New Biologic Frontiers in Ovarian Cancer: Olaparib and PARP Inhibition

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Abstract

Poly (ADP-ribose) polymerase (PARP) inhibition was first introduced as a cancer-targeting strategy in 2005 and has made rapid clinical progression, culminating in the Food and Drug Administration approval of olaparib as a fourth-line-and-beyond treatment in relapsed *BRCA*-mutated ovarian cancer in December 2014. This approval follows exciting phase I/II data showing activity in ovarian cancer, with particular success in *BRCA*-deficient and platinum-sensitive populations. This article will review the early clinical investigation of olaparib, emerging phase II and III data, and future directions, including forthcoming clinical trials and methods to predict response and expand the populations eligible to receive this innovative biologic therapy.

Key words: Ovarian cancer, olaparib, PARP

Introduction

Poly (ADP-ribose) polymerase (PARP) inhibition was first introduced as a novel cancer-targeting strategy in 2005, following the publication of preclinical work showing activity in *BRCA*-mutated tumor cells. Compared with wild-type cells, *BRCA1*- and *BRCA2*-deficient cells were up to 1000-fold more sensitive to PARP inhibition.[1] In vivo, the growth of *BRCA2*-deficient tumors was decreased by PARP inhibitors, the first demonstration that inhibition of a DNA repair mechanism could be used to target cancer cells.[2] These studies highlighted the application of synthetic lethality as a potentially effective anticancer therapy and inspired further clinical investigation.

PARP inhibitors are now known to work through a variety of mechanisms, in addition to inducing synthetic lethality.[1,2] PARP inhibition stimulates nonhomologous end joining (NHEJ) selectively in homologous repair-deficient cells.[3] This is achieved via inhibition of DNA-dependent protein kinase substrates, leading to genetic instability, chromosome rearrangement, and cell death. PARP inhibitors have also been shown to trap *PARP-1* and *PARP-2* on DNA, leading to PARP-DNA complexes.[4] This concept, known as "PARP trapping," is thought to be responsible for the synergism seen with PARP inhibition and alkylating agents and does not occur with all PARP inhibitors.

Since their introduction, PARP inhibitors have been studied in many *BRCA*-deficient cancers, including ovarian cancer, where they have had notable success. The most extensively studied PARP inhibitor in ovarian cancer is olaparib, an orally available compound with activity against *PARP-1* and *PARP-2*. The recent FDA approval of olaparib in relapsed ovarian cancer brings this drug class to the forefront of new anticancer therapy in this disease. This timely review will discuss the early clinical investigation of olaparib, as well as emerging phase II and III data and future directions in ovarian cancer.

Phase I Investigation

Early phase I investigation of olaparib confirmed activity in *BRCA*-mutated breast and ovarian cancers.[5] Sixty patients with solid tumors refractory to standard therapy were enrolled, including 21 patients with ovarian cancer and 9 patients with breast cancer. The majority of patients had received at least 4 prior lines of treatment. Nineteen *BRCA1* and *BRCA2* mutation carriers were evaluable following treatment, 9 of whom had a partial response (PR) or complete response (CR) to olaparib by Response Evaluation Criteria In Solid Tumors (RECIST; 8 patients with ovarian cancer and 1 with breast cancer).[6] Of the patients with ovarian cancer, 6 had a decrease of 50% or more in their CA125 levels. Twelve of the 19 patients (63%) with *BRCA1/2* mutation derived clinical benefit, defined by a decrease in tumor markers, radiographic response, or stable disease (SD) for 4 or more months. Further, olaparib was found to have an acceptable side-effect profile, with grade 1 and 2 nausea and fatigue being the most commonly experienced adverse events (AEs).

In a confirmatory trial, patients with *BRCA1/2*-mutated ovarian cancer were treated with olaparib as a part of a dose-escalation and expansion study.[7] This included 50 patients, 48 of whom had *BRCA1* or *BRCA 2* mutation, 1 with a missense *BRCA2* mutation of unclear significance, and 1 with a strong family history of *BRCA1/2* cancers who declined testing. Of the patients en-

rolled, 13 had platinum-sensitive disease, 24 had platinum-resistant disease, and 13 had platinum-refractory disease (progression of disease while receiving platinum chemotherapy). The majority of patients (39 of 50) received olaparib 200 mg twice daily as a part of the expansion cohort. The 11 patients in the escalation group received olaparib at dosages ranging from 40 mg daily up to 600 mg twice daily. Of the 50 patients, 4 were not evaluable and an additional 8 had no measureable disease by RECIST. Partial response or CR was seen in 14 patients (28.0%; 95% CI, 16.2%-42.5%). An additional 3 patients had SD for greater than 4 cycles (6.0%; 95% CI, 1.3%-16.5%). Of the patients with platinum-sensitive disease, 61.5% responded to treatment, as measured by RECIST or The Gynecological Cancer InterGroup (GCIG) criteria. Patients with platinum-resistant disease saw a 41.7% response rate, while no RECIST responses were observed in the platinum-refractory group. Two patients in this cohort did have response by GCIG criteria and 1 patient had SD. This trend toward decreasing response rates with decreasing platinum sensitivity was significant, although the responses seen in the platinum-resistant/-refractory groups were better than those seen in many other studies of this cohort.

Early Phase II Studies in Ovarian Cancer

Following the activity demonstrated in the phase I study, a proof-of-concept phase II study was initiated.[8] This multicenter trial enrolled *BRCA1* and *BRCA2* mutation carriers with recurrent ovarian cancer and at least 1 previous line of therapy to continuous olaparib at either 100 mg twice daily, demonstrated to be pharmacodynamically active, or 400 mg twice daily, the maximum tolerated dose in the initial phase I study, until disease progression.[5] Platinum status was also assessed at the time of enrollment. The primary endpoint was objective response rate (ORR). Fifty-eight patients were enrolled, with 1 patient death prior to treatment initiation, leaving 57 patients available for analysis, including 40 with *BRCA1* mutations and 17 with *BRCA2* mutations. The ORR in the 400 mg cohort was 33% (11 of 33 patients; 95% CI, 20-51), with 2 CRs and 9 PRs. An additional 36% of patients had SD and a median duration of response (DoR) of 290 days. In contrast, the ORR in the 100-mg cohort was 13% (3 of 24 patients; 95% CI, 4-31) with no CRs. Seven patients (29%) had SD. The median progression-free survival (PFS) was 5.8 (95% CI, 2.8-10.6) versus 1.9 (95% CI, 1.8-3.6) months in the 400-mg and 100-mg cohorts, respectively. The authors concluded that olaparib had antitumor activity in a heavily pretreated population of patients with *BRCA1*- and *BRCA2*-mutated ovarian cancer. Further, olaparib was noted to have activity in platinum-sensitive and platinum-resistant disease, with 38% (5 of 13 patients) and 30% (6 of 20 patients) responding to treatment, respectively. Importantly, this trial was not randomized, and the lower-dosage cohort had poorer prognostic features, perhaps confounding the apparent dose-dependent activity. This and other subsequently presented phase II studies are summarized in the **Table**.

An additional phase II study investigated olaparib versus pegylated liposomal doxorubicin (PLD) as monotherapy in relapsed *BRCA1/2*-mutated ovarian cancer with an interval of less than 12 months after previous platinum-based chemotherapy.[9] This study also sought to determine the most appropriate dosage of olaparib, either 200 mg or 400 mg twice daily, although it was not powered to detect a difference between these groups. PFS was the primary outcome of this multicenter, randomized prospective trial, in which 97 patients were enrolled in a 1:1:1 ratio to olaparib at 200 mg twice daily or 400 mg twice daily, or to PLD at 50 mg/m^2 every 28 days. Crossover from PLD to olaparib 400 mg twice daily was allowed at the time of disease progression. Median PFS was 6.5 months (95% CI, 5.5-10.1), 8.8 months (95% CI, 5.4-9.2), and 7.1 months (95% CI, 3.7-10.7) for the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively. There was no significant difference between either of the dosing cohorts of olaparib and PLD. The 31% ORR of patients receiving olaparib 400 mg was similar to previously published data.[5,8] While 50% of the patients enrolled were classified as platinum-resistant, response rates were not reported by platinum status. Notably, the PLD group performed better than expected, with a PFS of 7.1 months compared with a PFS of 4 months in a previously published large prospective trial of patients with relapsed ovarian cancer with unknown *BRCA1/2* mutation status.[10] Subsequently published data suggest that *BRCA1/2* mutation carriers may derive more clinical benefit from anthracycline-based chemotherapy than nonselected patients, as these compounds may capitalize on homologous repair deficiency.[11,12]

BRCA Status and Response to Olaparib

Kaufman et al[13] published the results of a large, multicenter, nonrandomized phase II trial in recurrent *BRCA1/2* mutant solid tumors, including breast, ovarian, prostate, and pancreatic cancer, among others. Enrolled patients with ovarian cancer were required to be platinum-resistant. The primary endpoint was tumor response rate by RECIST, with secondary endpoints of ORR, PFS, and DoR. A total of 298 patients were enrolled to receive oral olaparib 400 mg twice daily until disease progression, including 193 with epithelial ovarian, primary peritoneal, or fallopian tube cancer. *BRCA1* germline mutations made up 77% of this cohort, while 23% carried *BRCA2* mutations. The tumor response rate was 26.2% (95% CI, 21.3-31.6) in patients with ovarian cancer, with 40.4% (95% CI, 33.4-47.7) achieving SD. Median PFS was 7, 3.7, 4.6, and 7.2 months in the ovarian, breast, pancreatic, and prostate cancer groups, respectively. Importantly, ovarian cancer response rates were similar to those seen in previous studies, despite the platinum-resistant patient population, suggesting that the mechanisms of platinum resistance may not always confer resistance to PARP inhibition.[8,9] This study highlights the activity of olaparib in a variety of germ-

TABLE. Phase II Studies of Olaparib in High-Grade Serous Ovarian Cancer

Study	Patient Population	*BRCA* Status	Study Arms	Primary Objective	Results
Audeh et al[8]	Recurrent HGSOC, n = 57	Mutated	Olaparib 400 mg twice daily vs 100 mg twice daily	ORR	33% (95% CI, 20-51) olaparib 400 mg vs 13% (95% CI, 4-31) olaparib 100 mg
Kaye et al[9]	Recurrent platinum-sensitive HGSOC, n = 97	Mutated	Olaparib 200 mg twice daily vs 400 mg twice daily vs PLD (50 mg/m^2 q 28 day)	PFS	6.5 months vs 8.8 months vs 7.1 months No significant difference in PFS
Gelmon et al[14]	Recurrent HGSOC and TNBC, n = 91	Mutated and wild-type	Olaparib 400 mg twice daily	ORR	ORR not achieved in breast cancer cohort 41% (95% CI, 22-64) *BRCA1/2* -mutated HGSOC 24% (95% CI, 14-38) in *BRCA* wild-type
Liu et al[15]	Recurrent platinum-sensitive HGSOC, n = 90	Mutated, wild-type, or unknown	Olaparib 400 mg twice daily vs olaparib 200 mg twice daily plus cediranib 30 mg daily	PFS	9.0 months vs 17.7 months (HR = 0.42; 95% CI, 0.23-0.76; *P* =.005)
Oza et al[17]	Recurrent platinum-sensitive HGSOC, n = 162	Mutated, wild-type, or unknown	Olaparib 200 mg twice daily (days 1-10), paclitaxel (175 mg/m^2, day1) and carboplatin (AUC 4 mg/mL per minute, day 1); then olaparib at 400 mg twice daily until disease progression vs paclitaxel (175 mg/m^2) and carboplatin (AUC 6 mg/mL/minute)	PFS	12.2 months vs 9.6 months (HR = 0.51; 95% CI, 0.34-0.77; *P* =.0012) No OS difference
Ledermann et al[20]	Recurrent platinum-sensitive HGSOC, n = 265	Mutated, wild-type, or unknown	Olaparib 400 mg twice daily following completion of platinum-based chemotherapy vs placebo	PFS	8.4 months vs 4.8 months (HR = 0.35; 95% CI, 0.25-0.49; *P* <.001) No OS difference

AUC indicates area under the curve; HGSOC, high-grade serous ovarian cancer; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; TNBC, triple-negative breast cancer.

line *BRCA*-mutated solid tumors and helped to pave the way for FDA approval of this agent in fourth-line, relapsed, *BRCA*-mutated ovarian cancer on December 19, 2014.

The role of *BRCA* mutations in predicting response to olaparib in advanced high-grade serous ovarian cancer or undifferentiated ovarian cancer and triple-negative breast cancer was assessed in a phase II multicenter study by Gelmon et al.[14] In this nonrandomized, open-label trial, patients were stratified according to *BRCA* mutation status and received olaparib 400 mg twice daily. Ninety-one patients were enrolled, with 90 receiving treatment, including 17 patients with *BRCA1/2* mutations and 46 without mutations. The primary outcome of ORR failed to be met in the breast cancer cohort. Of the 63 patients with ovarian cancer who were evaluable, objective responses were seen in 7 of 17 patients (41%; 95% CI, 22-64) with *BRCA1* or *BRCA2* mutations and 11 of 46 patients (24%; 95% CI 14–38) without mutations. Post-hoc analyses revealed that 50% (10 of 20 patients) with *BRCA1/2* wild-type platinum-sensitive ovarian cancer had an objective response, while 60% (3 of 5) of patients with platinum-sensitive *BRCA1/2*-mutated disease had a response. Responses were seen

in 4 patients (33%) with platinum-resistant *BRCA1/2*-mutated ovarian cancer compared with only 1 (4%) of those in the *BRCA1*- or *BRCA2*-negative cohort. Although activity was seen in both platinum-sensitive and platinum-resistant cohorts, a greater response was observed in the platinum-sensitive cohort. While the majority of patients with *BRCA* mutations were noted to have a response, this study importantly demonstrates the activity of olaparib in patients without germline *BRCA1* or *BRCA2* mutations.

Olaparib in Platinum-Sensitive Ovarian Cancer

Based on previous studies suggesting a greater response to olaparib in patients with platinum-sensitive ovarian cancer, several trials selectively enrolled this population.[7,14] One such trial investigated olaparib alone versus the combination of olaparib plus cediranib.[15] Cediranib is an oral tyrosine kinase inhibitor with anti-angiogenic effects mediated through *VEGFR1*, *VEGFR2*, and *VEGFR3*, which has demonstrated activity in relapsed ovarian cancer.[15,16] Ninety-three patients were assessed for eligibility, with 3 patients not qualifying. The remaining patients were randomized to receive either olaparib alone at 400 mg twice daily or olaparib plus cediranib (200 mg twice daily and 30 mg daily, respectively). Patients were also stratified according to their *BRCA* status (mutation carrier, noncarrier, or unknown). Forty-six patients received olaparib alone; while 44 received combination treatment. Similar to previous studies, olaparib monotherapy resulted in a PFS of 9.0 months (95% CI, 5.7-16.5), whereas the combination group saw a PFS of 17.7 months (14.7–not reached; hazard ratio [HR] = 0.42; 95% CI, 0.23-0.76; P = .005).[9,14] Objective response rates of 47.8% and 79.6% were seen in the olaparib-only and olaparib-plus-cediranib groups, respectively. Six of 7 CRs occurred in patients with *BRCA*-mutated disease. A post hoc analysis of PFS and ORR data revealed a greater response to combination therapy in patients with *BRCA* wild-type disease and in those with unknown status. While this warrants further investigation, this analysis should be interpreted with caution, as the *BRCA*-mutated group may have performed better than expected with a PFS of 16.5 months. The combination group more frequently experienced grade 3 diarrhea, fatigue, and hypertension, with 75% of the cohort requiring dosage reductions. This study provides the first investigation into PARP inhibition in combination with an anti-angiogenic agent, and has paved the way for a phase III trial.

Olaparib has demonstrated activity in combination with chemotherapy in recurrent, platinum-sensitive ovarian cancer.[17] In a phase II, randomized study, 162 eligible patients were enrolled 1:1 to olaparib plus carboplatin and paclitaxel followed by olaparib monotherapy as maintenance or carboplatin and paclitaxel alone. The olaparib-plus-chemotherapy group received olaparib 200 mg twice daily on days 1-10 of a 21-day cycle plus paclitaxel (175 mg/m^2) and carboplatin (area under the curve [AUC] 4 mg/mL/minute) on day 1 for 6 cycles, followed by maintenance olaparib 400 mg twice daily until disease progression. The chemotherapy group received paclitaxel (175 mg/m^2) and carboplatin (AUC 6) on day 1 of a 21-day cycle for 6 cycles or disease progression. Thirty-eight percent of patients carried *BRCA1* or *BRCA2* mutations and were balanced between groups. The primary endpoint was PFS; overall survival (OS) served as a secondary endpoint. The majority of patients (75%) in both groups received 6 cycles of treatment. More AEs were reported in patients receiving olaparib plus chemotherapy, with 53 of 81 patients (65%) experiencing grade 3 or higher AEs compared with 43 of 75 patients (57%) receiving only chemotherapy. The addition of olaparib to standard chemotherapy significantly improved PFS compared with chemotherapy alone, with a median of 12.2 (95% CI, 9.7-15.0) versus 9.6 months (95% CI, 9.1-9.7), respectively (HR = 0.51; 95% CI, 0.34-0.77; P = .0012). The improvement in PFS was even more pronounced in patients with *BRCA* mutations, where PFS was not reached in this group after a median follow-up of 9.8 months (HR = 0.21; 95% CI, 0.08-0.55; P = .0015). While there was no significant difference in OS between the groups by treatment cohort or *BRCA* status, exploratory analyses showed an improvement in time to first subsequent therapy or death favoring the combination therapy with olaparib (HR = 0.60; 95% CI, 0.42-0.86; P = .0053). This has been proposed to reflect post-progression efficacy of maintenance therapy with olaparib.

Olaparib in Platinum-Resistant Ovarian Cancer

While response to olaparib has been correlated with platinum sensitivity, multiple studies have demonstrated activity in patients with platinum-resistant ovarian cancer.[7,14] Audeh et al[8] saw ORRs of 30% (6 of 20 patients) in this cohort. Other studies have shown ORRs ranging from 33% to 42% in platinum-resistant populations.[7,14] Kaufman et al[13] specifically enrolled patients with platinum-resistant *BRCA1/2*-mutated ovarian cancer in a phase II study and found an ORR of 26.2%, with 40.4% of patients achieving SD. Median PFS was 7 months, comparing favorably with other studies in platinum-resistant ovarian cancer.[18,19] Further clinical investigation of olaparib in platinum-resistant ovarian cancer is warranted.

Olaparib As a Maintenance Strategy

Ledermann et al[20] investigated olaparib as a maintenance strategy in relapsed, platinum-sensitive patients in a randomized, multicenter phase II trial. Patients were required to have received 2 or more platinum-based chemotherapy regimens and to have had a PR or CR with their most recent platinum therapy. Both patients with *BRCA*-mutant and wild-type disease were eligible for enrollment. A total of 265 patients were randomized, including 136 to the olaparib-400-mg-twice-daily cohort and 129 to the placebo arm. The primary endpoint of PFS was noted to be significantly longer in patients receiving olaparib maintenance than

those receiving placebo at 8.4 months versus 4.8 months (HR = 0.35; 95% CI, 0.25-0.49; *P* <.001). At the cutoff point for data analysis, the median exposure to olaparib was 206.5 days compared with 141 days for placebo. More AEs were seen in patients receiving olaparib, with the most common side effects being nausea, vomiting, and fatigue.

A subsequently published preplanned retrospective analysis of the original study assessed the efficacy of olaparib maintenance according to *BRCA* mutation status.[21] Of the 136 patients originally randomized to the olaparib maintenance arm, 74 of 131 patients (56%) with known mutation status carried germline *BRCA* mutations, while 62 of 123 (50%) had tumor mutations of *BRCA*. Patients with a *BRCA* mutation receiving olaparib had a significantly longer PFS at 11.2 months compared with 4.3 months in those with a *BRCA* mutation receiving placebo (HR = 0.18; 95% CI, 0.10-0.31; *P* <.0001). No OS differences were noted between the groups by treatment or *BRCA* mutation status.

In the previously presented study by Oza et al,[17] olaparib was administered with chemotherapy followed by maintenance olaparib. No separation in the PFS curves was seen during concomitant use relative to control chemotherapy; however, the curves separated significantly during the maintenance phase. Although the study was not designed to assess the contributions of each treatment phase, the late separation of the PFS curves seen in the trial suggests the maintenance phase to be the most important contributor to the improvement in PFS. This finding led the authors to conclude that olaparib plus chemotherapy does not provide any advantage over olaparib maintenance alone.

The findings from these trials have led to the development of 2 phase III trials investigating olaparib maintenance. SOLO-1 (NCT01844986) is a randomized, double-blind, placebo-controlled, multicenter trial investigating olaparib maintenance in advanced *BRCA*-mutated ovarian cancer following completion of first-line platinum chemotherapy. The primary endpoint is PFS, with secondary endpoints of OS and quality of life, among others. Planned accrual is 397 patients, with enrollment estimated to be completed in July 2016. Patients randomized to the treatment arm will receive olaparib 300 mg twice daily for up to 2 years or until disease progression.

SOLO-2 (NCT01874353) is a randomized, double-blind, placebo-controlled, multicenter phase III trial investigating olaparib maintenance in platinum-sensitive, recurrent *BRCA*-mutated ovarian cancer. Patients must have received 2 prior platinum-based chemotherapy regimens, with disease progression greater than 6 months after completion of their last dose of platinum chemotherapy. Randomization must occur within 8 weeks of completion of platinum-based chemotherapy. The olaparib maintenance arm will receive olaparib 300 mg twice daily until disease progression. PFS is the primary objective. Accrual for this trial has completed, with a final data collection date for primary outcome measure expected in July 2015.

The effectiveness of olaparib is being compared with chemotherapy in recurrent, platinum-sensitive germline *BRCA*-mutated ovarian cancer in the SOLO-3 trial (NCT02282020). In this phase III study, patients are randomized to either olaparib 300 mg twice daily or single-agent, nonplatinum-based chemotherapy, as chosen by the treating clinician. Patients must have completed 2 previous lines of platinum-based chemotherapy. The primary endpoint is PFS. This trial is open and currently recruiting patients. Of note, SOLO-1, SOLO-2, and SOLO-3 utilize the tablet form of olaparib rather than the capsule form studied in the phase I and II trials. While the dosage of 300 mg is lower than that used in many trials, it has higher bioavailability and provides equivalent drug exposure.

Resistance to PARP Inhibition

Despite their clinical promise, resistance to PARP inhibition remains a challenge to the implementation of these agents. Acquired resistance to both platinum-based chemotherapy and PARP inhibition has been linked to secondary mutations in *BRCA2* that restore the wild-type reading frame.[22] Cisplatin-resistant cells were found to acquire a variety of mutations, all of which restored the wild-type *BRCA2* reading frame and conferred resistance to both cisplatin and PARP inhibition. In an evaluation of recurrent *BRCA2*-mutated patient samples originally treated with cisplatin, those resistant to cisplatin were found to have reverted to a wild-type *BRCA2* phenotype. Ashworth[23] confirmed that resistance to PARP inhibition could be acquired through deletion of a *BRCA2* mutation. Additional mechanisms include increased activity of *BRCA1* or *BRCA2* variants encoded by hypomorphic alleles and rescue of DNA end-resection in *BRCA1*-deficient tumors through loss of 53BP1.[24] Resistance to PARP inhibition has also been shown to develop through increased expression of P-glycoproteins in *BRCA1*-mutated breast cancers.[25] This resistance was overcome with administration of 6-thioguanine (6TG), which in the case of *BRCA1*-mutated cancer probably results from it being a poor substrate for P-glycoprotein. However, it was also noted that 6TG was effective in inducing cell death among PARP inhibitor-resistant *BRCA2*-mutated tumors harboring a functional *BRCA2* reversion. Detailed investigation suggested that 6TG induces both mismatch-dependent and -independent DNA damage requiring homologous recombination repair. 6TG has been proposed as a potential strategy to combat acquired resistance to PARP inhibition.

Future Directions and Conclusions

An estimated 11% to 15% of unselected patients with ovarian cancer have germline *BRCA1* or *BRCA2* mutations.[26,27] Given the demonstrated activity of PARP inhibition in germline *BRCA1/2*- mutated ovarian cancer, Hennessy et al[28] sought to investigate whether loss of *BRCA* function can also occur through somatic mutations, potentially expanding the number of pa-

tients who could benefit from this treatment. Two-hundred and thirty-five ovarian cancer samples were randomly selected and analyzed for *BRCA* mutations. Forty-four *BRCA* mutations were detected in 43 tumors, including 1 cancer in which both *BRCA1* and *BRCA2* mutations were detected. Of these tumors, 28 samples had DNA available for analysis. Eleven mutations (9 *BRCA1* and 2 *BRCA2*) were found to be somatic, whereas 17 mutations were found in both tumor and germline DNA. There was no significant difference in clinical variables or PFS between patients with germline *BRCA* mutations and somatic *BRCA* mutations. *BRCA1/2* deficiency, as defined by the presence of germline or somatic mutations, deletion of *BRCA1* or *BRCA2*, or loss of expression of *BRCA1* or *BRCA2*, was present in 30% of the ovarian tumors analyzed and was associated with significantly prolonged PFS following surgical cytoreduction when compared with *BRCA* nonmutants (20.1 and 13.8 months, respectively). The surprising frequency of somatic aberrations found in *BRCA1/2* ovarian cancers, with resultant disruption in homologous repair, was postulated to increase the sensitivity of these tumors to PARP inhibition. The authors also suggest that somatic mutations and *BRCA1/2* expression loss be routinely assessed in clinical trials investigating the effectiveness of PARP inhibition, in addition to standard germline mutation testing.

The heterogeneous mechanisms by which tumors can acquire defects in homologous repair has been referred to as "BRCAness" or "BRCA-like" status.[29,30] A gene expression profile for the BRCA-like state has been developed and is associated with response to platinum-based chemotherapy, as well as response to PARP inhibition.[31] This 60-gene profile was developed after analysis of microarray data from 61 patients with somatic or germline *BRCA* mutations. Using the gene profile, the authors were able to predict platinum sensitivity in 8 of 10 patient-derived samples. They also were able to predict sensitivity or resistance to PARP inhibition in 100% (4 of 4) of cell lines. This profile was then used to categorize 70 patients with sporadic ovarian cancer as BRCA-like (BL) or non–BRCA-like (NBL). Patients with a BL profile had improved disease-free survival (34 months vs 15 months; log-rank $P = .013$) and OS (72 months vs 41 months; log-rank $P = .006$) compared with patients with a NBL profile. In a multivariate analysis, the BL profile maintained independent prognostic value when other clinical variables were controlled. BRCA-like phenotypes have also been observed with hypermethylation of the BRCA promoter and with alterations of BRCA-associated proteins, including BARD1.[32,33] Although further investigation is needed, this BL profile could potentially be used to offer PARP inhibition to a much larger population of patients with ovarian cancer, independent of *BRCA* mutation status.

Methods to predict response to PARP inhibition are currently being investigated. Homologous recombination deficiency (HRD) assays are in development, which use next-generation sequencing to identify genome-wide loss of heterozygosity, seen in patients lacking genes involved in homologous repair, not just *BRCA1* and *BRCA2*. These assays have been successful in predicting response to rucaparib, another PARP inhibitor.[34] The efficacy of HRD assays in predicting response to olaparib and other PARP inhibitors is now being investigated (NCT02401347). The production of Rad51, a known marker of homologous repair, following irradiation of patient-derived xenographs, has been shown to predict response to PARP inhibition ex vivo, with sensitive samples consistently having a low Rad51 foci formation rate.[35] CDK12 activity also has been proposed as a marker for resistance to PARP inhibition.[36] This kinase promotes homologous repair and confers resistance to PARP inhibitors. FOXO3a expression also is being explored as a potential biomarker in predicting response to inhibition of PARP.[37]

Further clinical investigation of olaparib is under way. A planned phase II study aims to detect a biomarker signature that correlates with durable response or SD to cediranib and olaparib in patients with platinum-sensitive ovarian cancer (NCT02345265). Cediranib in combination with olaparib also is being investigated in the phase III setting, following promising phase II results.[15] Other phase I/II studies are ongoing with olaparib in combination with PI3K pathway inhibitors (NCT01623349), AKT inhibitors (NCT02338622), and mTORC1/2 inhibitors (NCT02208375), among others. PARP inhibitors also are being investigated in patients with wild-type *BRCA*-associated disease (NCT02354586).

Olaparib and PARP inhibition as an anticancer strategy is an exciting addition to currently available treatment options for ovarian cancer. More studies are needed to determine the optimal settings and combinations in which to administer olaparib. A profile of a BRCA-like state may allow expansion of the population able to derive clinical benefit from PARP inhibition, and should be investigated in future trials.

Acknowledgments:
Dr Dalton is supported by NIH T32 training grant CA101642. Dr Coleman is supported in part by CPRIT RP120214, Ovarian Cancer Research Fund Program Project Development Grant, the Judy Reis, Albert L. Pisani MD Ovarian Cancer Research Fund, and the Ann Rife Cox Chair in Gynecology.

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Disclosures: Dr Dalton reports no relevant financial conflicts of interest to disclose. Dr Coleman has served as an uncompensated advisor for AstraZeneca; he also has received nonfinancial support and a grant from Merck, and has received clinical trial grants from the following companies: Janssen Pharmaceuticals, Clovis Oncology, Amgen, Novartis, Merrimack Pharmaceuticals, Millennium Pharmaceuticals, OncoMed, Array BioPharma, and EMD Serono.

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