New Biologic Frontiers in Ovarian Cancer: Olaparib Update

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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 followed exciting phase 1/2 data showing anti-tumor efficacy in patients with ovarian cancer, particularly in BRCA-deficient and platinum-sensitive populations. This article will review the early clinical investigation of olaparib, emerging phase 2 and 3 data, and future directions, including forthcoming clinical trials and methods to predict response and expand the populations eligible to receive this innovative biologic therapy.


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. 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. 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. PARP inhibition stimulates nonhomologous end joining (NHEJ) selectively in homologous repair-deficient cells. 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. 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 review will update our previous review and discuss the emerging clinical trial data and future directions of research on PARP inhibitors and ovarian cancer.

Phase 1 Investigation

Early phase 1 investigation of olaparib confirmed activity in BRCA-mutated breast and ovarian cancers. 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). 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. This included 50 patients, 48 of whom had BRCA1 or BRCA2 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 enrolled, 13 had platinum-sensitive disease, 24 had platinum-resistant disease, and 13 had platinum-refractory disease.
Early Phase 2 Studies in Ovarian Cancer

Following the activity demonstrated in the phase 1 study, a proof-of-concept phase 2 study was initiated. 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 1 study, until disease progression. 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, 20.5-51.0), 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, 4.3-31.0) 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 2 studies are summarized in the Table.

An additional phase 2 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. 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/m² 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. 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. 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.
of germline 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. An update to the long-term safety and efficacy of this study population has recently been reported. ORR was 34% (46/137) and median DoR was 7.9 months (95% CI, 5.6-9.6). ORR was 30% in platinum-resistant tumors. Median DoR for platinum-sensitive and platinum-resistant tumors was 8.2 (95% CI, 4.8-14.8) and 8 months (95% CI, 4.8-14.8), respectively. Three percent had an adverse outcome, which was death. No new safety signals were identified.15

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 2 multicenter study by Gelmon et al.16 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 was not achieved 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

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

<table>
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<th>Study</th>
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<td>Audeh et al</td>
<td>Recurrent HGSOC, n = 57</td>
<td>Mutated</td>
<td>Olaparib 400 mg twice daily vs 100 mg twice daily</td>
<td>ORR</td>
<td>33% (95% CI, 20-51) olaparib 400 mg vs 13% (95% CI, 4-31) olaparib 100 mg</td>
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<td>Kaye et al</td>
<td>Recurrent platinum-sensitive HGSOC, n = 97</td>
<td>Mutated</td>
<td>Olaparib 200 mg twice daily vs 400 mg twice daily vs PLD (50 mg/m² q 28 day)</td>
<td>PFS</td>
<td>6.5 vs 8.8 vs 7.1 months No significant difference in PFS</td>
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<td>Gelmon et al</td>
<td>Recurrent HGSOC and TNBC, n = 91</td>
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<td>Liu et al</td>
<td>Recurrent platinum-sensitive HGSOC, n = 90</td>
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<td>PFS</td>
<td>9.0 vs 17.7 months (HR, 0.42; 95% CI, 0.23-0.76; P=.003)</td>
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<td>Oza et al</td>
<td>Recurrent platinum-sensitive HGSOC, n = 162</td>
<td>Mutated, wild-type, or unknown</td>
<td>Olaparib 200 mg twice daily (days 1-10), paclitaxel (175 mg/m², day 1) and carboplatin (AUC 4 mg/mL per minute, day 1); then olaparib at 400 mg twice daily until disease progression vs paclitaxel (175 mg/m²) and carboplatin (AUC 6 mg/mL/minute)</td>
<td>PFS</td>
<td>12.2 vs 9.6 months (HR, 0.51; 95% CI, 0.34-0.77; P =.0012) No OS difference</td>
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<td>Ledermann et al</td>
<td>Recurrent platinum-sensitive HGSOC, n = 265</td>
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<td>Olaparib 400 mg twice daily following completion of platinum-based chemotherapy vs placebo</td>
<td>PFS</td>
<td>8.4 months vs 4.8 months (HR, 0.35; 95% CI, 0.25-0.49; P &lt;.001) No OS difference</td>
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AUCº 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.
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. One such trial investigated olaparib alone versus the combination of olaparib plus cediranib. 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. 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; \( P = .005 \)). 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 phase 3 trials (NCT02446600, NCT02502266).

Olaparib has demonstrated activity in combination with chemotherapy in recurrent, platinum-sensitive ovarian cancer. In a phase 2, 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 to 10 of a 21-day cycle plus paclitaxel (175 mg/m²) 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/m²) 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.

A phase 3 ongoing study includes NRG GY004, which is comparing single-agent olaparib or the combination of cediranib and olaparib to standard platinum-based chemotherapy in women with recurrent platinum-sensitive ovarian carcinoma (NCT02446600). In this study, patients are randomized 1:1:1 to either olaparib monotherapy or cediranib and olaparib combination or platinum-based chemotherapy. Platinum-based chemotherapy options may include carboplatin and paclitaxel, carboplatin and gemcitabine, or carboplatin and pegylated liposomal doxorubicin.

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. Audeh et al. 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. Kaufman et al. specifically enrolled patients with platinum-resistant BRCA1/2-mutated ovarian cancer in a phase 2 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.
Further clinical investigation of olaparib in platinum-resistant ovarian cancer is warranted. Early phase 1 studies are evaluating a newer PARP inhibitor, veliparib, in combination with pegylated liposomal doxorubicin, carboplatin, in combination with bevacizumab. This NRG Oncology/Gynecologic Oncology Group study’s objective was to determine the maximum tolerated dose and dose-limiting toxicities of this combination. Patient received PLD (30 mg/m², IV) and carboplatin (AUC 5, IV) on day 1 with veliparib on days 1 to 7 (intermittent) or days 1 to 28 (continuous). A 3 + 3 design was used in the dose escalation phase. Once the maximum tolerated dose was determined, a cohort of six patients were enrolled in each regimen with bevacizumab (10 mg/kg on days 1 and 15) to determine the feasibility. A total of 27 patients were treated at three dose levels and dose-limiting toxicities were noted in six patients, which included four patients with grade 4 thrombocytopenia and three patients with neutropenia greater than seven days. The maximum tolerated dose of veliparib was determined to be 80 mg twice daily for both arms and myelosuppression was the primary dose-limiting toxicity. Twelve patients were treated at this dose with the addition of bevacizumab, and nine patients experienced dose-limiting toxicities, which included thrombocytopenia, prolonged neutropenia, hypertension, and one patient experienced sepsis. Previous studies have hypothesized that the continuous dosing of veliparib would be the best dosing strategy for patients with BRCA mutations, while intermittent dosing may suffice when using PARP inhibition for chemo-sensitization in patients with homologous recombination deficiency. Significant hematologic toxicity was encountered in this early study, but warrant further research pre-clinically.

**PARP Synergy With Anti-Angiogenic Therapies**

Mounting pre-clinical evidence has suggested a synergistic or combinatorial effect with PARP inhibitors when combined with anti-angiogenic inhibitors. The mechanism for this rationale includes the downregulation of homologous recombination repair genes in hypoxic setting, which ‘resets’ PARP inhibitor sensitivity. In addition, BRCA1 and BRCA2 have been found to be downregulated in ovarian cancer cells with VEGF inhibition.

The safety and tolerability in a phase 1 study of bevacizumab in combination with another PARP inhibitor in development, niraparib, in platinum-sensitive ovarian cancer patients, the ENGOT-OV24/AVANOVA1 trial. This single-arm study evaluated patients in a 3 + 3 design. The patients received fixed dose bevacizumab (15 mg/kg IV every 21 days) with dose escalation of niraparib (100, 200, 300 mg orally daily). The objective was to establish the maximum tolerated dose and dose-limiting toxicities. Twelve patients were enrolled to three dose levels, of which three had a germline BRCA2 mutation. Commonly related toxicities included hypertension, anemia, thrombocytopenia, fatigue, constipation and nausea. The recommended phase 2 dose established was bevacizumab 15 mg/kg every 21 days with niraparib 300 mg orally daily. A phase 2 trial is currently ongoing (NCT02354131).

**PARP Inhibitors As a Maintenance Strategy**

Ledermann et al investigated olaparib as a maintenance strategy in relapsed, platinum-sensitive patients in a randomized, multi-center phase 2 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. 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, 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 3 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, and no longer recruiting.
patients. 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 3 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.

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 3 study, patients are randomized to either olaparib 300 mg twice daily or single-agent, non-platinum-based chemotherapy, as chosen by the treating clinician. Patients have 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 1 and 2 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. 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 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. Resistance to PARP inhibition has also been shown to develop through increased expression of P-glycoproteins in BRCA1-mutated breast cancers. 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.

Homologous Recombination Deficiency in Non-BRCA Mutant Patients
Patients with non-germline mutations in BRCA but have homologous recombination deficiency due to defects in this DNA damage pathway have been investigated. The ARIEL2 trial sought to prospectively identify patients with non-germline BRCA1 or BRCA2 mutations who may have a homologous recombination deficiency by using a next-generation sequencing assay. An analysis algorithm was developed to predict rucaparib sensitivity by detecting tumor BRCA status and whether there is a high genomic loss of heterozygosity representing a DNA “scar” reflecting prior loss of HR repair. Part 1 of ARIEL2 included 204 patients with recurrent, platinum-sensitive, high grade ovarian carcinoma and were classified into three homologous recombination deficiency subgroups based on tumor analysis: BRCA mutant (deleterious germline or somatic); BRCA wild type/loss of heterozygosity (LOH) high; or BRCA wild type/LOH low. Patients received 600 mg of rucaparib twice daily. The primary endpoint was PFS, but secondary endpoints also included response rate, response duration, and safety. The risk of progression during treatment was significantly reduced in the BRCA mutant subgroup (HR, 0.27; 95% CI, 0.16-0.44; P < .0001) and in the BRCA wild type/LOH high subgroup (HR, 0.62; 95% CI, 0.42-0.90) subgroup compared to the BRCA wild type/LOH low subgroup. More patients in the BRCA mutant subgroup (50.4%; P < .0001 for HR) and in the BRCA wild type/LOH high subgroup (28.0%; P = .011 for HR) were progression free at 12 months than the BRCA wild type/LOH low subgroup (9.6%). This study suggests that assessment of tumoral LOH can identify patients that have BRCA wild type platinum-sensitive ovarian cancers that may benefit from PARP inhibition with rucaparib.

Future Directions and Conclusions
An estimated 11% to 15% of unselected patients with ovarian cancer have germline BRCA1 or BRCA2 mutations. Given the demonstrated activity of PARP inhibition in germline BRCA1/2-mutated ovarian cancer, Hennessy et al sought to investigate whether loss of BRCA function can also occur through somatic mutations, potentially expanding the number of patients who could benefit from this treatment. Two-hundred 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 "BRCA-ness" or "BRCA-like" status. 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. 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 versus 15 months; log-rank P < .013) and OS (72 versus 41 months; log-rank P < .006) compared with patients with a NBL profile. In a multi-variante 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. 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. 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. CDK12 activity also has been proposed as a marker for resistance to PARP inhibition. 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.

Further clinical investigation of olaparib is under way. A planned phase 2 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 3 setting, following promising phase 2 results. Other phase 1/2 studies are ongoing with olaparib in combination with P13K pathway inhibitors (NCT01623349), AKT inhibitors (NCT02338622), and mTORC1/2 inhibitors (NCT02208375), Wec1 (NCT02511795), among others. PARP inhibitors also are being investigated in patients with wild-type BRCA-associated disease (NCT02354586). Other PARP inhibitors are being evaluated in combination with over targeted therapies including niraparib and pembrolizumab (NCT02657889).

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.

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