

# The Status of Poly(Adenosine Diphosphate-Ribose) Polymerase (PARP) Inhibitors in Ovarian Cancer, Part 1: Olaparib

Rowan E. Miller, MD, and Jonathan A. Ledermann, MD

Dr Miller is a specialist registrar in the Department of Medical Oncology at University College London Hospital in London, the United Kingdom. Dr Ledermann is a consultant in the Department of Medical Oncology at University College London Hospital and a professor of medical oncology at Cancer Research UK and the UCL Cancer Trials Centre at the University College London Cancer Institute in London, the United Kingdom.

Corresponding author:

Jonathan A. Ledermann, MD  
Cancer Research UK & UCL Cancer  
Trials Centre  
UCL Cancer Institute  
90 Tottenham Court Road  
London W1T 4TJ  
United Kingdom  
Tel: 020 7679 9898  
Fax: 020 7679 9899  
E-mail: j.ledermann@ucl.ac.uk

**Abstract:** Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors have shown promising clinical activity in epithelial ovarian cancer. Following the observation in vitro that PARP inhibition is synthetically lethal in tumors with *BRCA* mutations, PARP inhibition has become the first genotype-directed therapy for *BRCA1*- and *BRCA2*-associated ovarian cancer. However, it is becoming clear that PARP inhibition also may have clinical utility in cancers associated with defects or aberrations in DNA repair that are unrelated to *BRCA* mutations. Deficient DNA repair mechanisms are present in approximately 30% to 50% of high-grade serous ovarian cancers, the most common histologic subtype. Olaparib is the best-studied PARP inhibitor to date, and a number of phase 3 trials with this agent are underway. This article reviews the development of olaparib for ovarian cancer and discusses the current evidence for its use, ongoing studies, future research directions, and the challenges ahead.

## Introduction

Ovarian cancer is the most lethal gynecologic malignancy and the fifth-leading cause of cancer-related deaths in women.<sup>1</sup> The absence of a validated screening program and the nonspecificity of early disease symptoms mean that most women are diagnosed at an advanced stage. The 5-year survival rate is approximately 30%.<sup>1</sup> The current standard of care consists of aggressive cytoreductive surgery to remove all visible disease, plus platinum- and taxane-based chemotherapy.<sup>2,3</sup> Despite a high initial response rate to chemotherapy, most women with advanced ovarian cancer eventually will have a recurrence; median progression-free survival (PFS) is just 18 months from diagnosis.<sup>4</sup> Although the majority of patients will respond again to platinum-based chemotherapy, sensitivity decreases with each subsequent relapse. The disease inevitably becomes resistant or refractory to platinum agents, and is ultimately fatal.<sup>5</sup> In order to advance the management of ovarian

## Keywords

BRCA, olaparib, ovarian cancer, PARP inhibitor

cancer, new agents are required that improve the rate of durable remission and/or have activity against chemoresistant disease.

The treatment of cancer has changed dramatically over the last decade. Intensive research has increased our understanding of many of the cellular functions that go awry in cancer development and progression. Furthermore, the advent of next-generation sequencing has provided detailed information on the cancer genome for many cancer types. This understanding offers the prospect of targeting molecular alterations and pathways directly to develop more effective cancer therapy. High-grade serous ovarian cancer, the most common subtype of epithelial ovarian cancer, is characterized by almost ubiquitous *TP53* (96%) mutations and a high frequency of mutations in *BRCA1* (12%), *BRCA2* (11%), and other homologous recombination genes, such as *CDK12* and *RAD50*.<sup>6</sup> *BRCA1/2* and other genes in the Fanconi anemia (FA)/BRCA pathway play a key role in homologous recombination, the main mechanism that repairs double-strand DNA breaks. Inherited mutations in *BRCA1* and *BRCA2* account for the majority of familial ovarian carcinoma,<sup>7</sup> but mutations in other members of the FA/BRCA family, such as *BRIP1*, *RAD51C*, and *RAD51D*, are also associated with a susceptibility to ovarian cancer.<sup>8-10</sup> In addition to the familial ovarian cancer syndromes, a number of sporadic tumors also are defective in homologous recombination repair and share the phenotype associated with *BRCA1/2* cancers, a concept known as *BRCAness*.<sup>11</sup> Between 30% and 50% of high-grade serous ovarian cancers are associated with defects in homologous recombination pathways,<sup>6,12</sup> and targeting homologous recombination deficiency has become one of the first genotype-directed therapeutic approaches for ovarian cancer.

## Homologous Recombination and PARP Inhibition

DNA is constantly subjected to damage, and repair via several coordinated pathways is essential to allow cells to progress through the cell cycle and complete replication without errors.<sup>13</sup> DNA damage results in single-strand and double-strand breaks, and homologous recombination is the main mechanism by which the double-strand breaks are repaired. The *BRCA1/2* genes, among others, encode key proteins involved in homologous recombination. Double-strand DNA breaks can also be repaired with nonhomologous end-joining and single-strand repair mechanisms, although these are more error-prone than homologous recombination.<sup>14</sup> Different mechanisms exist for repairing single-strand breaks, including base excision repair, nucleotide excision repair, and

mismatch repair, processes which are modulated by poly(adenosine diphosphate-ribose) polymerase (PARP). PARP binds to the DNA break site and recruits other elements of the DNA repair complex.<sup>14</sup> If a cell fails to repair single-strand breaks before attempting replication, a double-strand break will then form.

Cells with defective homologous recombination pathways must rely on alternative pathways for DNA repair in order to survive, thereby providing a potential therapeutic target. PARP inhibitors capitalize on this concept. The development of PARP inhibitors as a treatment for ovarian cancer was prompted by observations that *BRCA1/2* gene mutations, which result in homologous recombination DNA repair deficiency, greatly increased the in vitro sensitivity of cancer cells to PARP inhibition, exploiting a concept known as synthetic lethality.<sup>15,16</sup> Synthetic lethality occurs when an otherwise innocuous defect in a gene or protein becomes lethal to certain cells when combined with another gene or protein defect.<sup>17</sup> Cells with defective homologous recombination are dependent on nonhomologous end-joining and single-strand DNA repair, and thus are sensitive to PARP inhibition. PARP inhibition produces stalled replication forks, increasing the number of double-strand breaks and leading to genetic chaos and cell death via apoptosis or senescence.<sup>15,16</sup> It is not only *BRCA1/2* mutations that confer sensitivity to PARP inhibition; in vitro studies have demonstrated that deficiencies in other homologous recombination proteins, such as ATM, CHEK1, CHEK2, RAD51D, and CDK12, also confer sensitivity to PARP inhibition.<sup>8,18,19</sup> Clinical studies have reinforced the in vitro concept of *BRCA1/2* mutations and PARP inhibitor synthetic lethality. Multiple PARP inhibitors are in clinical development either as single agents or in combination therapy for the management of ovarian cancer. This article, which is the first in a 2-part series, focuses on the development of olaparib (Lynparza, AstraZeneca). A number of other PARP inhibitors are in development and are discussed further in part 2 of this review.

## Early Phase 1 and Phase 2 Monotherapy Trials

Olaparib, formerly known as AZD2281, is a small-molecule, potent oral PARP inhibitor.<sup>20</sup> It is the best-studied PARP inhibitor to date. The first study of olaparib in humans provided clinical evidence for the efficacy of PARP inhibitors in cancers associated with *BRCA1* or *BRCA2* mutations.<sup>21</sup> This dose escalation study enrolled 60 patients and was enriched for carriers of *BRCA1* and *BRCA2* mutations. The olaparib dose and schedule were increased from 10 mg daily for 2 of every 3 weeks to 600 mg twice daily continuously. Reversible dose-limiting toxicity was seen in 1 of 8 patients treated

with 400 mg twice daily (grade 3 mood alteration and fatigue) and 2 of 5 patients receiving 600 mg twice daily (grade 3 somnolence and grade 4 thrombocytopenia). A dosage of 200 mg twice daily was chosen for the subsequent *BRCA1/2*-mutated expansion cohort. The majority of adverse effects observed were grade 1 or 2 and included nausea (32%), fatigue (30%), anorexia (12%), and anemia (5%). Pharmacodynamic analysis confirmed PARP inhibition in surrogate tissues (peripheral blood mononuclear cells and plucked eyebrow-hair follicles) with the induction of  $\gamma$ H2AX foci, a marker of double-strand DNA breaks.<sup>16</sup> Objective antitumor activity was observed only in cancers associated with the *BRCA1/2* mutations.<sup>21</sup> Overall, 23 patients carrying the *BRCA1/2* mutation were treated, 2 of whom could not be evaluated for response and 2 of whom had tumors not typically associated with *BRCA* mutations. Of the remaining 19 carriers of the *BRCA1/2* mutation with ovarian, breast, and prostate cancer, 63% had a clinical benefit from olaparib treatment with radiologic or tumor-marker responses or disease stabilization for a period of 4 months or greater.<sup>21</sup> The trial was subsequently expanded to include a total of 50 germline *BRCA1/2* mutation carriers (*BRCA1*, 41; *BRCA2*, 7; *BRCA2* variants of uncertain significance, 1; strong family history only, 1) with ovarian, primary peritoneal, or fallopian tube carcinoma.<sup>22</sup> The majority of patients were treated within the expansion cohort with 200 mg twice daily (39/50). A total of 40% of patients had either a partial response or a complete response based on Response Evaluation Criteria In Solid Tumors (RECIST), cancer antigen 125 (CA-125) responses by Gynecologic Cancer Intergroup (GCIg) criteria, or both, with a median duration of response of 28 weeks in responders.<sup>22</sup> The authors noted a significant association between platinum-free interval and response to olaparib, with an overall clinical benefit rate of 69.2%, 45.8%, and 23.1% in the *platinum-sensitive* (defined as recurrence  $\geq$ 6 months after prior platinum therapy), *platinum-resistant* (defined as recurrence  $<$ 6 months after prior platinum therapy), and *platinum-refractory* groups, respectively.<sup>22</sup> Despite this, there was no significant difference in the duration of response to olaparib or time to progression observed between patients whose tumors were platinum-sensitive, -resistant, or -refractory. The data suggest that although there may be some shared resistance mechanisms between platinum chemotherapy and PARP inhibition, the overlap is not complete because antitumor activity for olaparib was observed in patients with platinum-refractory disease.

Although the maximum tolerated dose of olaparib in the initial phase 1 study was 400 mg twice daily, maximal pharmacodynamic activity was observed in tumor biopsies and surrogate tissues with doses of 60 mg twice daily or greater.<sup>21</sup> Furthermore, clinical responses were

observed at doses of 100 mg twice daily.<sup>21</sup> Therefore, a multicenter phase 2 study was undertaken to assess the efficacy and safety of oral olaparib monotherapy at the maximum tolerated dose (400 mg twice daily) and at a pharmacodynamically active lower dose (100 mg twice daily) for treatment of recurrent ovarian cancer in carriers of *BRCA1/2* mutations.<sup>23</sup> This study was performed in heavily pretreated patients, with a median of 3 previous chemotherapy regimens (range, 1-16). An objective response was observed in 33% of patients in the 400 mg twice-daily group and in 13% of those in the 100 mg twice-daily group, with a median PFS of 5.8 months (95% CI, 2.8-10.6) and 1.9 months (95% CI, 1.8-3.6), respectively.<sup>23</sup> The majority of toxicity observed was grade 1 or 2 and similar to the profile seen in the phase 1 study. Grade 3 or 4 hematologic toxicity, however, was greater in the cohort treated with 400 mg twice daily (neutropenia, 9%; anemia, 3%).<sup>23</sup> Although clinical activity was seen in the population treated with 100 mg twice daily, the lower dose appeared to be less efficacious than the 400 mg twice-daily dose. Furthermore, the authors noted that the allocation was not randomized and there was a greater proportion of patients with poorer prognostic features in the 100-mg cohort.<sup>23</sup> Responses were observed in both platinum-sensitive and platinum-resistant tumors in the 400 mg twice-daily cohort, consistent with prior observations that the mechanisms of resistance to olaparib might only partly overlap with those for platinum salts.

Subsequent phase 2 studies evaluating the role of olaparib monotherapy in relapsed ovarian or primary peritoneal cancer have shown response rates of between 31% and 41% in carriers of *BRCA1/2* mutations<sup>24,25</sup> and up to 21% in patients without *BRCA1/2* mutations.<sup>24</sup> Study 42, a multicenter phase 2 trial, enrolled 298 patients with germline *BRCA1/2* mutations and recurrent cancer. Inclusion criteria included ovarian cancer resistant to prior platinum therapy; breast cancer with 3 prior chemotherapy regimens for metastatic disease; pancreatic cancer with prior gemcitabine treatment; or prostate cancer with progression on hormonal treatment and one systemic therapy.<sup>25</sup> The study included 193 patients with ovarian cancer. A total of 77% of these patients had *BRCA1* mutations and 23% had *BRCA2* mutations. Patients were heavily pretreated (mean number of prior regimens, 4.3), had received prior platinum therapy, and were considered to be platinum-resistant. The patients with ovarian cancer experienced a tumor response rate of 31.1% (95% CI, 24.6%-38.1%) and a rate of stable disease at 8 weeks or greater of 40% (95% CI, 33.4%-47.7%). Median PFS and overall survival (OS) were 7.0 months and 16.6 months, respectively, with a median duration of response of 225 days.<sup>25</sup> On the basis of this study and other data from a similar group of women, the US Food and Drug

Administration approved olaparib (400 mg twice daily) as monotherapy for patients with germline *BRCA*-mutated advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy.<sup>26</sup>

### Randomized Phase 2 and 3 Trials

The first randomized trial assessing the efficacy of olaparib in relapsed ovarian cancer used pegylated liposomal doxorubicin (PLD) in the comparator arm. PLD is approved as therapy for relapsed ovarian cancer, with a response rate of 20% and a median PFS of 16.1 weeks.<sup>27</sup> This multicenter, open-label phase 2 study included 97 patients with ovarian cancer that recurred within 12 months of prior platinum therapy and with confirmed germline *BRCA1* or *BRCA2* mutations. Patients were randomly assigned in a 1:1:1 ratio to olaparib 200 mg twice daily continuously, olaparib 400 mg twice daily continuously, or PLD 50 mg/m<sup>2</sup> intravenously every 28 days.<sup>28</sup> Median PFS was 6.5 months (95% CI, 5.5-10.1 months), 8.8 months (95% CI, 5.4-9.2 months), and 7.1 months (95% CI, 3.7-10.7 months) for the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively. There was no statistically significant difference in PFS (hazard ratio [HR], 0.88; 95% CI, 0.51-1.56; *P*=.66) for combined olaparib doses vs PLD. Overall response rates by RECIST were not significantly different, either (25% for olaparib 200 mg, 31% for olaparib 400 mg, and 18% for PLD).<sup>28</sup> It has been suggested that the better-than-expected performance of the comparator PLD arm confounded the ability to see a benefit in favor of olaparib. One possibility is that patients with germline *BRCA1/2* mutations derive greater benefit from anthracycline-based therapy than do unselected patients. This is consistent with a retrospective analysis suggesting a potential link between germline *BRCA1/2* mutations and a greater response to PLD.<sup>29</sup> In keeping with this, a correlation between functional homologous recombination deficiency and clinical benefit from the use of neoadjuvant anthracycline-based chemotherapy in sporadic breast cancer has been observed.<sup>30</sup>

This hypothesis is being tested in the SOLO-3 (Olaparib Treatment in Relapsed Germline Breast Cancer Susceptibility Gene [BRCA] Mutated Ovarian Cancer Patients Who Have Progressed at Least 6 Months After Last Platinum Treatment and Have Received at Least 2 Prior Platinum Treatments) phase 3 trial (NCT02282020). Patients with *BRCA1/2*-mutated ovarian cancer that has progressed at least 6 months after platinum therapy and who have received at least 2 prior platinum regimens are randomly assigned to physician's-choice single-agent nonplatinum chemotherapy or to olaparib.

### Olaparib as Maintenance Therapy

Emerging data from studies of olaparib have shown anti-tumor activity in patients with and without *BRCA1/2* mutations. Tumor responses were greatest in women with a platinum-sensitive relapse.<sup>24</sup> To test this hypothesis further, a randomized phase 2 trial was designed to study the effect of maintenance olaparib on PFS in all patients with high-grade serous ovarian cancer who had responded to platinum-based chemotherapy. For the Study 19 trial, researchers randomly assigned 265 patients with recurrent high-grade ovarian cancer following the completion of platinum-based chemotherapy to receive either maintenance olaparib or placebo.<sup>31</sup> A minimum of 2 prior platinum-containing regimens were required for study entry, and patients received a median of 3 regimens in both arms. At the time of study entry, more than 62% of patients in both study arms had unknown *BRCA1/2* mutation status. A total of 22.8% of patients in the olaparib arm and 21.7% of those in the placebo arm, respectively, had known germline mutations in *BRCA1/2*. PFS after the completion of chemotherapy was significantly longer with olaparib than with placebo (median, 8.4 vs 4.8 months; HR for progression or death, 0.35; 95% CI, 0.25-0.49; *P*<.001).<sup>31</sup> A retrospective analysis to determine tumor and germline *BRCA* status was undertaken so that a preplanned retrospective analysis of outcome by *BRCA* status could be performed. Data were available on 96% of patients, and 51.3% had either a germline *BRCA1/2* mutation or a *BRCA* mutation in the tumor. A greater benefit was seen in patients whose tumors harbored *BRCA1/2* mutations (either germline or somatic), with PFS extended from 4.3 to 11.2 months (HR, 0.18; 95% CI, 0.10-0.31).<sup>32</sup> Importantly, patients with *BRCA* wild-type tumors also derived a benefit from olaparib maintenance. The magnitude of benefit between the groups was smaller, however, at 7.4 vs 5.5 months (HR, 0.54; 95% CI, 0.34-0.85), confirming a sensitive *BRCA1/2*-wild-type group.

The median time to first subsequent therapy was determined in a secondary analysis. This provides clinically relevant information about the time interval between progression and the start of further treatment of cancer. Patients' treatment was not unblinded on progression. In the overall population, the time to initiation of further treatment was significantly longer in the olaparib group than with placebo (13.4 vs 6.7 months; HR, 0.40; 95% CI, 0.30-0.52) and in both the *BRCA1/2*-mutated population (15.6 vs 6.5 months; HR, 0.33; 95% CI, 0.22-0.50) and wild-type *BRCA* subgroups (12.9 vs 6.9 months; HR, 0.45; 95% CI, 0.30-0.67).<sup>32</sup> Olaparib also extended the time to second subsequent therapy in both *BRCA1/2*-mutated and *BRCA1/2*-wild-type tumors,<sup>32</sup> suggesting that olaparib treatment did not alter subsequent response to platinum



or other therapies, a conclusion supported by subsequent reports.<sup>33</sup> Despite improvements in PFS and time to subsequent therapy, no statistically significant improvement in OS was observed (77% maturity) between the groups (HR, 0.73; 95% CI, 0.55-0.96, *P* value, not significant), with an increased benefit observed for patients with mutated *BRCA1/2* (HR, 0.62; 95% CI, 0.41-0.94) compared with wild-type *BRCA1/2* (HR, 0.83; 95% CI, 0.55-1.24).<sup>34</sup> The failure of PFS to translate into an OS benefit is likely multifactorial. First, a significant number of patients with a *BRCA1/2* mutation who received placebo (14/62; 23%) went on to receive a PARP inhibitor after progression. Secondly, the study was not designed to evaluate OS with statistical significance. Importantly, 13% of the total population (15% of the *BRCA1/2*-mutated population) remained on olaparib for more than 5 years.<sup>34</sup> In terms of toxicity, the olaparib group reported more nausea (68% vs 35%), fatigue (49% vs 38%), vomiting (32% vs 14%), and anemia (17% vs 5%), although the majority of adverse events were grade 1 or 2.<sup>31</sup>

Based on these data, the European Medicines Agency approved olaparib as maintenance treatment in women with platinum-sensitive, relapsed *BRCA1/2*-mutated (germline and/or somatic) ovarian cancer who have sustained either a complete or partial response to platinum-based chemotherapy.<sup>35</sup> Furthermore, these data have led to an additional phase 3 maintenance study of olaparib vs placebo after first-line platinum chemotherapy; SOLO-1 (Olaparib Maintenance Monotherapy in Patients With BRCA Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy; NCT01844986), the results of which are awaited.

### Olaparib Combination Therapy

It is still unclear whether olaparib is best deployed as a single agent, combined with chemotherapy, or as maintenance following platinum chemotherapy. Combination with chemotherapy is an attractive concept because it exploits the potential synergy between PARP inhibition and DNA-damaging cytotoxic agents. The clinical development of olaparib has included many phase 1 trials in which it is combined with chemotherapy. This often leads to exacerbation of toxicity—most often myelosuppression—and subsequent dose reductions. For example, the combination of olaparib plus topotecan was associated with significant dose-limiting hematologic adverse events, resulting in a subtherapeutic maximum tolerated dose.<sup>36</sup> Likewise, the combination of cisplatin and olaparib was considered intolerable owing to hematologic toxicity,<sup>37</sup> and the combination of paclitaxel and olaparib was complicated by significant clinical interaction and greater-than-anticipated neutropenia despite secondary prophylaxis.<sup>38</sup>

The combination of PLD with either continuous or intermittent olaparib yielded an overall response rate of 50% in patients with recurrent ovarian cancer ( $\leq 3$  prior chemotherapy regimens),<sup>39</sup> with the majority of responses observed in patients with germline *BRCA1/2* mutations (11/13 responders). However, grade 3 to 4 toxicity was observed in 61% of patients, with 1 possible treatment-related death from pneumonia/pneumonitis.<sup>39</sup> These results suggest that although additive or even synergistic chemopotential effects may exist in vitro, there is not a wide therapeutic index between normal tissue and tumor tissue. Therefore, delivering these combinations is problematic without dosing or scheduling modifications. For example, when combining olaparib with carboplatin and paclitaxel, continuous olaparib dosing exacerbated hematologic toxicities and led to schedule delays.<sup>40</sup> Tolerability improved with intermittent olaparib and reduced-dose carboplatin (area under the curve [AUC], 4 mg/mL/min), prompting a randomized phase 2 study.<sup>41</sup>

Oza and colleagues randomly assigned 162 patients with recurrent platinum-sensitive ovarian cancer to receive either olaparib (200 mg twice daily, administered orally on days 1-10 of each 21-day cycle) plus paclitaxel (175 mg/m<sup>2</sup>, administered intravenously on day 1) and carboplatin (AUC, 4 mg/mL/min administered intravenously on day 1), then olaparib monotherapy (400 mg twice daily, given continuously) until progression, or paclitaxel (175 mg/m<sup>2</sup> on day 1) and carboplatin (AUC, 6 mg/mL/min on day 1), then no further treatment.<sup>41</sup> The *BRCA1/2* mutation status was known for 107 patients (either at baseline or determined retrospectively): 41 (38%) of 107 had a *BRCA1/2* mutation (20 in the olaparib/chemotherapy group and 21 in the chemotherapy-alone group). The addition of olaparib to chemotherapy significantly improved the median PFS (12.2 vs 9.6 months with chemotherapy alone; HR, 0.51; 95% CI, 0.34-0.77). In an exploratory analysis, the benefit was greatest in the *BRCA1/2*-mutated group (median PFS not reached in the olaparib group vs 9.7 months with chemotherapy alone; HR, 0.21; 95% CI, 0.08-0.55). Overall survival did not differ significantly between groups for either the overall population (33.8 months for olaparib/chemotherapy vs 37.6 months with chemotherapy alone; HR, 1.17; 95% CI, 0.79-1.73) or the *BRCA1/2*-mutated population (not reached with olaparib/chemotherapy vs 39.2 months with chemotherapy alone; HR, 1.28, 95% CI, 0.39-4.18). A significant benefit in favor of olaparib/chemotherapy was noted in time to first subsequent therapy (HR, 0.60; 95% CI, 0.42-0.86) but not time to second therapy (HR, 0.83; 95% CI, 0.57-1.20).<sup>41</sup> Adverse events were greater in the olaparib/chemotherapy group and were mostly mild or moderate: nausea (69% vs 57%), neutropenia (49% vs

**Table 1.** Ongoing Randomized Phase 3 Olaparib Combination Studies

NCT Trial Number or Trial Name	Combination	Platinum Status	Inclusion Criteria
NCT02477644 (PAOLA-1)	Olaparib or placebo in combination with platinum/taxane and bevacizumab and as maintenance therapy	First-line treatment	HGSOC/endometrioid, stage IIIb/IV
NCT02446600	Olaparib and cediranib or platinum-doublet chemotherapy	Platinum-sensitive	HGSOC/endometrioid or gBRCA and any high-grade histology
NCT02502266	Olaparib and cediranib or chemotherapy	Platinum-resistant	HGSOC/endometrioid or gBRCA and any high-grade histology
ICON9	Olaparib with cediranib vs cediranib and placebo as maintenance therapy following platinum-based chemotherapy with cediranib	Platinum-sensitive	HGOC

gBRCA1/2, germline *BRCA1/2* mutation; HGOC, high-grade ovarian cancer; HGSOC, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer; ICON9, Randomised Trial of Cediranib and Olaparib Maintenance in Patients with Relapsed Platinum Sensitive Ovarian Cancer; NCT, National Clinical Trial; PAOLA-1, Platine, Avastin and Olaparib in 1st Line.

39%), diarrhea (42% vs 27%), headache (33% vs 9%), and peripheral neuropathy (31% vs 19%). The most common grade 3 or higher adverse events during the combination phase were neutropenia (43% vs 35%) and anemia (9% vs 7%). The rate of serious adverse events was similar in both arms (15% with olaparib/chemotherapy and 21% with chemotherapy alone). It was noted that the PFS benefits occurred despite the lower carboplatin dose (AUC, 4 mg/mL/min),<sup>40</sup> suggesting that olaparib might provide an additive effect or potentiate the cytotoxic effect of the lower carboplatin dose. However, the authors noted that although the study was not designed to measure the contribution of each treatment phase, the late separation of the PFS curves suggested that the maintenance phase was probably the key contributor to the improvement in PFS. They concluded that the combination of olaparib and chemotherapy in this context does not provide an additional advantage over olaparib alone as maintenance therapy.<sup>41</sup>

Perhaps more promising combinations are those of olaparib with other molecularly targeted agents, owing to the potential synergy with other signaling pathways and lack of overlapping toxicity profiles. Several randomized trials have shown efficacy in ovarian cancer for antiangiogenic agents in combination with platinum therapy in first-line and salvage settings.<sup>42-44</sup> Preclinical studies have demonstrated the additive effect of antiangiogenesis and PARP inhibition, given that hypoxia leads to downregulation of homologous recombination repair proteins and enhanced PARP inhibitor sensitivity.<sup>45-47</sup>

A dose-finding phase 1 trial that combined cediranib (the oral ATP-competitive vascular endothelial growth factor receptor inhibitor) with olaparib demonstrated activity in recurrent ovarian cancer, with an objective response rate of 44%.<sup>48</sup> This finding prompted a randomized phase 2 study, the results of which were reported in 2014. Liu and colleagues randomly assigned patients with

relapsed high-grade serous or endometrioid ovarian cancers to receive olaparib (400 mg twice daily, n=46) or the combination of olaparib and cediranib (cediranib 30 mg daily and olaparib capsules 200 mg twice daily, n=44).<sup>49</sup> *BRCA1/2* mutations were present in 52% of patients in both treatment arms. Median PFS was significantly longer in the combination arm than with olaparib alone (17.7 vs 9.0 months; HR, 0.42; 95% CI, 0.23-0.76), as was objective response rate (79.6% vs 47.8%; odds ratio, 4.24; 95% CI, 1.53-12.22). An exploratory analysis was performed in *BRCA*-mutated and *BRCA*-wild-type or unknown subsets, although the results should be interpreted with caution owing to the small numbers in each subset. Greater activity for the combination arm was noted in both populations. In the *BRCA1/2*-wild-type/unknown group, median PFS was 16.5 vs 5.7 months (HR, 0.32; 95% CI, 0.14-0.74). In the *BRCA1/2*-mutant group, median PFS was 19.4 vs 16.5 months (HR, 0.55; 95% CI, 0.24-1.27). This trial did not include a single-agent cediranib arm; however, phase 2 single-agent studies have suggested a median PFS of approximately 5 months with cediranib alone.<sup>50,51</sup> These results suggest that the combination of olaparib and cediranib could be synergistic and have greater activity than either agent alone in patients with platinum-sensitive, high-grade serous ovarian cancers. The magnitude of benefit observed for combination therapy was greater in the absence of *BRCA1/2* mutation; one possible explanation is that greater synergy is observed with more proficient homologous recombination.

Whether the combination of olaparib and cediranib is better than standard chemotherapy for recurrent ovarian cancer is currently being evaluated in 2 randomized phase 3 trials for both platinum-sensitive (NCT02446600) and platinum-resistant disease (NCT025022660, Table 1). Furthermore, whether olaparib and cediranib maintenance therapy is superior to cediranib therapy alone, following platinum-based chemotherapy with cediranib

**Table 2.** Ongoing Early-Phase Olaparib Combination Studies

NCT Trial Number	Phase	Combination	Inclusion Criteria	BRCA Status
NCT022208375	1/2	AZD2014 (mTORC1/2) AZD5363 (AKT)	HGSOC	Mutant and WT
			Endometrial	
			TN breast	
NCT02338622	1	AZD5363 (AKT)	Part A, any solid tumor	Mutant or PI3K/AKT activated
			Part B, <i>BRCA</i> -mutated or PI3K/AKT hyperactivated	
NCT01623349	1	BKM120 (PI3K) or BYL719 (PI3K)	HGSOC TN breast	Mutant and WT
NCT02571725	1/2	Tremelimumab (CTLA-4)	EOC	gBRCA1/2
NCT02484404	1/2	MEDI4376 (PD-L1)	Any solid tumor or recurrent ovarian cancer	Mutant and WT
NCT02485990	1/2	Tremelimumab (CTLA-4)	HGSOC	Mutant and WT

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; EOC, epithelial ovarian, fallopian tube, or primary peritoneal carcinoma; gBRCA1/2, germline *BRCA1/2* mutation; HGSOC, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer; mTORC1/2, mammalian target of rapamycin complex 1/2; NCT, National Clinical Trial; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; TN, triple-negative; WT, wild-type.

for the first platinum-sensitive recurrence will be evaluated in the ICON9 study (Randomised Trial of Cediranib and Olaparib Maintenance in Patients with Relapsed Platinum Sensitive Ovarian Cancer). In the first-line setting, the PAOLA-1 trial (Platine, Avastin and Olaparib in 1st Line; NCT02477644) is investigating the addition of olaparib to bevacizumab (Avastin, Genentech) maintenance in women receiving carboplatin, paclitaxel, and bevacizumab (Table 1).

### Early-Phase Olaparib Combination Studies

Activation of the phosphoinositide 3-kinase (PI3K) and RAS signaling pathways is common in high-grade serous ovarian cancer, occurring in up to 45% of patients.<sup>6</sup> Pre-clinical studies have suggested that inhibition of the PI3K pathway results in genomic instability, accompanied by a concomitant reduction in the expression of BRCA1 and BRCA2 and a reduction in the cellular capacity to conduct homologous recombination. The result is cells that are sensitized to olaparib<sup>52</sup>; an in vivo study<sup>53</sup> has shown suppression of tumor growth with the combination of olaparib and the PI3K inhibitor BKM120. A number of early-phase trials are currently underway that are examining the combination of olaparib with inhibitors of the PI3K signaling pathway (Table 2), including the PI3K inhibitor BKM120 (NCT01623349), the AKT inhibitor AZD5363 (NCT02338622), and the dual mammalian target of rapamycin complex 1/2 (mTORC1/2) inhibitor AZD2014 (NCT022208375).

Immune checkpoint blockade using antibodies to

cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4, CD152) or programmed death protein 1 (PD-1, CD279) have demonstrated sustained clinical efficacy in melanoma and other solid tumors. Emerging evidence suggests that genetically heterogeneous tumors with greater mutational burden are more likely to respond to checkpoint blockade.<sup>54</sup> Although ovarian cancers have been considered relatively resistant to anti-CTLA-4 blockade, there is evidence that a subset of ovarian cancers associated with germline mutations in *BRCA1/2* genes may be more immunogenic, and therefore more vulnerable to checkpoint blockade.<sup>55-57</sup> This is supported in vitro by *BRCA1*-mutant human cell lines and by animal-based studies in which a CTLA-4 antibody, synergized therapeutically with the investigational PARP inhibitor veliparib, resulted in immune-mediated tumor clearance and long-term survival in a majority of animals.<sup>58</sup> Early-phase combination studies with olaparib and both PD-1/programmed death-ligand 1 (PD-L1) and CTLA-4 antibodies are underway (Table 2) in both *BRCA1/2*-mutant and wild-type patients.

### Expanding the Scope for PARP Inhibition

Dramatic responses to PARP inhibition have been observed in germline-associated *BRCA*-mutated tumors. However, significant challenges exist in identifying other patients with homologous recombination deficiency who are also likely to derive benefit from PARP inhibitors. BRCA1/2 function may also be disrupted by somatic mutations or epigenetic silencing. For example, of the 103 cases with BRCA dysfunction identified in the

genomic analysis of high-grade serous ovarian cancer by The Cancer Genome Atlas (TCGA), 34 cases were associated with *BRCA1* silencing via DNA hypermethylation.<sup>6</sup> Interestingly, data from TCGA and others have failed to correlate *BRCA1* hypermethylation with either platinum sensitivity or improved survival,<sup>6</sup> suggesting that epigenetic *BRCA1* downregulation may have less of an effect on homologous recombination and PARP inhibition than *BRCA1*-inactivating mutations. Somatic *BRCA1/2* mutations are also common, present in 19 of the 103 cases from TCGA.<sup>6</sup> Similarly, 18 (14%) of 136 patients with a *BRCA1/2* mutation in study 19 had tumor *BRCA1/2* mutations of somatic origin.<sup>32</sup> It will be important to identify patients who harbor sporadic somatic *BRCA1/2* mutations or other homologous recombination-deficient tumors and who may benefit from PARP inhibitor therapy. This is discussed further in part 2 of this review.

## Conclusions and Future Directions

The introduction of olaparib and other PARP inhibitors represents one of the most promising genotype-directed therapies, which are destined to change the management of *BRCA*-associated ovarian cancer. However, a number of challenges still remain.

Firstly, it is uncertain how olaparib should be incorporated into the clinical management of both *BRCA1/2*-associated and sporadic ovarian cancers. It has yet to be established whether olaparib should be introduced before or after platinum therapy, in the first-line or relapsed setting, or as maintenance therapy. Secondly, it is not clear whether, as maintenance therapy, additional benefit would be obtained if olaparib (or indeed, another PARP inhibitor) maintenance were to be reinstated at each chemotherapy-induced remission. Another challenge is determining whether combination therapy is superior to single-agent olaparib use. Owing to overlapping toxicities, particularly myelosuppression, work is required to define the optimal schedules for the combination of chemotherapy and olaparib. Furthermore, it is unclear where combination treatment with vascular endothelial growth factor and other signaling inhibitors is best employed. In addition, the role of olaparib in platinum-resistant disease requires clarity. Finally, it is not yet known whether clinical differences exist between PARP inhibitors in terms of efficacy and toxicity, or indeed whether there is a role for rechallenge with a different PARP inhibitor following progression on another.

Several phase 3 trials are underway to address many of the above questions, and it is hoped that the use of olaparib and other PARP inhibitors can be optimized to maximize PFS—and ultimately, OS—for patients with ovarian cancer.

## Disclosures

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

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