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PARP inhibitors in ovarian cancer: evidence, experience and clinical potential

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***Abstract*:** Inhibitors of poly(ADP-ribose) polymerase (PARP) are considered one of the most active and exciting new therapies for the treatment of ovarian cancer. The anticancer activity of PARP inhibitors is based on the DNA repair vulnerability of many ovarian cancer cells, and multiple mechanisms of action of PARP inhibitors have been identified. As single agents, PARP inhibitors have demonstrated their greatest activity in ovarian cancer cells that harbor mutations in *BRCA* genes. Additionally, recent phase III studies have shown that single-agent PARP inhibitor activity extends beyond BRCA-related cancers and can benefit patients with ovarian cancers that do not have known *BRCA* mutations, especially when clinical characteristics such as platinum sensitivity and high-grade serous histology are present. PARP inhibitors have also been combined with chemotherapy, however, overlapping myelosuppression observed with PARP inhibitor and chemotherapy combinations has hampered development of these combinations. Contrariwise, PARP inhibitor and biologic agent combinations, specifically antiangiogenic agents, appear well tolerated and show promising activity in both *BRCA* mutated (*BRCA*m) and *BRCA* wild-type (*BRCA*wt) cancers. Currently, multiple clinical trials are underway examining the antitumor activity of PARP inhibitor combination therapy.

Keywords: PARP inhibitors, ovarian cancer, BRCA mutations, targeted therapy

Introduction

Inhibitors of poly(ADP-ribose) polymerase (PARP) have emerged as one of the most exciting new therapies for the treatment of ovarian cancer, based on the vulnerability of ovarian cancer cells to agents that interrupt DNA repair. In 2014, PARP inhibitors received regulatory approval for the treatment of ovarian cancer by both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The greatest efficacy for the use of PARP inhibitors in ovarian cancers, resulting in initial regulatory approval, has been for patients with cancers harboring *BRCA*m, either germline BRCA mutations (g*BRCA*m) or somatic/tumor *BRCA* mutations (t*BRCA*m). However, PARP inhibitor activity also exists in *BRCA*wt cancers especially in those such as high-grade serous cancers (HGSCs) that exhibit homologous recombination deficiency (HRD) through mutations or other molecular aberrations in critical DNA repair genes. Largely, PARP inhibitors exhibit their antitumor effect through catalytic inhibition of single-strand DNA break repair [Plummer and Calvert, 2007; Murai *et al.* 2012], ultimately having a damaging impact on cells defective in homologous recombination. However, other mechanisms of action of PARP inhibitors have been identified beyond the inactivation of the PARP1 and PARP2 enzymes concomitantly in the setting of underlying *BRCA* deficiency such as interference with other DNA repair pathways and PARP trapping [Murai *et al.* 2012; Konstantinopoulos *et al.* 2015]. Though many histologies of ovarian cancer possess some degree of DNA repair defects [Cancer Genome Atlas Research Network, 2011; Pennington *et al.* 2014], eligibility of PARP inhibitor trials has primarily been limited to HGSC, where DNA repair defects have been found in approximately 50% of cancers as well as high-grade endometrioid cancers [Pennington *et al.* 2014]. Olaparib was the first PARP inhibitor to receive regulatory approval in the United States and Europe in 2014 to treat

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recurrent g*BRCA*m ovarian cancer and *BRCA*m recurrent ovarian cancer as maintenance therapy postplatinum treatment, respectively. The first reported phase III PARP inhibitor trial tested the PARP 1 and 2 inhibitor niraparib *versus* placebo as maintenance therapy following response to platinum therapy for patients with platinum-sensitive recurrent ovarian cancer and demonstrated the benefit of a PARP inhibitor beyond BRCA-related cancers, extending the benefit of PARP inhibitors to all HGSCs in this clinical setting [Mirza *et al.* 2016]. Other phase III studies are ongoing, examining the role of single-agent PARP inhibitors both in *BRCA*m ovarian cancer, as well as in *BRCA*wt ovarian cancer, both in newly diagnosed patients, as well as those with recurrent ovarian cancer. In addition, strategies to increase the anti-cancer activity of PARP inhibitors by combining them with cytotoxic agents and other biologic agents, such as antiangiogenic or immune checkpoint inhibitors are being tested in ongoing clinical trials. This review will focus on the published data of single-agent and combination studies with PARP inhibitors, currently open studies actively accruing patients, the toxicities of PARP inhibitors, and discuss future directions of this drug class in the treatment of ovarian cancer.

Single-agent poly(ADP-ribose) polymerase inhibitors

Two papers published in 2005 were the first to show *in vitro* activity of PARP inhibitors against cancer cells harboring a *BRCA*m [Farmer *et al.* 2005; Bryant *et al.* 2005]. Since then, single-agent PARP inhibitors have been tested in both *BRCA*m *and BRCA*wt cancers as well as platinum-resistant and platinum-sensitive cancers [Liu and Matulonis, 2016; Fong *et al.* 2009; Kaufman *et al.* 2015; Audeh *et al.* 2010; Gelmon *et al.* 2011].

Olaparib

The first publication of PARP inhibitor monotherapy in ovarian cancer occurred in 2009, in a phase I study testing single-agent olaparib administered as a twice-daily (BID) capsule in patients with recurrent ovarian cancer [Fong *et al.* 2009]. Notably, the greatest efficacy and most durable responses were noted in patients whose cancers harbored a *BRCA*m, specifically patients with a g*BRCA*m, thus confirming the results of previous *in vitro* studies [Farmer *et al.* 2005; Bryant *et al.* 2005]. Fong and colleagues in this phase I study of olaparib escalated the dose and scheduling of olaparib from 10 mg/day for 2 of every 3 weeks to 600 mg BID daily and continuously [Fong *et al.* 2009]. Of the patients receiving the 600 mg BID, grade 3 somnolence and grade 4 thrombocytopenia resulted in the 400 mg BID capsule formulation of olaparib being deemed the maximally tolerated dose (MTD).

Based on these encouraging phase I study results, additional phase II studies of single-agent olaparib were undertaken, demonstrating the drug's activity in patients with g*BRCA*m as well as noncarriers, with a lower but observed efficacy noted in patients with wt*BRCA*m ovarian cancers [Fong *et al.* 2009; Kaufman *et al.* 2015; Audeh *et al.* 2010; Gelmon *et al.* 2011]. In a proof-of-concept trial, Audeh and colleagues demonstrated an overall response rate (ORR) of 33%, using the 400 mg BID dosing of olaparib in recurrent g*BRCA*m cancers *versus* 13% for patients receiving the 100 mg BID-dosing schedule [Audeh *et al.* 2010]. Gelmon and colleagues showed an ORR of 24% for olaparib in *BRCA*wt HGSC or undifferentiated ovarian cancer [Gelmon *et al.* 2011].

Olaparib was also the first PARP inhibitor to enter into randomized phase II studies, and two trials were performed to identify a possible registration strategy for olaparib as a single agent; one of these studies was Study 19, which was a randomized phase II, double-blinded placebo-controlled trial of olaparib maintenance therapy *versus* placebo in patients with relapsed platinum-sensitive HGSC [Ledermann *et al.* 2012, 2014, 2016]. This study enrolled 265 patients with platinum-sensitive relapsed HGSC and demonstrated that postplatinum-response-maintenance olaparib, administered at a dose of 400 mg BID capsule *versus* placebo, resulted in a significant improvement in median progression-free survival (PFS) from 4.8 months on placebo to 8.4 months on olaparib [hazard ratio (HR) = 0.35, $p < 0.001$] [Ledermann *et al.* 2012] (Table 1). Furthermore, in a retrospective preplanned analysis, this study investigated the benefit of olaparib in women with *BRCA*m ovarian cancer, including patients with g*BRCA*m or t*BRCA*m; PFS benefit was 11.2 months with olaparib maintenance *versus* 4.3 months with placebo (HR = 0.18, $p < 0.0001$) [Ledermann *et al.* 2014]. More recently, overall survival (OS) of Study 19, as well as the exploratory endpoints of time-to-first subsequent therapy or death, time-to-second subsequent therapy or death, and toxicities have been updated using the

Table 1. Randomized phase II studies of PARP inhibitors in recurrent ovarian cancer.

Trial name [ClinicalTrials.gov identifier]	Patient population and key eligibility	Total patient accrual	Treatment arms	Primary endpoint	Results
Olaparib					
Study 19 NCT00753545 Ledermann *et al.* [2012, 2014, 2016]	Platinum sensitive recurrent HGSOC (both germline BRCA and sporadic)	265	(1) Olaparib 400 mg BID (2) Placebo Given as maintenance following platinum-based chemotherapy	PFS	11.2 months (m)/5.6 months (wt) $p < 0.00001$ For placebo: 4.3 months (m)/5.5 months (wt) $p = 0.007$
Study 12 NCT00628251 Kaye *et al.* [2012]	g*BRCA* mutation carriers, No prior PLD	97	(1) Olaparib 400 mg BID (2) Olaparib 200 mg BID (3) PLD 50 mg/m^2	PFS	No difference amongst arms for PFS; 6.5 mos (200), 8.8 mos (400), 7.1 mos (PLD)
NCT01081951 Oza *et al.* [2015]	Platinum sensitive recurrent HGSOC (both germline BRCA and sporadic)	162	(1) Olaparib (200 mg BID, d1–10/21) Pac (175 mg/m^2 iv, d1) C (AUC4 iv, d1), olaparib 400 BID maintenance (2) C AUC 6, Pac 175 mg/m^2	PFS	Median PFS 12.2 (olaparib arm) *versus* 9.6 mos (no olaparib) $p = 0.0012$
NCT01116648 Liu *et al.* [2014a]	Platinum-sensitive recurrent HGSOC (both germline BRCA and sporadic allowed)	90	(1) Cediranib 30 mg daily and olaparib 200 mg BID (ced/olap) (2) olaparib 400 mg BID (olap)	PFS	Median PFS 17.7 months (ced/olap) *versus* 9 months (olap) For gBRCA pts: 19.4 *versus* 16.5 months For *BRCA*wt or unknown: 16.5 *versus* 5.7 months
Veliparib					
NCT01113957	Recurrent HGSOC (both germline BRCA and sporadic allowed)	168	(1) Veliparib and temozolomide (2) PLD	ORR	Results not available
NCT01306032 Kummar *et al.* [2015]	Recurrent HGSOC (both germline BRCA and sporadic allowed)	74	(1) Oral cyclophosphamide 50 mg daily and veliparib 60 mg daily (2) Oral cyclophosphamide 50 mg daily	ORR	No improvement of ORR with additional of veliparib

C, carboplatin; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; AUC, area under the curve; iv, intravenous; wt, wild-type BRCA; m, BRCA mutation carrier; PFS, progression free survival; ORR, overall response rate; HGSOC, high-grade serous ovarian cancer.

data cut off from 28 August 2008 to 30 September 2015 (7 years after randomization) with 77% OS data maturity [Ledermann *et al.* 2016]. For the overall Study 19 population, median OS for the olaparib-treated group was 29.8 months *versus* 27.8 months for the placebo group {HR = 0.73 [95% confidence interval (CI): 0.55–0.96]; nominal $p = 0.025$}. For the *BRCA*m group, median OS was 34.9 months for the olaparib-treated patients and 30.2 months for the placebo group [HR = 0.62 (95% CI: 0.41–0.94) nominal $p = 0.025$]. For those patients who were *BRCA*wt, OS was 24.5 months for olaparib treated patients and 26.6 months for the placebo group [HR = 0.83 (95% CI: 0.55–1.24) nominal $p = 0.37$]. Although the predefined study criteria for statistical significance for OS was not achieved ($p < 0.0095$), it is important to note that Study 19 was not designed to demonstrate a difference in OS that was statistically significant, as there were no criteria to control for type 1 error within the study subgroups. Crossover of patients initially

randomized to placebo who received a PARP inhibitor off trial may have had a confounding effect on OS, given that 23% of patients in the placebo arm received a PARP inhibitor after evidence of disease progression [Matulonis *et al.* 2016a].

The second randomized phase II study design testing single-agent olaparib was a study by Kaye and colleagues, comparing two different doses of olaparib *versus* pegylated liposomal doxorubicin (PLD) in patients with recurrent g*BRCA*m ovarian cancer, who had never received PLD nor a PARP inhibitor, and had a platinum-free interval of <12 months [Kaye *et al.* 2012] (Table 1). Patients were randomized 1:1:1 to PLD 50 mg/m^2 IV every 4 weeks, olaparib capsules 200 mg BID or olaparib capsules 400 mg BID. The primary endpoint was PFS, and 90 patients were entered. Median PFS amongst the three arms was not statistically significant; median PFS for olaparib 200 mg BID was 6.5 months (95% CI: 5.5–10.1 months), 8.8 months for olaparib 400 mg BID (95% CI: 5.4–9.2 months), and 7.1 months for PLD (95% CI: 3.7–10.7 months) [Kaye *et al.* 2012]. In addition, ORR was also not significantly different amongst the three arms; RECIST response rate was 25% for olaparib 200 mg BID, 31% for 400 mg BID, and 18% for PLD [Kaye *et al.* 2012]. This study concluded the three arms had comparable median PFS and response rates in recurrent g*BRCA*m ovarian cancer and also suggested that PLD chemotherapy also has significant activity in *BRCA*m-related ovarian cancer.

Olaparib as a single agent also demonstrated activity in recurrent ovarian cancer regardless of platinum sensitivity status. A pooled analysis of 300 patients from phase I and II studies of olaparib monotherapy in patients with recurrent ovarian/fallopian/peritoneal cancer and a deleterious g*BRCA*m treated with 400 mg BID of olaparib capsules, objective response rate (ORR) and duration of response (DoR) was evaluated [Matulonis *et al.* 2016b]. The ORR for the pooled population was 36%, and the median DoR was 7.4 months. Furthermore, amongst patients who had received three or more lines of chemotherapy, the ORR was 31% and the DoR was 7.8 months, supporting durable response rates with olaparib monotherapy even after multiple lines of chemotherapy. For those patients who had received three or more lines of treatment, the ORR was 42% for platinum-sensitive recurrent patients *versus* 26% for platinum resistant cancer, though the DoR was quite similar for platinum-sensitive (7.8 months) *versus* platinum-resistant cancers (7.4 months) [Matulonis *et al.* 2016b].

Based upon the Study 19 results, the EMA approved olaparib in 2014 as maintenance for women with relapsed platinum-sensitive *BRCA*m ovarian cancer following response to platinum-based chemotherapy. Olaparib was also filed with the United States FDA for accelerated approval; however, the Oncologic Drugs Advisory Committee of the FDA voted against accelerated approval for olaparib as maintenance therapy in g*BRCA*m mutation carriers, waiting instead for the results of phase III clinical trials [US FDA, 2014]. Despite this negative vote, the FDA conditionally granted accelerated approval for olaparib in December 2014 based on single agent olaparib data in recurrent g*BRCA*m ovarian cancer in patients who had received at least three prior lines of therapy, demonstrating an ORR of 30% and response duration of approximately 8 months [Kaufman *et al.* 2015]. This accelerated approval is conditional on the results of the phase III SOLO2 study (see Table 2). SOLO2 was designed similarly to Study 19, except eligibility is restricted to ovarian cancers with a *gBRCA*m or t*BRCA*m. Accrual has been met for the SOLO2 study, and a recent press release from AstraZeneca in October 2016 stated that SOLO2 met its primary endpoint and demonstrated that PFS for olaparib is significantly longer compared with placebo in the platinum-sensitive maintenance setting for *BRCA*m patients [SOLO2 press release 26 October 2016, www.astrazeneca.com]. Final published results are pending [Moore *et al.* 2014].

Initial phase I and II studies of olaparib have used the 50 mg capsule and the recommended single-agent 400 mg BID daily dosing; phase III studies testing olaparib are using the 100 mg tablet dose. The recommended monotherapy dose of olaparib has been determined to be 300 mg BID, and olaparib dosing comparing the capsule and tablet dosing has been performed with exposures using the tablet dosing matching or exceeding exposures using the capsule dosing [Mateo *et al.* 2016]. Toxicities of the tablet and capsule dosing of olaparib appeared comparable [Mateo *et al.* 2016].

Niraparib

Niraparib is a potent oral PARP 1 and PARP 2 inhibitor. Initially, niraparib was tested in patients

Table 2. Phase III studies of PARP inhibitors for ovarian cancer treatment.

Trial and NCI trial identifier	Study arms	Trial population	Primary endpoint	Total accrual	Trial status
Newly diagnosed ovarian cancer					
SOLO1 (NCT01844986)	Olaparib *versus* placebo maintenance postplatinum-based chemotherapy	*BRCA*m only, HGSOC or endometrioid stage III and IV	PFS	344	Accrual completed; results pending
NCT02655016	Niraparib *versus* placebo as maintenance postresponse to platinum based chemotherapy	HRD positive, stage III and IV	PFS	305	Accrual ongoing
GOG-3005 (NCT02470585)	Carboplatin and paclitaxel *versus* carboplatin, paclitaxel, and veliparib *versus* carboplatin, paclitaxel, and veliparib followed by veliparib maintenance therapy	Advanced HGSOC, both *BRCA*m and *BRCA*wt	PFS	1100	Accrual ongoing
PAOLA1 (NCT02477644)	Platinum/taxane/bev, bev maintenance *versus* platinum/taxane/bev, bev/olaparib maintenance	Newly diagnosed high grade ovarian cancer	PFS	612	Accrual ongoing
Recurrent ovarian cancer					
NOVA (NCT01847274) Mirza *et al.* [2016]	Niraparib *versus* placebo as maintenance post response to platinum-based chemotherapy in recurrent platinum sensitive ovarian cancer	Platinum-sensitive, HGSOC, *BRCA*-and HRD status stratified	PFS	360	Median PFS gBRCAm 21 mo (niraparib) *versus* 5.5 months (placebo) $p < 0.00001$ Non-gBRCAm HRD + 12.9 months (niraparib) *versus* 3.8 months (placebo) $p < 0.00001$ All Non-g*BRCA*m 9.3 months (niraparib) *versus* 3.9 months (placebo) $p < 0.00001$

(Continued)

Table 2. (Continued)

Trial and NCI trial identifier	Study arms	Trial population	Primary endpoint	Total accrual	Trial status
SOLO2 (NCT01874353) [Press release 26 October 2016; www.astrazeneca.com]	Olaparib *versus* placebo postplatinum-based chemotherapy	Platinum-sensitive BRCAm only, HGSOC or endometrioid	PFS	264	Accrual completed; improved PFS for olaparib group
ARIEL3 (NCT01968213)	Rucaparib *versus* placebo postplatinum-based chemotherapy	Platinum-sensitive recurrence, HGSOC or endometrioid BRCA-stratified	PFS	540	Accrual completed; results pending
SOLO3 (NCT02282020)	Olaparib *versus* MD choice non-platinum chemotherapy	Platinum-sensitive BRCAm HGSOC	PFS	411	Accrual ongoing
PARP inhibitor combinations for recurrent ovarian cancer					
NRG-GY004 (NCT02446600)	Olaparib *versus* olaparib/cediranib *versus* platinum doublet	Platinum sensitive recurrent high-grade ovarian cancer BRCA stratified	PFS	450	Accrual ongoing
NRG-GY005 (NCT02502266)	Olaparib/cediranib *versus* single agent chemotherapy	Platinum resistant recurrent high-grade ovarian cancer	PFS (phase II) OS (phase III)	680	Accrual ongoing

HGSOC, high-grade serous ovarian cancer; BRCAm, germline BRCA mutation carrier; PFS, progression free survival; HRD, homologous recombination deficiency; OS, overall survival.

with sporadic cancer as a phase I dose-escalation study evaluating 10 different doses from 30 mg to 400 mg PO daily in a 21-day cycle; 300 mg per day was found to be the MTD, with two patients having grade 4 thrombocytopenia at the 400 mg dose level [Sandhu *et al.* 2013]. Other DLTs during the first cycle included grade 3 fatigue (one patient dosed at 30 mg per day) and grade 3 pneumonitis (one patient dosed at 60 mg per day). There were 49 patients with ovarian or peritoneal cancer enrolled in this study; 22 had known g*BRCA*m, and 27 had *BRCA*wt cancer [Sandhu *et al.* 2013]. Twenty of the 22 patients with g*BRCA*m had RECIST 1.1 measurable cancer, and 8 of these 20 [40% (95% CI: 19–64)] had a confirmed RECIST and C-125 GCIG partial response. In this phase I study the median response duration was 387 days. Ten patients with known *BRCA* mutations had platinum-sensitive cancer, and the ORR by RECIST and CA125 was 50% (95% CI: 19–81); median duration of the response was 431 days (range from 159 to 518 days). Of the 27 patients with sporadic HGSC, 22 patients had RECIST measurable cancer; two out of three patients with platinum-sensitive sporadic HGSC had responses by RECIST or CA125, and the doses received by these responders were 30 mg and 60 mg [Sandhu *et al.* 2013]. Three out of 19 patients with platinum-resistant sporadic HGCS responded by RECIST or CA125 [16% (95% CI: 3–40)] [Sandhu *et al.* 2013].

Niraparib has undergone randomized double-blind phase III testing against placebo in the NOVA trial; this study by Mirza and colleagues randomized women with platinum-sensitive recurrent HGSC, 2:1 to either niraparib (300 mg) *versus* placebo (Table 2) [Mirza *et al.* 2016]; patients were randomized into either a g*BRCA*m group or non-g*BRCA*m group, based on prospective g*BRCA* testing prior to starting on study treatment. Eligibility included histologically proven ovarian, peritoneal or tubal cancer and high grade serous histology. HRD testing was performed retrospectively on the non-g*BRCA*m group, and statistical analysis was performed simultaneously on both the g*BRCA*m and non-*BRCA*m HRD groups; sample size and statistical significance for both groups was 90% power and a HR of 0.50, and primary endpoint was PFS. If the non-*BRCA* HRD population met this endpoint, thus demonstrating statistical significance, the third primary efficacy population was then analyzed which was the overall non-g*BRCA*m group. A total of 553 patients were enrolled (546 received treatment) into the g*BRCA*m and non-g*BRCA*m cohorts. PFS was prolonged by niraparib *versus* placebo in all three predefined primary efficacy populations [Mirza *et al.* 2016]; a PFS of 21.0 months *versus* 5.5 months in favor of niraparib for g*BRCA*m cancers (95% CI: 0.17–0.41, HR = 0.27, $p < 0.0001$), a PFS of 12.9 months *versus*. 3.8 months in favor of niraparib for non-*BRCA*m with HRD tumors (95% CI: 0.24–0.59, HR = 0.38, $p < 0.0001$) and a PFS of 9.3 months *versus* 3.9 months in favor of niraparib for the non-g*BRCA*m cohort (95% CI: 0.34–0.61, HR = 0.45, $p < 0.001$) was observed [Mirza *et al.* 2016]. The exploratory population of HRD-negative and non-g*BRCA*m patients also derived benefit with niraparib *versus* placebo; median PFS for niraparib was 6.9 months *versus* 3.8 months for placebo (95% CI: 0.36–0.92, HR = 0.58, $p = 0.02$). NOVA is the first successful reported prospective phase III trial of any PARP inhibitor demonstrating the benefit of a PARP inhibitor in recurrent platinum-sensitive ovarian cancer; the NOVA results have expanded the role and efficacy of PARP inhibitors beyond *BRCAm* ovarian cancers with an improved median PFS with the use of niraparib maintenance therapy in all patient populations studied in the NOVA trial [Mirza *et al.* 2016] (Table 2). Niraparib was granted fast track designation by the United States FDA in October 2016.

Rucaparib

Rucaparib is another PARP 1 and PARP 2 oral inhibitor that was tested in a phase I study with a continuous daily dose range of 40–500 mg, as well as 240–840 mg BID. The resultant recommended phase II dose of rucaparib monotherapy was 600 mg BID [Kristeleit *et al.* 2014]. In a phase II trial of rucaparib monotherapy in advanced stage g*BRCA*m advanced stage breast and ovarian cancers, rucaparib was well tolerated in doses of 480 mg daily, however aside from the recognition that its activity correlated with the platinum-free interval, no clearly defined phase II dose was established [Drew *et al.* 2016]. Rucaparib has demonstrated anticancer responses in both platinum-sensitive and platinum-resistant recurrent ovarian cancer, similar to olaparib and niraparib. Rucaparib is currently undergoing further testing in recurrent ovarian cancer as part of two clinical trials: ARIEL2 and ARIEL3. ARIEL2 is a phase II biomarker study of 204 patients receiving rucaparib at a dose of 600 mg BID with HGSC or high-grade

endometrioid ovarian cancer who have received one or more prior platinum-based chemotherapy regimens and whose last treatment regimen was platinum based; fresh tumor biopsy and archival tumor are both required for participation [Swisher *et al.* 2016; Kristeleit *et al.* 2015]. The primary endpoint was to evaluate the clinical activity of rucaparib at 600 mg BID in the following groups: *BRCA*m, *BRCA*wt//LOH^{high} (loss of heterozygosity) and *BRCA*wt//LOH^{low}. RECIST Responses were seen in 85% of *gBRCAm* and 74% of *tBRCA*m cancers. RECIST and CA-125 ORR was 85% (BRCAm), 44% (*BRCAwt*//LOH^{high}), and 20% (*BRCAwt*/LOH$^{low)}$ but PFS for *BRCA*wt cancers was similar for LOH^{high} and LOH^{low} cancers (median PFS 5.7 months *versus* 5.2 months), and thus the LOH test was not particularly robust in predicting PARP inhibitor activity in non-*BRCA* related cancers. Tumors with RAD51C mutations were deemed '*tBRCAm*-like' and were responsive to therapy with rucaparib. In 2015, the US FDA granted rucaparib breakthrough status and was subsequently FDA approved in December 2016.

ARIEL3 has the same histological requirements as ARIEL2 and is a phase III randomized trial of oral rucaparib *versus* placebo (2:1 randomization) following platinum-based therapy [ClinicalTrials.gov identifier: NCT01968213] (Table 1). Like the published phase II study 19 testing olaparib and the niraparib phase III study, eligibility required a demonstrated response to platinum-based chemotherapy for both the most recent platinum regimen and the penultimate platinum regimen.

Veliparib

Veliparib is an orally bioavailable inhibitor of both PARP1 and PARP2 that has been evaluated as monotherapy in relapsed g*BRCA*m ovarian cancer in a Gynecologic Oncology Group (GOG) study [Coleman *et al.* 2015]. In this phase II study, single-agent veliparib was administered orally at 400 mg BID on a 28-day cycle to patients with g*BRCA*m and measurable disease, who had received at least three prior regimens of chemotherapy. This dosing schedule demonstrated a response rate of 26%, with a median PFS of 18.8 months [Coleman *et al.* 2015].

Talazoparib

BMN 673 is a potent oral PARP 1 and PARP 2 inhibitor [Shen *et al.* 2013; Murai *et al.* 2014]. Toxicities of this agent are similar to other PARP inhibitors but BMN 673 has the added side effect of alopecia, which was observed in the phase I study [Shen *et al.* 2013]. A total of 23 patients were enrolled with either ovarian or primary peritoneal cancer, and 17 of these patients had a g*BRCA*m. RECIST and/or CA-125 responses occurred at doses $\geq$ 100 µg per day in 11 out of 17 ovarian or peritoneal cancer patients who had a g*BRCA*m. Currently, BMN673 is not being studied in any ongoing randomized phase II or III ovarian cancer trials.

PARP inhibitors combined with chemotherapy

PARP inhibitors, specifically olaparib and veliparib, have been combined with chemotherapy with the rationale of disrupting base excision repair *via* PARP inhibition to synergize with chemotherapy [Lee *et al.* 2014; Oza *et al.* 2015; Bell-McGuinn *et al.* 2015; Kummar *et al.* 2015]. A major barrier to combining PARP inhibitors with chemotherapy is a frequent inability to achieve full doses of both regimens secondary to overlapping myelosuppressive toxicities [Matulonis and Monk, 2017]. Phase I and single-arm nonrandomized phase II studies of combined PARP inhibitors and chemotherapy have been reviewed elsewhere [Liu *et al.* 2014b; Miller and Ledermann, 2016].

Olaparib added to carboplatin and paclitaxel chemotherapy has been compared with carboplatin and paclitaxel alone [Oza *et al.* 2015] (Table 1). This phase II study randomized 162 patients to either six cycles of olaparib (200 mg BID, days 1 through 10), paclitaxel (175 mg/m^2 IV day 1), and carboplatin (AUC 4 IV day 1), followed by olaparib monotherapy as maintenance (400 mg BID, continuous) (Arm A) *versus* paclitaxel (175 mg/m^2 IV day 1) and carboplatin (AUC 6 IV day 1) and no maintenance therapy (Arm B) [Oza *et al.* 2015]. The primary endpoint was PFS by central review for RECIST 1.1. PFS was prolonged in the olaparib plus chemotherapy group [median 12.2 months (95% CI: 9.7–15.0)] compared with the group receiving chemotherapy only [median 9.6 months (95% CI: 9.1–9.7)] [HR = 0.51 (95% CI: 0.34–0.77); p = 0.0012]. The benefit of PARP inhibition was especially noted in patients with *BRCA* mutations [HR = 0.21 (0.08–0.55); p = 0.0015]. Overall RR was similar for Arm A and Arm B (64 *versus* 58%). Grade 3 and 4 hematologic toxicity was higher in the olaparib containing group: neutropenia (43% in Arm A *versus* 35% arm B) and anemia (9% in Arm A *versus* 7% Arm B). Other toxicities such as alopecia, nausea, neutropenia, dyspepsia, and peripheral neuropathy were slightly

higher in arm A, but were only mild to moderate [Oza *et al.* 2015].

Phase I testing has been completed, combining veliparib with carboplatin and paclitaxel chemotherapy in patients with previously untreated stages II–IV epithelial ovarian cancer or carcinosarcoma [Bell-McGuinn *et al.* 2015]. The three regimens were: carboplatin IV AUC 6 and paclitaxel IV 175 mg/m^2 on day 1 of a 21-day cycle; carboplatin IV AUC 6 on day 1 and paclitaxel IV 80 mg/m^2 on days 1, 8, and 15 of a 21-day cycle; and paclitaxel IV 135 mg/m^2 on day 1, cisplatin 75 mg/m^2 IP on day 1 or 2, and paclitaxel 60 mg/m^2 IP on day 8 of a 21-day cycle [Bell-McGuinn *et al.* 2015]. Veliparib starting at 30 mg PO BID was administered on days 1–21 for cycles 1–6. All study participants received bevacizumab 15 mg/kg IV on day 1 for cycles 2 through 22. The recommended phase II dosing for continuous daily veliparib was 150 mg twice daily when combined with all of the 3-carboplatin and paclitaxel regimens. Based on these findings, GOG-3005 has opened, a randomized double-blind placebo-controlled trial evaluating carboplatin and paclitaxel *versus* carboplatin, paclitaxel, and veliparib *versus* carboplatin, paclitaxel, and veliparib followed by veliparib maintenance therapy in patients with newly diagnosed ovarian cancer [ClinicalTrials.gov identifier: NCT02470585] (Table 2).

In the setting of recurrent ovarian cancer, veliparib has also undergone phase II study in combination with oral cyclophosphamide in patients with recurrent g*BRCA*m ovarian cancer randomized to cyclophosphamide alone (50 mg orally once/day) or with continuous veliparib (60 mg orally once/day) [Kummar *et al.* 2015] (Table 2). A total of 74 patients were enrolled and randomized. The primary outcome was ORR and the addition of veliparib to cyclophosphamide did not improve RR compared with cyclophosphamide alone. This study concluded that the addition of 60 mg of veliparib to cyclophosphamide failed to improve response rate or the median PFS when compared with monotherapy with oral cyclophosphamide [Kummar *et al.* 2015]. Veliparib is also currently being tested in combination with temozolomide *versus* PLD in a randomized phase II study in patients with recurrent HGSC [ClinicalTrials.gov identifier: NCT01113957]. This study's aim was to determine the ORR between treatment arms based on tumor measurements and CA-125 levels; it has completed accrual and results are pending.

PARP inhibitors combined with biologic agents

Combinations of biologics that target differing aberrant and exploitable pathways in ovarian cancer may represent a new treatment paradigm for HGSC given the genomic complexity. PARP inhibitor combinations specifically may induce greater DNA damage and induce more HRD. In this section, we will review the previously reported phase I and II studies, as well as newer and ongoing phase I, II, and III trials.

PARP inhibitors and antiangiogenics

The first PARP inhibitor combinations to be studied were with antiangiogenic agents. A phase I study tested the combination of olaparib and the oral VEGFR inhibitor cediranib, and the recommended phase II dose of olaparib was determined to be 200 mg BID capsule formulation and cediranib 30 mg PO daily, both given continuously [Liu *et al.* 2013]. Toxicities included myelosuppression, diarrhea, hypertension, and fatigue; two dose-limiting toxicities occurred which were grade 4 neutropenia lasting greater than 4 days and grade 4 thrombocytopenia at the highest dose level (cediranib 30 mg daily and olaparib capsules 400 mg BID). This combination was tested against olaparib alone in a randomized phase II study of patients with g*BRCA*m recurrent platinum-sensitive HGSC [Liu *et al.* 2014a] (Table 1). A total of 90 patients were randomized to olaparib alone *versus* the combination of cediranib/olaparib; median PFS was significantly longer with cediranib/olaparib compared with olaparib alone [17.7 months *versus* 9 months, HR = 0.42 (95% CI: 0.23–0.76), $p = 0.005$]. Preplanned subset analysis by gBRCAm status demonstrated a significant improvement in PFS in gBRCAm, *BRCA*wt or unknown patients receiving cediranib/olaparib compared with olaparib alone [16.5 *versus* 5.7 months, HR = 0.32 (95% CI: 0.14–0.74), $p = 0.008$]; for gBRCAm patients, PFS was not superior with the doublet compared with single-agent olaparib [19.4 *versus* 16.5 months, HR = 0.55 (95% CI: 0.24–1.27), $p = 0.16$]. Because of these positive results, two phase III studies have been launched and are underway as of February 2016: GY004 and GY005, both supported by NRG. GY004 [ClinicalTrials.gov identifier: NCT02446600] is a phase III study comparing olaparib monotherapy *versus* olaparib and cediranib *versus* standard platinum-based chemotherapy in patients with platinum-sensitive recurrent ovarian/fallopian/

peritoneal cancer. GY005 [ClinicalTrials.gov identifier: NCT02502266] is a phase II/III study testing olaparib and cediranib combination therapy *versus* physician's choice chemotherapy as well as single-agent olaparib and cediranib. ICON 9 is a planned phase III study to examine maintenance cediranib and olaparib *versus* maintenance olaparib alone following platinum-based chemotherapy in patients with recurrent platinum sensitive high-grade ovarian cancer.

Other antiangiogenic agents have been combined with olaparib. A phase I study was performed combining olaparib and bevacizumab; patients with advanced cancers received increasing doses of continuous oral olaparib (100, 200 and 400 mg BID using the capsule formulation) in combination with bevacizumab 10 mg/kg IV every 2 weeks [Dean *et al.* 2012]. A total of 12 patients were enrolled and the combination of olaparib 400 mg BID and bevacizumab 10 mg/kg was well tolerated [Dean *et al.* 2012]. PAOLA-1 is an ENGOT/GCIG phase III trial currently enrolling patients examining the use of olaparib (using the tablet formulation) *versus* placebo combined with bevacizumab as maintenance treatment in patients with stage IIIB through IV HGSC or endometrioid ovarian/fallopian/peritoneal cancers treated with standard first-line platinum-based chemotherapy plus bevacizumab [ClinicalTrials.gov identifier: NCT02477644]. This study aims to address the efficacy and safety of the tablet formulation of olaparib in HGSC patients receiving maintenance therapy with bevacizumab. (Table 2).

Regarding velaparib, a phase I study was undertaken to determine the MTD of this PARP inhibitor when used in combination chemotherapy with bevacizumab. Veliparib was combined with carboplatin and PLD for relapsed platinum-sensitive ovarian cancer [Landrum *et al.* 2016]. The MTD of veliparib with carboplatin and PLD was deemed to be 80 mg PO BID in women with recurrent, platinum-sensitive ovarian cancer. An additional 12 patients were treated with veliparib, carboplatin and PLD with bevacizumab. Nine patients experienced DLTs: grade 4 thrombocytopenia ($n = 4$), prolonged neutropenia >7 days ($n = 1$), grade 3 hypertension ($n = 5$), and grade 5 sepsis ($n = 1$) [Landrum *et al.* 2016]. For future use of this four-drug combination, further study is needed to determine the lowest effective doses to prevent DLTs.

PARP inhibitors and PI3 Kinase pathway inhibitors

Other novel combinations in clinical testing include PARP inhibitors and PI3K inhibitors based on observed preclinical *in vivo* synergy [Juvekar *et al.* 2012; Ibrahim *et al.* 2012; Wang *et al.* 2016a, 2016b] which served as a preclinical rationale for the development of several combination phase I studies such as olaparib/BKM120 and olaparib/BYL719 [ClinicalTrials.gov identifier: NCT01623349], as well as olaparib/AZD5363 [ClinicalTrials.gov identifier: NCT02338622] (Table 3). In a phase I study of olaparib and BKM120, an oral PI3K inhibitor, patients with either breast cancer or ovarian cancer were enrolled; dosing started at BKM120 60 mg QD/olaparib 100 mg BID [Dose level (DL) 1] [Matulonis *et al.* 2015]. The MTD was BKM120 50 mg QD/olaparib 300 mg BID, and DLT toxicities included grade 3 depression and transaminitis. Anticancer activity was observed in both breast and ovarian cancer regardless of *BRCA* mutation status. This trial is currently testing BYL719 and olaparib. Michalarea and colleagues recently presented data combining olaparib with AZ5363, an AKT inhibitor using a study design that employed an accelerated intrapatient dose-escalation schema in order to bypass the sometimes slowed pace of a traditional 3 + 3 design. The RP2D was 640 mg BID 2 out of 7 days AZD5363 and 300 mg BID olaparib based on tolerability [Michalarea *et al.* 2015].

PARP inhibitors and immune checkpoint inhibitors

Immunotherapy research in ovarian cancer is based on the understanding that immunosuppressive microenvironments can influence tumor growth, metastasis, and even treatment resistance. In ovarian cancer, the existence of tumor-infiltrating T cells within the tumor are associated with improved PFS and OS [Zhang *et al.* 2003; Sato *et al.* 2005]. Immune checkpoints are essential for avoidance of autoimmune activity, thus immune checkpoint inhibitors have been utilized to prevent the suppression of cytotoxic immune cells, facilitating immune system tumor destruction [Pardoll, 2012]. Examining how various molecular targets such as PARP inhibitors influence immunoregulatory effects and act synergystically with immune checkpoint inhibitors to prevent tumor progression is an important consideration and area in immunotherapy research.

Table 3. Examples of ongoing trials combining PARP inhibitors and other biologic agents.

Trial identifier /phase	Study drugs	Study population
NCT02511795 Phase 1b	AZD1775 and olaparib AZD1775 (6 doses/week) plus olaparib AZD1775 (10 doses/week) plus olaparib	Refractory solid tumors
NCT02485990 Phase I/II	Tremelimumab and olaparib Arm A: Tremelimumab alone DESE Tremelimumab and olaparib Arm B2: Tremelimumab and olaparib	Recurrent or persistent epithelial ovarian/fallopian/peritoneal cancers
NCT02484404 Phase I/II	MEDI4736 (PD-L1 mAb) with olaparib or cediranib	Advanced solid tumors and advanced ovarian or recurrent ovarian, triple-negative breast, lung, prostate and colorectal cancers
NCT02264678 Phase I/Ib	AZD6738 with olaparib AZD6738 with carboplatin AZD6738 with olaparib AZD6738 with MEDI4736 AZD6738 alone	Advanced solid malignancies
NCT02657889 Phase I/II	Pembrolizumab with niraparib	Advanced or metastatic triple-negative breast cancer or recurrent ovarian cancer

The PARP inhibitor BMN673 has been shown *in vitro* using *BRCA*-deficient ovarian cancer cell lines and animal models to inhibit ovarian tumor progression, evoking cell apoptosis in the setting of BRCA deficiency [Huang *et al.* 2015]. Applying this information to mouse models, researchers found that treatment with BMN673 increased the proportion of cytotoxic immune cells (CD8+ T cells, B cells and NK cells) while simultaneously decreasing the proportion of immunosuppressive cells [Huang *et al.* 2015]. It was concluded that the improved survival noted in mice treated with BMN 673 was, in part, a result of the immunomodulatory effects of PARP inhibition. Such findings suggest there may be a role for combination therapy of PARP inhibitors with immunotherapy for ovarian cancers exhibiting *BRCA*ness characteristics to promote a more favorable microenvironment.

Further support for enhanced antitumor activity with combined PARP and immune checkpoint inhibitors has been demonstrated [Higuchi *et al.* 2015]. Blockade of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) using CTLA-4 antibody in combination with veliparib produced a synergistic therapeutic effect on immune-mediated antitumor response in *BRCA1* deficient mice models and in *BRCA1* deficient ovarian cancer cell lines [Higuchi *et al.* 2015]. The animal model survival benefit was found to be mediated by T-cells and the increase in tumor microenvironment IFNγ. Currently, several trials combining PARP and immune checkpoint inhibitors are ongoing (Table 3) [Konstantinopoulos *et al.* 2016].

PARP inhibitors and other biologic agents

Several other strategies are being tested combining PARP inhibitors and other biologic agents; these studies are underway, are mostly in phase I testing, and examples are listed in Table 3. PARP inhibitors are now being combined with different types of other biologic agents such as those additionally inhibiting DNA repair (i.e. Wee1), as well as other molecules (heat shock protein 90 inhibitors).

Toxicities associated with PARP inhibitors

Published phase I through III trials support that PARP inhibitors are relatively well tolerated either as single agents or in combination with other cytotoxic or biologic agents in the treatment of ovarian cancer; their main toxicities are gastrointestinal, fatigue, and hematologic, and these toxicities are common to all PARP inhibitors. The observed myelosuppression which includes thrombocytopenia, anemia, and neutropenia make combination with other myelosuppressive agents such as chemotherapy challenging.

In phase I trials of olaparib, most adverse effects likely associated the drug were grades 1 and 2, and included nausea, fatigue, vomiting, taste alteration, and anorexia [Fong *et al.* 2009]. In Study 19, olaparib was associated with higher rates of all-grade toxicities compared with placebo, specifically nausea (68% *versus* 35%), vomiting (32% *versus* 14%), anemia (17% *versus* 5%), and fatigue (49% *versus* 38%) (14). Other phase II trials of olaparib also identified gastrointestinal (GI) symptoms, fatigue and anemia as the most common adverse effects, the majority of which were grades 1 or 2, associated with 400 mg-BID dosing of olaparib Kaufman *et al.* 2015; Audeh *et al.* 2010; Gelmon *et al.* 2011]. Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) were first described with olaparib in Study 19; two patients in the olaparib group were diagnosed with AML/MDS and one patient in the placebo group [Ledermann *et al.* 2012]. Updated Study 19 results reported no new cases of AML or MDS which is reassuring [Ledermann *et al.* 2016]. Moore and colleagues have reviewed the toxicities and their management observed with both single-agent olaparib and olaparib in combination with other agents; this comprehensive review covers toxicity management, which is beyond the scope of this manuscript [Moore and Monk, 2016].

In phase II testing of single agent veliparib, Coleman and colleagues reported grade 1 and 2 anemia rates of 24/50, 9/50 thrombocytopenia, mostly grade 1, 15/50 neutropenia also mostly grade 1 and 2 [Coleman *et al.* 2015]. Similarly, phase II testing of rucaparib showed >15% of patients experienced adverse effects of GI symptoms, fatigue and anemia [Kristeleit *et al.* 2014, 2015]; final published results are still pending. In the NOVA trial, the most frequent grade 3 or 4 adverse events included thrombocytopenia (33.8%), anemia (25.3%) and neutropenia (19.6%); these side effects were managed with dose reductions, and few patients were removed from study (<3%) for hematologic toxicities [Mirza *et al.* 2016]. In NOVA, 1.4% of patients developed AML/MDS and 1.1% of patients in the placebo, which is proportional to the 2:1 randomization of niraparib: placebo [Mirza *et al.* 2016]. Thus, the most commonly reported adverse events likely associated with the use of PARP inhibitors are gastrointestinal symptoms, fatigue and anemia. Additionally, these side effects are predominantly grades 1 and 2, fairly well tolerated by patients, and can generally be managed with dose reductions.

Conclusion

PARP inhibitors have emerged as an important addition to the treatment of HGSC, and have become standard of care treatment for patients with recurrent *BRCA*m-associated ovarian cancers. Currently, in the US, olaparib has been approved for g*BRCA*m ovarian cancer patients who have received at least three prior lines of therapy and in Europe as maintenance following platinum based chemotherapy in patients with *BRCA*m-associated cancer. Several phase III studies have completed accrual (SOLO1, SOLO2) and will also determine the efficacy of olaparib in newly diagnosed *BRCA*m ovarian cancers; SOLO2 has demonstrated that olaparib has a longer median PFS compared with placebo as platinum sensitive maintenance postplatinum. Recently reported results demonstrated the benefits of niraparib maintenance on PFS for recurrent ovarian cancer in the phase III NOVA trial for all patient populations following response to platinum, representing an exciting breakthrough for the expanded use of PARP inhibitors [Mirza *et al.* 2016].

Ongoing research to evaluate broadening the spectrum by which we select and utilize PARP inhibitors to enhance antitumor effects either as monotherapy or synergistically with other agents, while minimizing toxicities offers exciting prospects in efforts to better treat ovarian cancer. Phase II and III testing of PARP inhibitors, combined with biologic agents and chemotherapeutic agents are now underway. These studies will hopefully provide information to improve our understanding of PARP inhibitors as chemosensitizers or immune-sensitizers, and perhaps provide clarity for the appropriate selection of PARP inhibition.

Since DNA repair defects are also found in other histologies for ovarian cancer, perhaps the use of PARP inhibition will have broader use in future trials; a review of biomarkers that may assist in patient selection for PARP inhibitors has been undertaken by Stover and colleagues [Stover *et al.* 2016]. Studies like the one by Higuchi and colleagues highlight the importance of evaluating additional tumorigenic pathways that may be affected by PARP inhibition as monotherapy or in combination with other cytotoxic, angiogenic or immune-modulating agents to enhance antitumor efficacy [Higuchi *et al.* 2015]. Potentiating effects of PARP inhibition in combination with immune checkpoint inhibitors in *BRCA*m ovarian cancers has shown survival benefit in animal and cell models. These *in vitro* findings showing a

therapeutic advantage using cytotoxic T-cell modulation and enhancement of PARP inhibition support the need for additional clinical trials examining the use of PARP inhibitors combined with immune checkpoint inhibitors.

Other areas needing study are improved understanding of PARP inhibitor resistance and clinical trial strategies when patients have progression through PARP inhibitors. Several mechanisms of PARP inhibitor resistance have been identified, including loss of PARP1 expression, upregulation of PgP pump which decreases PARP inhibitor activity, or restoration of the homologous recombination repair in *BRCA*m or *BRCA*-like cancers [Lord and Ashworth, 2013]. In addition, other mechanisms may enhance PARP inhibitor sensitivity such as CDK12 mutations [Bajrami *et al.* 2014]. Other important future directions of PARP inhibition in the management of ovarian cancers is to further explore the role of PARP inhibitors both as single agents and in combinations beyond the populations defined in Study 19 and the NOVA study.

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