The Status of Poly(Adenosine Diphosphate-Ribose) Polymerase (PARP) Inhibitors in Ovarian Cancer, Part 2: Extending the Scope Beyond Olaparib and *BRCA1/2* Mutations

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Abstract: Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors have shown clinical activity in epithelial ovarian cancer, leading both the US Food and Drug Administration (FDA) and the European Medicines Agency to approve olaparib for tumors characterized by *BRCA1* and *BRCA2* mutations. However, it is becoming increasingly evident that tumors that share molecular features with *BRCA*-mutant tumors—a concept known as *BRCAness*—also may exhibit defective homologous recombination DNA repair, and therefore will respond to PARP inhibition. A number of strategies have been proposed to identify BRCAness, including identifying defects in other genes that modulate homologous recombination and characterizing the mutational and transcriptional signatures of BRCAness. In addition to olaparib, a number of other PARP inhibitors are in clinical development. This article reviews the development of PARP inhibitors other than olaparib, and discusses the evidence for PARP inhibitors beyond *BRCA1/2*-mutant ovarian cancer.

Introduction

Epithelial ovarian cancer (EOC), which is the most lethal gynecologic malignancy, is the fifth-leading cause of cancer-related deaths in women.[1] The majority of women present with advanced-stage disease, and eventually relapse after initial therapy.[2] The current standard of care is a combination of aggressive cytoreductive surgery and platinum-based chemotherapy, with a response to first-line chemotherapy seen in 65% to 80% of patients.[3] Despite high initial response rates, most patients die of their disease. The 5-year survival rate for those with advanced-stage disease is approximately 5% to 22%.[1] The current management of relapsed EOC is based on sensitivity to platinum chemotherapy. Although initial response rates are high, sensitivity to platinum therapy diminishes with time; the majority of patients eventually develop platinum-resistant disease.[4-7] Although recent advances have led to improvements in progression-free survival (PFS), few have resulted in improved

overall survival, and recurrent ovarian cancer remains a lethal disease. As a consequence, considerable room for improvement remains.

Our greater understanding of the cancer genome and the complex processes that underlie cancer development and progression offers a fundamental change in the treatment of cancer. It is now possible to target molecular alterations and pathways directly. An example of this is the ability to target tumors with defective DNA repair by exploiting the molecular differences between tumor and normal cells, thereby inducing cancer-specific synthetic lethality. The best example of this to date is the use of poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors for the treatment of *BRCA1*- or *BRCA2*-mutant EOC.[8,9] BRCA1 and BRCA2 are involved in the error-free repair of DNA double-strand breaks via the highly conserved homologous recombination repair pathway, and are essential for the maintenance of genomic stability.[10] Cells with defective homologous recombination, such as those with *BRCA1/2* mutations, rely on alternative means of DNA repair, including base excision repair, nucleotide excision repair, and mismatch repair, processes that are modulated by PARP. This defective homologous recombination pathway renders the cells sensitive to PARP inhibition, a concept known as synthetic lethality.[11,12] The synthetic lethality between *BRCA1/2* mutations and PARP inhibition is well established[11,12] and is discussed in part 1 of this review.[13]

It is becoming increasingly evident that tumors that share molecular features with *BRCA*-mutant tumors, a concept known as *BRCAness*, also may respond to similar therapeutic approaches. The BRCAness phenotype describes the situation whereby a homologous recombination defect exists in a tumor in the absence of a germline *BRCA1* or *BRCA2* mutation.[14] As many as 30% to 50% of high-grade serous ovarian cancers are associated with defects in homologous recombination pathways,[15,16] and targeting homologous recombination deficiency using PARP inhibitors has become one of the first genotype-directed therapies for ovarian cancer.

Olaparib (Lynparza, AstraZeneca) is the most established PARP inhibitor to date. However, multiple other PARP inhibitors—including rucaparib (CO-338), veliparib (ABT-888), niraparib (MK-4827), and talazoparib (BMN-673)—are in clinical development either as single agents or as a component of combination therapy for the management of EOC (Table 1). Early-phase clinical studies with olaparib have confirmed the synthetic lethality previously observed in vitro, with dramatic responses to olaparib observed in patients with *BRCA1/2*-mutant EOC.[17,18] As a result of these and other studies, olaparib has been licensed for patients with *BRCA1/2*-mutant ovarian cancer in both North America and Europe.[19,20] In part 1 of this review, we discussed the evidence for the use of olaparib in ovarian cancer and the mechanisms behind BRCA1/2 and PARP inhibitor synthetic lethality.[13] In this part, we consider the data regarding novel PARP inhibitors (other than olaparib) and evaluate the role for expanding the use of PARP inhibitors in ovarian cancer beyond *BRCA1/2* mutations.

Expanding the Scope of PARP Inhibition

Targeting Homologous Recombination Deficiency

Dramatic responses to PARP inhibition have been observed in germline-associated *BRCA1/2*-mutated tumors. However, based on early clinical trials with PARP inhibitors, it was clear that a sensitive *BRCA*–wild-type cohort also existed, and that identifying these patients would be essential to increasing the utility of PARP inhibition in EOC. A number of sporadic EOCs are also defective in homologous recombination and share the BRCAness phenotype.[15,16,21] Significant challenges exist in identifying these patients, and a number of approaches have been suggested for identifying those tumors characterized by BRCAness. This includes identifying defects in other genes that modulate homologous recombination and characterizing the mutational and transcriptional signatures of BRCAness.

Not only did The Cancer Genome Atlas project identify almost-universal *TP53* mutations (96%) in high-grade serous ovarian cancer, it also identified mutations in homologous recombination pathway genes in approximately 50% of these cancers.[15] In addition to germline mutations in *BRCA1* (9%) and *BRCA2* (8%), this included somatic mutations in *BRCA1/2* (3%), *ATM* and *ATR* (2%), and the *FANC* family (5%), as well as hypermethylation of *RAD51C* (3%) and *EMSY* amplification (8%), which is proposed to inactivate BRCA2.[15,22] In vitro studies have demonstrated that deficiencies in many of these genes and other homologous recombination proteins, such as checkpoint kinase 1 (CHEK1), checkpoint kinase 2 (CHEK2), and cyclin-dependent kinase 12 (CDK12), also confer sensitivity to PARP inhibition, although this remains to be prospectively validated in clinical populations.[16,23-25]

In an attempt to further characterize homologous recombination deficiency in EOC, Pennington and colleagues employed targeted capture and massively parallel genomic sequencing to look for germline and somatic loss-of-function mutations in 30 genes, including 13 homologous recombination genes in 390 EOCs.[16] Overall, 31% of EOCs had a deleterious germline (24%) and/or somatic (9%) mutation in 1 or more of the 13 homologous recombination genes, with similar incidence noted in serous (31%) and nonserous histologies (28%,

P=.06). Both platinum sensitivity (*P*=.0002) and improved overall survival (*P*=.0006) were associated with the presence of a germline or somatic homologous recombination gene mutation.[16] Although the majority of homologous recombination mutations were either germline or somatic *BRCA1/2* mutations, 26% occurred within other homologous recombination genes. The authors hypothesized that these individuals would also have increased response rates to PARP inhibitors, and should be considered for inclusion in PARP inhibitor trials.[16] Anecdotal reports support this. For example, a number of clinical responses to rucaparib have been observed in patients with both germline and somatic *RAD51C* mutations within the ongoing phase 2 ARIEL2 study (Assessment of Rucaparib in Ovarian Cancer: Phase 2 Trial; NCT01891344).[26] It is of interest that in this study by Pennington, similar rates of homologous recombination deficiency were noted in nonserous histology, including clear cell carcinoma, endometrioid carcinoma, and carcinosarcoma. These types of cancer normally are considered homologous recombination–proficient, and therefore are not included in many clinical trials of PARP inhibitors.[16] There was a greater proportion of non-BRCA homologous recombination deficiencies in the nonserous histology cohort, although *BRCA1/2* mutations did exist. These findings suggest that patients with nonserous histology also may be considered for studies of PARP inhibitors.

Although using a targeted panel of homologous recombination genes is one approach to identifying tumors characterized by BRCAness, it remains to be tested prospectively. Furthermore, a number of limitations exist with this approach. First, each individual homologous recombination gene defect—with the exception of *BRCA1/2*—is present at low frequency, and therefore a large number of genes need to be analyzed to capture all homologous recombination–deficient tumors. Secondly, not all homologous recombination genes contribute equally to the BRCA phenotype, and functional studies still are required to correlate many of the homologous recombination mutations to clinical responses. Finally, defective homologous recombination arises via a variety of mechanisms, which include epigenetic changes, gene amplifications, and chromosomal translocations, not all of which are identified using simple sequencing technologies. Rather than concentrating on identifying individual defects in homologous recombination genes, a number of groups have focused on the identification of a biomarker to identify tumors characterized by BRCAness—one that captures the diverse epigenetic and genetic mechanisms of homologous recombination. This approach utilizes the transcriptional and mutational signatures of BRCAness.

Identifying a BRCAness Biomarker

Transcriptional biomarkers usually consist of a pattern of gene expression that is associated with germline *BRCA1/2* gene defects and also is present in sporadic tumors. For example, Konstantinopoulos and colleagues interrogated publicly available gene expression data from *BRCA1/2*-mutant or wild-type high-grade serous ovarian cancer to derive a BRCAness gene expression profile.[27] This profile was validated in vitro and correlated with increased responsiveness to platinum and to PARP inhibitors in cell line models.[27] The assay was then applied to a validation cohort of 70 patients with sporadic EOC. The authors noted that patients with a high BRCAness profile had improved disease-free survival and overall survival compared with those who had a *BRCA* wild-type profile, after correcting for traditional disease-specific prognostic markers.[27] Although further prospective validation is required, in the future it may be possible to use gene expression profiling to identify patients with sporadic disease who might benefit from PARP inhibition.

An alternative approach to the use of gene expression signatures is to classify tumors according to their underlying mutational spectrum.[28] Owing to the reliance on error-prone DNA repair pathways, tumors with defective homologous recombination have a characteristic mutational signature or "mutational scar."[29] Homologous recombination–deficient tumors harbor large (<15 megabase) subchromosomal deletions, allelic imbalance, and single-nucleotide polymorphisms. Genotyping and comparative genomic hybridization have shown that the genomes of high-grade serous ovarian cancer harbor common loss of single parental alleles, which are detected as loss of heterozygosity (LOH).[29,30] High levels of LOH are associated with reduced platinum resistance and improved PFS in patients with high-grade serous ovarian cancer.[31]

Prospective validation of an LOH assay is ongoing within the ARIEL2 phase 2 study of rucaparib. Here, next-generation sequencing is performed on fresh tumor biopsies, allowing patients to be classified in 1 of 3 molecularly defined subgroups: those with *BRCA1/2*-mutant tumors (germline and somatic), those with *BRCA*-like tumors, and those whose tumors are biomarker-negative. *BRCA*-like tumors are defined as those with high levels of genomic LOH in the context of wild-type *BRCA*.[32] Early results suggest increased activity for rucaparib within the *BRCA*-like population compared with the low-LOH population, although the benefit was not quite as great as that seen in the *BRCA1/2*-mutant cohort (see below).[32] We await with interest the final results, to see whether this homologous recombination deficiency LOH assay can predict an additional subset of patients with sporadic EOC who are likely to respond to PARP inhibition.

Other Genes Conferring PARP Inhibitor Sensitivity

Until recently, the role of PARP inhibitors has focused on homologous recombination deficient, high-grade serous ovarian cancer. However, in vitro data suggest that other molecular aberrations may sensitize tumors to PARP inhibition in other histologic subtypes. For example, deficiency in AT-rich interaction domain 1A (ARID1A), a key component of the chromatin-remodeling complex, sensitizes cancer cells to PARP inhibition in vitro and in vivo.[33] ARID1A is recruited to DNA double-strand breaks, facilitates efficient processing of double-strand breaks, and sustains DNA damage signaling. Mutations in *ARID1A* are common in both clear cell and endometrioid ovarian epithelial carcinomas, occurring in up to 57% and 30% of cases, respectively.[34,35] This finding suggests that a trial of PARP inhibitors should be used in these patients. Loss of phosphatase and tensin homolog (PTEN) function has been shown to sensitize tumors to PARP inhibition in endometrioid endometrial cancer owing to defects in repair of DNA double-strand breaks by homologous recombination. Therefore, loss of PTEN function may sensitize cells to PARP inhibition.[36] *PTEN* mutations are common in endometrioid and clear cell ovarian cancer,[37,38] and these patients may therefore represent an additional group that may benefit from PARP inhibition. This use of PARP inhibitors requires clinical validation.

It is clear that a subset of patients with *BRCA1/2*–wild-type EOC exists who would benefit from PARP inhibition, but as yet it has not been established how to best identify this population. With improved understanding of PARP biology and homologous recombination–directed biomarker studies, it will be possible to identify the population that is most likely to benefit.

Novel PARP Inhibitors

In addition to olaparib, a number of novel PARP inhibitors are in various stages of clinical development (Table 1).

Rucaparib

Rucaparib is an oral PARP-1/2 inhibitor that also has activity against tankyrase 1 and 2 (TNKS1/2).[39] The initial phase 1 trial established a recommended dose of 600 mg twice daily and demonstrated early clinical activity in patients with both platinum-sensitive and platinum-resistant ovarian and peritoneal cancers.[39] Further evaluation of rucaparib in recurrent ovarian cancer is ongoing. Results of the first part of ARIEL2, a phase 2 biomarker study in 206 women with relapsed platinum-sensitive high-grade serous or endometrioid cancer, recently were reported.[26] As discussed earlier, ARIEL2 was designed to assess sensitivity to rucaparib in 3 prospectively defined molecular subgroups of patients who had received at least 1 prior chemotherapy regimen. Overall response rates by Response Evaluation Criteria in Solid Tumors (RECIST) and CA 125 response criteria were 82%, 43%, and 22% for the *BRCA1/2*-mutant, *BRCA*-like, and biomarker-negative populations, respectively, with median PFS of 286 days, 216 days, and 111 days. Interestingly, the median duration of response to rucaparib among the responders was similar in the *BRCA1/2*-mutant and *BRCA*-like cohorts (9.5 and 8.2 months, respectively), and work is ongoing to identify those patients with the *BRCA*-like phenotype who are most likely to respond.

The same prospective molecular stratification of patients is being applied to 2 ongoing ovarian cancer trials: the second part of ARIEL2, a single-arm study in patients with high-grade ovarian cancer who have received at least 3 prior chemotherapy regimens, and ARIEL3, a randomized maintenance study of rucaparib vs placebo in patients with high-grade ovarian cancer who have received at least 2 platinum regimens (NCT01968213, Table 2). In addition to being explored for use as a single agent, rucaparib also has been combined with temozolomide in patients with melanoma, with some evidence of chemopotentiation.[40]

Table 1. PARP Inhibitors in Clinical Development

PARP Inhibitor		Route	Phase of Development
Olaparib	AZD-2281	PO	Phase 1-3
Rucaparib	CO-338	PO	Phase 1-3
Veliparib	ABT-888	PO	Phase 1-3
Niraparib	MK-4827	PO	Phase 1-3
Talazoparib	BMN-673	PO	Phase 1-2

PARP, poly(adenosine diphosphate-ribose) polymerase inhibitor; PO, by mouth.

Niraparib

Niraparib is an orally bioavailable PARP-1/2 inhibitor that inhibits tumor growth in models with loss of BRCA and PTEN function.[41] A total of 60 patients in the initial dose-finding study received 30 to 400 mg of oral niraparib daily in a 21-day cycle. A further 40 patients were enrolled in the study's expansion phase, which established 300 mg daily as the maximum tolerated dose.[42] Dose-limiting toxic effects reported in the first cycle were grade 3 fatigue (1 patient given 30 mg/day), grade 3 pneumonitis (1 patient given 60 mg/day), and grade 4 thrombocytopenia (2 patients given 400 mg/day). Included in the trial were 22 patients with *BRCA1/2*-mutated ovarian or primary peritoneal cancer, of whom 20 were radiologically assessable. Eight (40%) of these 20 patients achieved a confirmed RECIST and Gynecologic Cancer Intergroup CA 125 partial response at doses ranging from

Table 2. Ongoing PARP Inhibitor Single-Agent Studies

NCT Identifier Number	Phase	Trial type	Platinum Status	Previous Lines of Treatment	Inclusion Criteria	PARP Inhibitor	Comparator
NCT01482715	2	Maintenance	PS	≥3 chemotherapy	*BRCA1/2* (germline or somatic)	Rucaparib	NA
NCT01968213 (ARIEL3)	3	Maintenance	PS	≥2 platinum	HGSOFPC or endometrioid cancer	Rucaparib	Placebo
NCT02354586 (QUADRA)	2	Single-arm	PS	≥3 chemotherapy	HGSOFPC or endometrioid cancer	Niraparib	NA

ARIEL3, A Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients With Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer; HGSOFPC, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer; NA, not available; PARP; poly(adenosine diphosphate-ribose) polymerase; PS, platinum-sensitive; QUADRA, A Study of Niraparib in Patients With Ovarian Cancer Who Have Received Three or Four Previous Chemotherapy Regimens.

Table 3. Ongoing Early-Phase PARP Inhibitor Combination Studies

NCT Identifier Number	Phase	PARP Inhibitor	Combination	Inclusion Criteria	*BRCA* Status
NCT02354131 (AVANOVA)	1/2	Niraparib	Bevacizumab (VEGF)	HGSOFPC, PS to ≥1 platinum	Mutant and WT
NCT02358200	1	Talazoparib	Carboplatin and paclitaxel	*BRCA1/2*-mutant solid tumor or TN breast	Mutant
NCT02627430	1	Talazoparib	AT13387 (HSP90 inhibitor)	Advanced solid tumour, EOFPC, or TN breast	Mutant and WT
NCT01145430	1	Veliparib	PLD	EOFPC or TN breast	Mutant and WT
NCT00989651	1	Veliparib	Carboplatin, paclitaxel, and bevacizumab	HGSOFPC, treatment-naive	Mutant and WT

AVANOVA, Niraparib and/or Niraparib-Bevacizumab Combination Against Bevacizumab Alone in HRD Platinum Sensitive Ovarian Cancer; EOFPC, epithelial ovarian, fallopian tube, or primary peritoneal carcinoma; HGSOFPC, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer; HSP90, heat shock protein 90; PARP; poly(adenosine diphosphate-ribose) polymerase; PLD, pegylated liposomal doxorubicin; PS, platinum-sensitive; TN, triple-negative; VEGF, vascular endothelial growth factor; WT, wild-type.

80 to 400 mg per day with a median response duration of 387 days.[42] Responses also were observed in platinum-sensitive and platinum-resistant sporadic ovarian cancers. Treatment-related adverse events were mostly grade 1 or 2, and included anemia (48%), fatigue (42%), thrombocytopenia (35%), neutropenia (24%), and anorexia (26%). In a phase 3 trial of niraparib vs placebo as maintenance therapy called NOVA (A Maintenance Study With Niraparib Versus Placebo in Patients With Platinum Sensitive Ovarian Cancer; NCT01847274), patients with platinum-sensitive high-grade serous ovarian cancer were randomly assigned in a 2:1 ratio to receive either niraparib or placebo. The agent's manufacturer announced in June that niraparib significantly improved PFS in patients with germline *BRCA* mutations and in those without germline *BRCA* mutations who had homologous recombination–deficient tumors[43]; full results will be presented later this year. Two additional trials of niraparib in ovarian cancer are underway: a single-arm phase 2 study in patients with high-grade serous ovarian cancer who have received 3 or more prior lines of chemotherapy called QUADRA (A Study of Niraparib in Patients With Ovarian Cancer Who Have Received Three or Four Previous Chemotherapy Regimens; NCT02354586; Table 2) and a phase 1/2 combination study with bevacizumab called AVANOVA (Niraparib and/or Niraparib-Bevacizumab Combination Against Bevacizumab Alone in HRD Platinum Sensitive Ovarian Cancer; NCT02354131; Table 3).

Veliparib

Veliparib is an oral bioavailable PARP-1/2 inhibitor that has been predominately studied in combination with

Table 4. Ongoing Randomized Phase 3 PARP Inhibitor Combination Studies

NCT Identifier Number	Phase	PARP Inhibitor	Combination	Platinum Status	Inclusion Criteria
NCT02470585	3	Veliparib	Veliparib or placebo in combination with carboplatin and paclitaxel and as maintenance therapy	First-line treatment	HGSOFPC, stage III/IV
NCT01113957	2	Veliparib	Veliparib and temozolomide or PLD	Platinum-resistant	HGSOFPC

HGSOFPC, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer; PARP; poly(adenosine diphosphate-ribose) polymerase; PLD, pegylated liposomal doxorubicin.

cytotoxic chemotherapy. Phase 1 studies have been performed using veliparib in combination with topotecan, doxorubicin, and cyclophosphamide (both oral and intravenous), with significant myelosuppression observed when combined with DNA-damaging agents.[44-46] The combination of veliparib and topotecan led to significant myelosuppression, necessitating dose reductions. The maximum tolerated dose was established as topotecan 0.6 mg/m^2 per day and veliparib 10 mg twice a day on days 1 to 5 of each 21-day cycle.[44] No responses to treatment were reported.[44] For recurrent, platinum-resistant high-grade serous ovarian cancer, the combination of veliparib and temozolomide is currently being tested vs pegylated liposomal doxorubicin (NCT01113957). The combination of veliparib and metronomic cyclophosphamide (50 mg once daily) was well tolerated, with grade 2 myelosuppression the most common dose-limiting toxicity in the phase 1 trial. Although responses were observed in patients with known *BRCA1/2* mutations (6 out of 13 patients) in the phase 1 trial,[45] the combination of veliparib and cyclophosphamide failed to improve the response rate or PFS vs cyclophosphamide alone in a randomized phase 2 trial in patients with *BRCA1/2*-mutant high-grade ovarian cancer.[47] The platinum sensitivity status of tumors in this trial was unknown. Other ongoing veliparib and chemotherapy combination trials include the Gynecologic Oncology Group phase 1 study with carboplatin, paclitaxel, and bevacizumab (Avastin, Genentech; NCT00989651).

The role of veliparib as a single agent was recently explored in a single-arm phase 2 study in 50 ovarian cancer patients with germline *BRCA1/2* mutations who had received 3 or fewer chemotherapy regimens.[48] In 60% of patients, the disease was considered platinum-resistant. The overall response rate was 26% (90% CI, 16%-38%), the response rate for platinum-resistant disease was 20%, and the response rate for platinum-sensitive disease was 35%.[48] Grade 3 adverse events included fatigue (3 patients), nausea (2 patients), and neutropenia (1 patient), with the most common grade 2 events including nausea (46%), vomiting (18%), and anemia (14%). The role of veliparib vs placebo in combination with carboplatin and paclitaxel and then as maintenance therapy in newly diagnosed high-grade serous ovarian cancer (stages III and IV) is currently undergoing evaluation in a randomized phase 3 trial (NCT02470585, Table 4).

Talazoparib

Talazoparib is a potent PARP-1/2 inhibitor that selectively targets *BRCA1/2*-mutant tumor cells in preclinical models. Its potency is 20- to 200-fold greater than that of other PARP-1/2 inhibitors, such as olaparib, rucaparib, and veliparib.[49] In the phase 1 dose-escalation study, 39 patients were enrolled in 9 cohorts and received doses from 25 to 1100 µg per day, resulting in the establishment of 1000 µg per day as the maximum tolerated dose. A total of 17 patients with *BRCA1/2*-mutant high-grade ovarian cancer were included and treated with doses of at least 100 µg per day. Within this group, RECIST and/or CA 125 responses were observed in 11 patients.[50] Dose-limiting thrombocytopenia occurred in 1 of 6 patients receiving 900 µg per day and 2 of 5 patients receiving 1100 µg per day. Potentially related adverse events included fatigue (10 patients), nausea (10 patients), anemia (6 patients, including 2 with grade 3/4), neutropenia (7 patients, including 3 with grade 3/4), and thrombocytopenia (4 patients, including 3 with grade 3/4). A single-arm phase 2 study is currently underway evaluating talazoparib activity in platinum-sensitive *BRCA1/2*-mutant solid tumors (NCT01989546), with phase 3 trials ongoing in metastatic breast cancer but not in ovarian cancer. Whether this more-potent PARP inhibitor has activity following progression on another PARP inhibitor is currently being evaluated (NCT02326844). This phase 2, single-arm study is examining the role of talazoparib in patients with *BRCA1/2*-associated ovarian cancer who have received prior PARP inhibitor therapy. Eligible patients must have progressed on prior PARP inhibitor monotherapy after attaining a response (complete response, partial response, or stable disease for ≥4 months). This study addresses an important issue as to whether rechallenge with an alternative PARP inhibitor can induce further clinical response.

Resistance to PARP Inhibitors

Despite promising response rates to PARP inhibition in *BRCA*-mutant and other homologous recombination–deficient tumors, de novo and acquired resistance are significant clinical problems. One surprising mechanism of resistance observed in vitro is the development of secondary mutations in *BRCA1* or *BRCA2* that restore the open reading frame of the gene, enabling translation of the functional BRCA protein and the ability to repair the DNA damage caused by PARP inhibitors (and platinum salts).[51,52] Similar *BRCA1/2* reversion mutations have been observed in platinum-resistant and PARP inhibitor–refractory disease,[53,54] with up to 46% of patients with platinum-resistant disease harboring tumor-specific secondary mutations that restored the open reading frame of either *BRCA1* or *BRCA2*.[53]

A second observed resistance mechanism occurs via reduced activity of nonhomologous end joining due to loss of 53BP1. Loss of 53BP1 in cell-line and animal models restores homologous recombination activity in *BRCA1*-mutant cells, leading to olaparib resistance.[55] Interestingly, sensitivity to cisplatin is maintained, possibly owing to the more complex nature of the DNA cross-link lesions induced by cisplatin.[55] The importance of 53BP1 in clinical resistance to PARP inhibitors is not clear, but it may be one mechanism by which ongoing platinum responses are observed after PARP inhibitor therapy.[9,56] Although the above resistance mechanism involves changes in the DNA damage response mediating resistance, pharmacologic effects that alter the cellular response to PARP inhibitors also may be relevant. Increased expression of adenosine triphosphate (ATP)-binding cassette transporters, which are transmembrane proteins that shuttle substrates across extracellular and intracellular membranes, alters PARP inhibitor response.[57,58] The contribution of ATP-binding cassette transporter overexpression to PARP inhibitor resistance in clinical samples has yet to be established.

To date, clinical studies evaluating PARP inhibitor resistance mechanisms have been performed in only small numbers of patients. Additional studies are required to conclusively define the frequency of various resistance mechanisms for both acquired and de novo PARP inhibitor resistance. Clearly under the selective pressure of PARP inhibition (and indeed platinum treatment), the high-grade ovarian cancer genome is able to adapt in a number of ways, and overcoming resistance will require a variety of approaches. Further clarification of resistance mechanisms will aid in the discovery of novel approaches to overcome PARP inhibitor resistance, and may help determine the optimal sequence of these agents in the management of ovarian cancer.

Conclusions and Future Directions

Although it is clear that a benefit exists for PARP inhibitors in EOC characterized by *BRCA1/2* mutations, there is also a role in tumors displaying the BRCAness phenotype, which harbor homologous recombination defects via alternative mechanisms. Furthermore, there may be an additional role for PARP inhibition in EOCs that are traditionally thought to be homologous recombination–proficient, such as nonserous histology, or those characterized by mutations in nonhomologous recombination genes, such as *PTEN*, that may modulate homologous recombination pathways. It remains unclear what determines the best predicator of response to PARP inhibition, although a number of clinical trials are ongoing that are beginning to address this. Furthermore, it is not yet established how to optimize the use of PARP inhibitors (eg, as single agents, in combination with chemotherapy/targeted therapy, or as maintenance therapy) or whether clinical differences exist among PARP inhibitors. As yet, there are no ongoing direct comparative trials to evaluate for differences in efficacy and/or toxicity between PARP inhibitors, although these may become necessary if the newer PARP inhibitors prove efficacious.

Disclosures

Dr Miller has no conflicts of interest. Dr Ledermann is the Principal Investigator of AstraZeneca's Study 19 and Clovis Oncology's ARIEL3. He has participated in Advisory Boards for both companies, and has undertaken speaking engagements for AstraZeneca with institutional remuneration.

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