001$). Given the concern that PARPi may negatively affect subsequent responses to chemotherapy, time to second recurrence was also measured; it remained significantly improved in the olaparib arm (HR 0.50, 95% CI 0.34–0.72, $p = 0.0002$).

Maintenance niraparib was tested in a similar fashion in the NOVA trial [7••]. In this phase III trial, subjects were randomized to 300 mg of niraparib daily versus placebo. All patients had platinum-sensitive recurrent high-grade serous ovarian, primary peritoneal, or fallopian tube cancer with ≥ 2 previous platinum-based regimens with a complete or partial response. To be eligible for this trial, patients needed to have ≥ 6 month interval without disease progression following their penultimate platinum-based regimen. *BRCA* mutation was known at study enrollment, and patients were analyzed according to mutation status. Of the 37% of patients with a germline *BRCA* mutation, niraparib-treated patients had greater PFS, 21.0 versus 5.5 months (HR 0.27, 95% CI 0.17–0.41). A PFS advantage was also seen in the non-germline *BRCA* group with a HR of 0.45 (95% CI 0.34–0.61). Patients without a germline BRCA mutation with homologous recombination deficiency (HRD) via tumor testing still had a significant PFS advantage (12.9 vs 3.8 months, HR 0.38). The provocative results of the NOVA study led to the FDA approval of niraparib for maintenance therapy with platinum-sensitive EOC (https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm548487.htm).

Just as niraparib and olaparib therapy were associated with a significant improvement in PFS when used as maintenance therapy after a platinum-sensitive recurrence, preliminary

results from the ARIEL3 trial (NCT01968213) also demonstrated an improvement in PFS with rucaparib maintenance [13]. Eligibility for ARIEL3 was similar to the NOVA trial [7••]. Subjects were randomized to 600 mg of rucaparib twice daily versus placebo. The primary endpoint was PFS. For the entire intention-to-treat population, PFS was improved in the rucaparib arm (10.8 vs 5.4 months; HR 0.35, $p < 0.0001$). Predefined subgroups were also assessed for treatment effect. Patients with a *BRCA* mutation (germline or somatic) demonstrated maximum effect from rucaparib therapy with a HR of 0.23 ($p < 0.0001$), but patients with somatic HRD also had improved PFS with a HR of 0.32 ($p < 0.0001$).

SOLO2, NOVA, and ARIEL3 evaluated the effects of PARP as maintenance therapy after recurrent high-grade ovarian cancer treatment. Ongoing studies are investigating the earlier use of PARP as maintenance therapy following upfront chemotherapy.

Maintenance Therapy after Primary Treatment

In the SOLO1 trial (NCT01844986), women with a deleterious *BRCA* mutation and complete or partial response to upfront platinum-based therapy are randomized to placebo or olaparib 300 mg twice daily.

Additional upfront trials are enrolling women regardless of *BRCA* status. Niraparib is being evaluated in the PRIMA trial (NCT02655016), which randomizes women to PARPi versus placebo following a complete or partial response to first-line platinum-based chemotherapy. All women will undergo tumor HRD testing as part of study enrollment.

In the three-arm phase III Gynecology Oncology Group 3005 trial (NCT02470585), veliparib is being used in combination with upfront chemotherapy and then continued on for up to 30 cycles of maintenance therapy. One arm contains placebo, one arm includes veliparib with upfront chemotherapy only (then placebo maintenance), and one arm includes veliparib with upfront chemotherapy and then veliparib for maintenance. All patients undergo germline and tumor *BRCA* testing.

Finally, PAOLA-1 (NCT02477644) is a phase III trial of olaparib in combination with bevacizumab for maintenance following upfront therapy. Eligible patients are those who had a complete or partial response following initial platinum chemotherapy plus bevacizumab, and for whom bevacizumab maintenance therapy is planned. Tumor *BRCA* testing will be performed on all patients.

Toxicity of PARP Inhibition

Current toxicity data comes from phase 2 and 3 trials that investigated the efficacy of PARPi either as primary treatment or maintenance therapy. Nearly all patients enrolled in these trials experienced at least one adverse event. The most common non-hematologic adverse events were nausea and fatigue. Any grade nausea was reported as > 60% in all trials with the highest reported rate of 86% with veliparib [10, 11••, 14, 27, 7••, 29, 30]. Nausea and vomiting were major contributors to dose delays and reductions [11••, 14, 27]. Fatigue was reported in approximately 50% or more of patients taking a PARPi with the highest reported rate of 78–86% with rucaparib; additionally, fatigue was the most common reason for discontinuation of treatment [10, 11••]. The most common hematologic side effect was anemia, with a reported rate of any grade anemia occurring in approximately 30–70% [10, 11••, 14, 27,7••, 29, 30]. Table 3 notes the frequency of adverse events for each of the FDA approved PARP inhibitors in phase 3 trials.

While the majority of these side effects were effectively managed with supportive care and dose reductions, perhaps the most concerning long-term complication is the development of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). *BRCA1* and *BRCA2* interact with members of the Fanconi anemia pathway. Patients with homozygous mutations in this pathway lack adequate DNA repair mechanisms and are at high risk of developing a malignancy, specifically AML. In patients with *BRCA* mutations, cells rely on base-excision repair for which PARP enzymes are instrumental. Therefore, while utilizing the theory of synthetic lethality to treat *BRCA*-mutated cancers with PARP inhibition, it likely leads to an increased rate of MDS and AML [31, 32]. The incidence of AML and MDS with olaparib treatment was approximately 2% on both the single-arm and randomized controlled trial; however, in all reported patients treated with olaparib, this occurred in < 1% (22/2618 patients). It is important to note that majority of these cases were fatal (17/22) [33].

Table 3 Adverse Events Noted with PARP Inhibitors

	Anemia G1-4/G3-4	Neutropenia G1-4/G3-4	Low Plts G1-4/G3-4	Fatigue G1-4/G3-4	Nausea G1-4/G3-4	Vomiting G1-4/G3-4	Diarrhea G1-4/G3-4	Elevated Cr G1-4/G3-4	Elevated LFTs G1-4/G3-4
Olaparib (phase 2; FDA label)	90%/15%	25%/7%	30%/3%	66%/8%	64%/3%	43%/4%	31%/1%	30%/2%	NR/NR
Rucaparib (phase 3)[73]	37%/19%	18%/7%	28%/5%	69%/7%	75%/4%	37%/4%	32%1%	15%/1%	34%/10%
Niraparib (phase 3)[57]	50%/25%	30%/20%	61%/34%	60%/8%	74%/3%	34%/2%	19%/0%	NR	NR

In addition to the data on olaparib, recently published data on niraparib reports the development of MDS in 1.4% (5/367) patients [7••].

Response rates to PARPi have been promising, particularly in patients with *BRCA* mutations. However, as with most other cancer therapies, the development of resistance remains a major challenge and is particularly problematic as PARPi gain more indications and broader use. There are several proposed mechanisms for resistance to PARPi therapy. First, reversion mutations have been identified, which involve reprogramming of the DNA damage response and homologous repair proficiency [34]. Therein, the open reading frame of *BRCA* 1 or 2 is restored, resulting in a functional BRCA protein and loss of synthetic lethality. One report looked at pre- and post-treatment biopsies of patients that were initially sensitive to olaparib but subsequently developed resistance. Post-treatment biopsies demonstrated a full-length BRCA 2 protein [35]. These mutations have been reported to lead to both platinum and PARPi resistance in *BRCA 1* and *2* germline-deficient patients [36, 37], and recently it has been demonstrated that reversion mutations are detectable in circulating cell-free DNA [38]. A second mechanism of PARPi resistance is a decrease in activation of the NHEJ pathway (which is normally upregulated with PARPi use), which may lead to PARPi resistance [39]. Third, lower activity of PARP-1 can decrease the efficacy of PARPi use. Two final mechanisms of PARPi resistance are upregulation of efflux pumps, thereby decreasing intracellular concentration of PARPi, and increased *RAD51 levels*, an important HR protein. Further research is needed to elucidate the rate of development and conditions associated with reversion mutations and other mechanisms of PARPi resistance, with an emphasis on their role as a potential biomarker for sensitivity to PARPi therapy.

Conclusion

PARPi are a prime example of a modern drug in which molecular profiling technologies can identify patients who are likely to receive benefit. Use of precision medicine in ways such as this is smart and individualized but is also of keen interest in this population given the rampancy of disease recurrence and the emergence of resistance and toxicities. There is accumulating data which suggests that PARPi have impressive activity in heavily pretreated and even platinum-resistant patients, for whom there are few effective therapies. Determining the optimal mode and setting in which to deliver these drugs remains a burning clinical and laboratory question for those who care for women with EOC. Although these drugs have overlapping toxicities with traditional chemotherapy, their overall tolerability and activity are encouraging and have ignited broader study in various settings such as maintenance therapy and active treatment combination strategies.

Compliance with Ethical Standards

Conflict of Interest Britt K. Erickson and Megan E. Buechel declare no conflict of interest. Camille C. Gunderson is on the Clovis advisory board Dr Gunderson is also a consultant for Celsion. Kathleen N. Moore is on the advisory boards for Genentech Roche, Astra Zeneca, Amgen, Immunogen, Clovis, Tesaro, Janssen, and VBL Therapeutics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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