HHS Public Access

Author manuscript

Pharmacol Ther. Author manuscript; available in PMC 2021 September 01.

Published in final edited form as:

Pharmacol Ther. 2020 September ; 213: 107588. doi:10.1016/j.pharmthera.2020.107588.

PARP Inhibition in the Ovarian Cancer Patient: Current Approvals and Future Directions

Katherine C. Kurnit[1], **Monica Avila**[2], **Emily Hinchcliff**[2], **Robert L. Coleman**[2], **Shannon N. Westin**[2,*]

[1]Department of Obstetrics and Gynecology, Section of Gynecologic Oncology, The University of Chicago, Chicago, IL, United States

[2]Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

Abstract

Poly (ADP-ribose) polymerase (PARP) inhibitors have transformed the therapeutic management of solid tumors, particularly ovarian cancer. Initially studied in *BRCA* deficient tumors, the Food and Drug Administration (FDA) indications have expanded to include other homologous recombination deficient tumors as well as biomarker-wildtype tumors. They have also gained momentum not only as a treatment strategy, but as a maintenance strategy as well. While PARP inhibitors were initially evaluated in the recurrent setting, they have now moved to frontline therapy. This review will discuss the current FDA indications of the clinically available PARP inhibitors for treatment and maintenance therapies. We will then review the recently completed and ongoing clinical trials which may inform future clinical approvals.

Keywords

PARP inhibitors; ovarian cancer; clinical trials; targeted therapy

INTRODUCTION

The discovery of the enzymatic inhibitor Poly (ADP-ribose) polymerase, commonly known as PARP, has transformed the therapeutic management of solid tumors. In ovarian cancer, this has led to a series of Food and Drug Administration (FDA) indications in the frontline, recurrent, and maintenance settings.

[*]Corresponding author at: Associate Professor, University of Texas, M.D. Anderson Cancer Center, Department of Gynecologic Oncology & Reproductive Medicine, 1155 Herman Pressler Dr. CPB 6.3279, Houston, TX 77030, snwestin@mdanderson.org.

Conflict of Interest Statement:
All other authors have no conflicts of interest to report.

During cellular growth and division, errors in DNA sequences are common and are repaired through a series of DNA repair pathways. Five major pathways exist for DNA repair: direct repair, mismatch repair, base excision repair, nucleotide excision repair, and double-strand break repair (Plummer, 2010). Double-strand break repair occurs by high fidelity homologous recombination repair and non-homologous end-joining, which is much more error prone (Plummer, 2010).

Homologous recombination deficient cells are particularly sensitive to PARP inhibitors (Brody, 2005; Bryant, et al., 2005). *BRCA1* and *BRCA2* are tumor suppressor genes that have been linked to a fundamental role in DNA repair through formation of homologous recombination repair complexes (Venkitaraman, 2002). Any mutation leading to inactivation of *BRCA* leaves cells vulnerable to inactivation of the second *BRCA* allele, resulting in homologous recombination deficiency via impaired double-stranded DNA break repair. This concept of biallelic *BRCA* loss is referred to as "synthetic lethality" or "synthetic sickness," and is the mechanism by which *BRCA* deficient tumors treated with PARP inhibitors induce cellular apoptosis (Konstantinopoulos, Ceccaldi, Shapiro, & D'Andrea, 2015). Hence, the role of PARP inhibitors was first explored in clinical trials of patients harboring a germline *BRCA* mutation. Given that ovarian cancer is the second most common *BRCA* mutation-associated malignancy for women (Ford, Easton, Bishop, Narod, & Goldgar, 1994; Struewing, et al., 1997), it is not surprising that some of the first approvals for PARP inhibitor therapies occurred for women with ovarian, fallopian tube, and primary peritoneal cancers. Although these malignancies are clinically considered to be distinct, recent research supports a common progenitor for all three tumor origins (Kurman & Shih Ie, 2010), and thus these three tumor types are treated similarly in the clinical setting. For the purposes of this review, we will henceforth refer to women with "ovarian cancer," but will be including women with fallopian tube and primary peritoneal malignancies under this distinction as well.

PARPs constitute a family of 18 enzymatic proteins that facilitate DNA repair primarily through base excision repair, preventing double-stranded breaks and non-homologous end-joining (Konstantinopoulos, et al., 2015). After binding to altered DNA, PARP uses NAD^+ to create polymers of poly(ADP-ribose) (PAR) and transfers it to acceptor proteins, including PARP itself (Plummer, 2011). This process is called auto-poly(ADP-ribosyl)ation and leads to recruitment of multiple proteins to form a repair complex at the site of DNA-damage (Plummer, 2011). It has also been suggested that mutations in PARP at sites of endogenous damage results in trapping of PARP itself (Konstantinopoulos, et al., 2015). Through the formation of PAR-complexes there is reduced PARP affinity for DNA (Satoh & Lindahl, 1992). Mutated PARP is unable to synthesize poly(ADP-ribose) polymers and PARP becomes trapped on DNA, inhibiting DNA repair (Satoh & Lindahl, 1992). PARP inhibitors create a similar scenario leading to inactivation of PARP, and likely induce PARP trapping and inhibition of DNA repair simultaneously (Satoh & Lindahl, 1992). In fact, recent studies show that PARP inhibitor mediated trapping of PARP–DNA complexes are linked to cytotoxicity irrespective of the unrepaired single-strand breaks caused by inhibition of PARP (Murai, et al., 2012). This publication suggests that the biggest anti-cancer activity for this class of drugs may be mediated via PARP trapping.

This review will describe the FDA indications for PARP inhibitors in the management of patients with primary and recurrent ovarian cancer (Table 1). We will also discuss relevant clinical considerations and will review the most recent clinical trials which may serve as the basis for future clinical indications.

Frontline PARP Inhibition: Current Approvals

In December 2018, the FDA granted olaparib approval in the frontline maintenance setting in patients with either a germline or somatic *BRCA* mutations that exhibited either a partial or complete response to first-line platinum chemotherapy. This came as a result of findings from SOLO1, a Phase III randomized, multicenter trial that assigned patients with germline or somatic *BRCA* mutations and stage III/IV ovarian, fallopian tube, or primary peritoneal cancer (K. Moore, et al., 2018). Following a complete or partial response to adjuvant platinum-based chemotherapy, patients were randomized to olaparib tablets 300 mg twice daily or placebo. Importantly, patients with complete, optimal, and suboptimal cytoreductive surgeries were allowed to enroll. Maintenance therapy was continued for up to two years in the setting of a complete response, or indefinitely in the setting of a partial response (K. Moore, et al., 2018). In this study, treatment with olaparib was associated with a statistically significant improvement in progression-free survival (PFS) compared with those who had received placebo (K. Moore, et al., 2018). The estimated median progression-free survival had not been reached in those who received olaparib, compared with13.8 months in those who were given placebo (HR, 0.30; 95% CI, 0.23–0.41; P <.0001) (K. Moore, et al., 2018). Approximately 10% of patients on the trial continued treatment beyond two years and 12% experienced a discontinuation rate for adverse events. Importantly, benefit persisted beyond two years, with 60% of patients treated with olaparib alive progression free at three years compared to 27% of patients treated with placebo. This suggests that two years of maintenance is adequate to achieve benefit.

Until this year, olaparib was the only PARP inhibitor with an FDA approval for frontline use in ovarian cancer. For patients with germline *BRCA* mutations, maintenance olaparib in the frontline setting has become the new standard of care. Although patients with somatic *BRCA* mutations were allowed to enroll in SOLO1, only two patients were ultimately included (K. Moore, et al., 2018). Despite these small numbers, the FDA approval does include women with somatic *BRCA* mutations, and thus many oncologists are testing for these alterations in the frontline setting in order to prescribe olaparib maintenance even in women without germline mutations.

In April 2020, the FDA approved niraparib for women with advanced epithelial ovarian cancer who have had a complete or partial response to platinum-based chemotherapy. This approval was based on the PRIMA trial (PRIMA/ENGOT-OV26/GOG-3012). This Phase III randomized controlled trial evaluated the use of maintenance niraparib following primary platinum-based chemotherapy (Gonzalez-Martin, et al., 2019), and followed closely on the success from the SOLO1 trial. Patients had Stage III or IV disease, with either high grade serous or endometrioid tumors. They must have had a complete or partial response after six to nine cycles of chemotherapy. In contrast to SOLO1, however, patients with complete cytoreduction at surgery were not eligible for this trial. Patients were only enrolled if they

had visible residual tumor after primary debulking for Stage III disease, had inoperable Stage III disease, or had Stage IV disease. Patients were then randomized to niraparib or placebo, with doses ultimately adjusted to include the weight and platelet count considerations. Based on data presented at the Society for Gynecologic Oncology 2019 Annual Meeting, use of a modified starting dose of niraparib based on weight and platelet count resulted in improved tolerability (Monk, et al., 2019). Tumors were evaluated for homologous recombination deficiency (HRD) using the presence of a *BRCA* mutation and/or an HRD score of 42 or greater on the myChoice CDX (Myriad Genetics). For those patients whose tumors demonstrated HRD (primary endpoint), the use of niraparib was associated with a median PFS of 21.9 months compared with 10.4 months for the placebo group (HR 0.43, 95% CI 0.31–0.59, $p < 0.001$) (Gonzalez-Martin, et al., 2019). When the entire cohort was evaluated (a conditional primary endpoint based on the HRD analysis), the median progression-free survival was 13.8 months in the niraparib group compared with 8.2 months in the placebo group (HR 0.62, 95% CI 0.50–0.76, $p < 0.001$). Overall survival data are not mature. These data are particularly intriguing as the study included patients irrespective of *BRCA* mutation status (Gonzalez-Martin, et al., 2019), in contrast to SOLO1 (K. Moore, et al., 2018).

In addition to the single agent options described above, in May 2020, the FDA approved the addition of olaparib maintenance to bevacizumab in patients with advanced ovarian cancer after response to first-line platinum-based chemotherapy with bevacizumab in the setting homologous recombination deficiency. HRD is defined by either a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability.

This approval is based on the PAOLA-1 (PAOLA-1/ENGOT-ov25) trial which investigated use of maintenance olaparib and bevacizumab in combination patients with newly diagnosed stage III or IV high grade serous or endometrioid tumors (Ray-Coquard, et al., 2019). They must have received a tumor debulking surgery, in the primary or interval setting. Patients with and without macroscopic disease after surgical debulking were included. Patients must have received at least three cycles of bevacizumab as part of their neoadjuvant and/or adjuvant chemotherapy, and must have had a complete or partial response. They were then randomized to either twice daily olaparib or placebo. Both cohorts continued to receive bevacizumab every three weeks; total bevacizumab exposure was up to 22 cycles. Tumors were analyzed for *BRCA* mutation status as well as HRD by myChoice (score ≥ 42; Myriad Genetics), but patients both with and without HRD and/or *BRCA* mutations could enroll. Overall, the median progression-free survival for the olaparib/bevacizumab group was 22.1 months, compared with 16.6 months in the placebo/bevacizumab group (Primary endpoint; HR 0.59, 95% CI 0.49–0.72, $p < 0.001$). Several exploratory analyses were then performed. When the analysis was limited only to patients with a somatic *BRCA* mutation, the median progression-free survival was 37.2 months for the olaparib/bevacizumab group compared with 21.7 months for the placebo/bevacizumab group (HR 0.31, 95% CI 0.20–0.47). When the analysis was limited to patients with HRD but without somatic *BRCA* mutations, the median progression-free survival decreased to 28.1 months for olaparib/bevacizumab, compared with 16.6 months for placebo/bevacizumab (HR 0.43, 95% CI 0.28–0.66). Patients with tumors that were HRD negative or unknown HRD status had no significant difference in progression-free survival across treatment groups (HR 0.92, 95% CI 0.72–

1.17). There were no clinically significant differences in quality of life scores across treatment groups (Ray-Coquard, et al., 2019).

Although olaparib and now niraparib maintenance has become standard of care for many women, some oncologists cite concerns regarding the possibility of over-treatment. An alternative strategy that has not yet been explored is the use of active surveillance following completion of primary treatment, with early initiation of a PARP inhibitor once a recurrence is detected. The efficacy of PARP inhibitors as salvage therapy in this situation is not known, but theoretically, this treatment approach could reduce the number of months that a patient is receiving therapy. On the other hand, if overall survival is realized in the SOLO1 and PRIMA trials, such delay-in-treatment strategies would need to be revisited to assess risk/benefit trade-offs. Future studies will need to address these concerns, especially as the number of women who receive frontline maintenance therapy continues to rise.

Recurrent Setting: Current Approvals for Treatment

In the recurrent setting, PARP inhibitors currently have approvals both as treatment and maintenance strategies, and each of the approved PARP inhibitors (olaparib, niraparib, and rucaparib) have slightly different indications for use. Additionally, although the first PARP inhibitor approval was limited to those patients with germline *BRCA* mutations, indications have since expanded.

In 2014, olaparib obtained accelerated approval for use in patients with recurrent ovarian cancer who had germline *BRCA* mutations and who had received at least three prior lines of therapy. This approval was based on a multicenter, Phase II clinical trial that enrolled patients with germline *BRCA* mutations who had ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, or other solid tumor types (Kaufman, et al., 2015). Specifically, the ovarian cancer patients must have been considered to have platinum-resistant disease. Among ovarian cancer patients with three or more prior lines of therapy, this trial reported an objective response rate of 31%, with a median duration of response of approximately 8 months (Kaufman, et al., 2015). As a regulatory commitment, the Phase III study, SOLO3 was launched; difficulties in recruitment due to PARPi availability led to revision of the sample size and primary endpoint. The authors demonstrated that for ovarian cancer patients with germline *BRCA* mutations who had recurrence six to 12 months after their last platinum-based chemotherapy, those that received olaparib had significantly better responses than those that received physician's choice of chemotherapy (paclitaxel, topotecan, gemcitabine, or pegylated doxorubicin). The objective response rate was 72% for the olaparib arm compared with 51% in the chemotherapy arm, and the hazard ratio for progression-free survival was 0.62 (95% CI 0.43–0.91). This study confirmed the activity of single agent olaparib for women with recurrent, platinum-sensitive ovarian cancer (Penson, et al., 2019).

In 2016, rucaparib received an accelerated approval for monotherapy treatment in women with germline or somatic *BRCA* mutations who have received at least two lines of prior chemotherapy. This was based in part on Study 10, a Phase I/II clinical trial which reported an objective response rate of 60% (Kristeleit, et al., 2017) and ARIEL2, a Phase II clinical trial of women with platinum-sensitive ovarian cancer who had received at least one prior

chemotherapy line (Swisher, et al., 2017). This was the first study that attempted to define an additional population sensitive to PARP inhibition in the absence of *BRCA* mutation. Patients were subdivided into three groups: those with *BRCA* mutations, those with tumors showing high genomic loss of heterozygosity (LOH-high), and those with tumors showing low genomic loss of heterozygosity (LOH-low). Loss of heterozygosity, a marker of genomic instability similar to homologous recombination deficiency with the potential to predict response to PARP inhibition, was defined by Foundation Medicine T5 next-generation sequencing assay (Foundation Medicine). The median progression-free survival was 12.8 months for patients with *BRCA* mutations, 5.7 months for patients with LOH-high tumors, and 5.2 months for patients with LOH-low tumors (Swisher, et al., 2017). A combined analysis of patients in ARIEL2, Part 1 and Study 10 who received two or more lines of chemotherapy and who had either germline or somatic *BRCA* mutations was subsequently reported (Oza, et al., 2017). The objective response rate for this population was 54%, and this combined analysis served as the basis for the initial rucaparib FDA approval.

Most recently, results from the QUADRA study (K. N. Moore, et al., 2019) led to an FDA approval for niraparib as monotherapy treatment in women previously treated with at least three chemotherapy lines, who either have a *BRCA* mutation (germline or somatic), or who have platinum-sensitive tumors with HRD (myChoice CDX, Myriad Genetics). HRD in this study was considered to be positive if the tumor demonstrated a *BRCA* mutation, or if it demonstrated genomic instability as defined by the presence of loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions. This complex indication is based in part on the evolution of the QUADRA trial's enrollment criteria. Initially, the QUADRA trial enrolled women with any number of prior therapies, and included women with both platinum-sensitive and platinum-resistant or -refractory disease (K. N. Moore, et al., 2019). After enrollment of 292 patients, the study changed inclusion criteria to only allow for enrollment of women with platinum-sensitive, recurrent ovarian cancer who had received three or four lines of prior therapy. A third amendment subsequently excluded women with HRD negative (myChoice CDX, Myriad Genetics) tumors. The FDA indication ultimately was based on an analysis of 98 patients from the trial (Administration, 2019), although a total of 463 patients were enrolled and received at least one dose of niraparib during the QUADRA study (K. N. Moore, et al., 2019). When only the platinum-sensitive patients were included in a subset analysis, the study found an overall response rate of 39% in the BRCA-mutated group, 26% in the HRD-positive group, and 4% in the HRD-negative or unknown group.

Recurrent Setting: Current Approvals for Maintenance

The first PARP inhibitor to receive an FDA indication for maintenance therapy in recurrent ovarian cancer was niraparib. ENGOT-OV16/NOVA was a Phase III trial that included patients with recurrent ovarian cancer, both with and without germline *BRCA* mutations (Mirza, et al., 2016). However, the investigators then used the companion testing myChoice CDX (Myriad Genetics) to further stratify patients without germline BRCA mutation into those with tumors exhibiting HRD and those without. Again, the clinical benefit was greatest among women with *BRCA* mutations, with a hazard ratio of 0.27 (95% CI 0.17–0.41) (Mirza, et al., 2016). However, even those patients without germline *BRCA* mutations still

derived clinical benefit, with a hazard ratio of 0.45 (95% CI 0.34–0.61) for the combined *BRCA* wildtype group, and 0.38 (95% CI 0.24–0.59) for those without *BRCA* mutations but with HRD. Based on this study, niraparib received an FDA approval in March 2017 for use as a maintenance therapy in women with recurrent, platinum-sensitive ovarian cancer regardless of biomarker expression who had received at least two prior lines of platinum-based therapy.

In August 2017, olaparib subsequently received an approval as maintenance therapy for women with recurrent, platinum-sensitive ovarian cancer regardless of *BRCA* mutation status. The data for this approval began with Study 19, which was a double-blind placebo-controlled Phase II trial in patients with recurrent, platinum-sensitive ovarian cancer (Ledermann, et al., 2012). The progression-free survival was significantly longer in women treated with olaparib compared with placebo, demonstrating a hazard ratio of 0.35 (95% CI 0.25–0.49). Furthermore, in the subset of patients with *BRCA* mutations, the clinical benefit was even greater. This study was then followed by SOLO2/ENGO-Ov21 (Pujade-Lauraine, et al., 2017), a Phase III trial which included only those women with germline *BRCA* mutations. This randomized placebo-controlled design demonstrated an improvement in median progression-free survival of almost 14 months at the median (19.1 months vs 5.5 months, HR 0.30 (95% CI 0.22–0.41)) (Pujade-Lauraine, et al., 2017). Ultimately, these data in aggregate, along with a large safety database were considered sufficient to yield an approval in biomarker unrestricted cases.

In April 2018, Rucaparib also received an indication for women with platinum sensitive, recurrent ovarian cancer as a maintenance therapy. This approval was based on data from ARIEL3 (Coleman, et al., 2017). Similar to ARIEL 2 (Swisher, et al., 2017), this Phase III trial included three different patient groups: those with *BRCA* mutations, those whose tumors demonstrated HRD as defined by Foundation Medicine T5 next-generation sequencing assay (Foundation Medicine), and an all-comer group. Rucaparib showed benefit in all patients, but again had greatest impact in those with *BRCA* mutations. The progression-free survival hazard ratio for the all-comer population was 0.36 (95% CI 0.30–0.45), with an improvement in median progression-free survival of approximately 5 months (10.8 vs 5.4 months). This is compared to a progression-free survival hazard ratio of 0.32 (95% CI 0.24–0.42) in patients with HRD, and a hazard ratio of 0.23 (95% CI 0.16–0.34) in patients with *BRCA* mutations (each with a median progression-free survival of 13.6 and 16.6 months, respectively) (Coleman, et al., 2017).

Toxicity Considerations

The three Phase III maintenance trials provide some indicators of the differences in the use and toxicity profile between the three approved PARP inhibitors. There are demonstrated class effects in terms of safety, which were confirmed to be similar across all PARP inhibitors in recent meta-analysis when considering all grade toxicity (Staropoli, et al., 2018). However, when considering only high-grade toxicity, there were significant differences in safety profile for each of the three FDA approved PARP inhibitors. In general, though, most toxicities tended to be low grade and can be managed with simple

interventions. Furthermore, quality of life data from the above clinical trials demonstrated no negative impact on quality of life.

Niraparib was found to have the greatest hematologic toxicity. Specifically, hematologic adverse events were the most common cause of dose delay or discontinuation for patients receiving niraparib, with 25% (93 of 367) patients experiencing a grade 3 or 4 anemia, 20% (72 of 367) with grade 3 or 4 neutropenia, and 34% (124/367) with grade 3 or 4 thrombocytopenia (Mirza, et al., 2016). Dose interruption occurred in 68.9% of patients on niraparib as compared with only 5.0% of those patients on placebo (Berek, et al., 2018). Dose modifications varied by the type of hematologic toxicity. For anemia, with a dose reduction to 200 mg/day from 300 mg/day by cycle 3, the risk of a grade 3 or 4 anemia was reduced from 23.2% to 18.1%. Similarly, severe neutropenia was reduced from 4.9% to 2.9% in the same dose reduction by cycle 3. Thrombocytopenia is generally an early adverse event, typically occurring in the first month of therapy. Exploratory analyses revealed that patients with baseline body weight less than 77 kg or baseline platelet count less than 150 were at higher risk of grade 3 thrombocytopenia, with 39.3% for patients with one factor and 16.1% for patients without either risk factor (Berek, et al., 2018). Therefore, the clinical recommendation is to start patients who meet either criteria on 200 mg daily, with consideration of a dose escalation if no hematologic events occur within the first two to three months. Further exploration of the impact of this dose reduction has been reported in the PRIMA trial (as described above).

Gastrointestinal toxicity is a common class effect with PARP inhibition. Nausea is the most common, with 74–76% of patients reporting nausea across each of the three FDA approved drugs in the recurrent setting, though only 3–4% had grade 3 or 4 toxicity (Coleman, et al., 2017; Mirza, et al., 2016; Pujade-Lauraine, et al., 2017). In terms of management, routine use of antiemetic regimens and prophylactic preventative administration are recommended. Notably, aprepitant, a neurokinin-1 receptor antagonist, should be avoided with olaparib as it is a CYP3A inhibitor and therefore may impact olaparib concentrations (K. N. Moore & Monk, 2016).

Rucaparib is somewhat more uniquely associated with an elevation in serum creatinine, typically seen in the first weeks of treatment. In ARIEL3, creatinine elevation was noted in 15% of patients on rucaparib compared with 2% of the placebo (Coleman, et al., 2017), while 11% of patients in SOLO2 on olaparib had grade 1 or 2 creatinine elevations (Pujade-Lauraine, et al., 2017). The mechanism for this is thought to be related to inhibition of the proximal tubule transporters MATE1, MATE2-K, OAT1, OAT3, and OCT-2 (Kikuchi, et al., 2013). As increases in creatinine are not always secondary to true renal dysfunction, some experts recommend evaluating changes in creatinine during PARP inhibitor therapy using a glomerular filtration rate scan rather than relying on calculated glomerular filtration rates to ensure no true renal toxicity (Zibetti Dal Molin, et al., 2020).

Acute myelodysplastic syndrome is a rare but serious adverse event, reported to be on the order of 1–2% (Korach, et al., 2018; Mirza, et al., 2016). Fatigue is another of the most commone side effects, occurring on the order of 59–69% in maintenance therapy trials in the recurrent setting (Coleman, et al., 2017; Mirza, et al., 2016; Pujade-Lauraine, et al., 2017).

In ARIEL3, 34% of patients had an elevation in AST or ALT values, and 10% had a grade 3 elevation (Coleman, et al., 2017). Other less common adverse events are listed in Table 2.

RECENTLY COMPLETED PHASE III TRIALS

At the European Society for Medical Oncology (ESMO) Congress 2019, three Phase III trials of PARP inhibitors in the upfront treatment of patients with ovarian cancer were presented and subsequently published (Table 3). The first two were the PRIMA and PAOLA-1 trials, described above, which ultimately led to FDA approvals for upfront ovarian cancer.

The third study presented was in some ways the most novel, as it was the first completed Phase III trial that evaluated the use of a PARP inhibitor in combination with primary chemotherapy. The VELIA trial (VELIA/GOG-3005) enrolled women with Stage III or IV high grade serous tumors who received either primary or interval tumor debulking surgery (Coleman, et al., 2019). Patients were randomized to carboplatin/paclitaxel/veliparib followed by veliparib maintenance, carboplatin/paclitaxel/veliparib followed by placebo maintenance, and carboplatin/paclitaxel/placebo followed by placebo maintenance. The primary progression-free survival analyses, however, compared the patients who received the veliparib for both treatment and maintenance with the patients who did not receive any veliparib. Data are not yet available for those patients who received veliparib concurrently with chemotherapy but did not receive maintenance therapy. Of note, there was also no arm that only included veliparib maintenance. Patients were evaluated for germline *BRCA* mutation status, somatic *BRCA* mutation status, and HRD status using myChoice CDX (Myriad Genetics) using a cut-off of 33 (adjusted mid-trial from an initial cutoff of 42). The hierarchical testing algorithm first compared the veliparib-throughout arm to placebo in women identified with a *BRCA1/2* mutation; if this was statistically significant, women whose tumors were considered HRD by the modified myChoice CDX criteria were added to the *BRCA* cohort. If this analysis was statistically significant, formal hypothesis testing was performed on the entire intent-to-treat (ITT) population. In this manner, the median PFS for women with *BRCA* mutation 34.7 months in the veliparib-throughout arm compared with 22.0 months for the control group (HR 0.44, 95% CI 0.28–0.68, $P < 0.001$). Adding the HRD cohort, median PFS was similarly lengthened 31.9 months compared with 20.5 months (HR 0.57, 95% CI 0.43–0.76, $P < 0.001$). Since these two analyses were statistically significant, testing then followed in the intention to treat population. In this analysis, the progression-free survival for patients who received veliparib throughout was 23.5 months compared with 17.3 months (HR 0.68, 95% CI 0.56–0.83, $P < 0.001$). (Coleman, et al., 2019). Overall survival data were not mature. Of note, given the increased myelosuppressive and gastrointestinal side effects seen with the veliparib combination group, this trial raised additional concerns that giving any of the other commercially available PARP inhibitors in combination with chemotherapy may not be tolerable. However, it is also possible that an improved response rate to the combination of veliparib and chemotherapy could allow a greater proportion of patients to respond and ultimately begin maintenance therapy, potentially adding justification to the additional adverse events seen with the combination.

All of these studies highlight the potential for PARP inhibitor therapy in the frontline setting, even in patients without germline *BRCA* mutations. Although subanalyses in the above studies highlighted the seemingly modest effects of PARP inhibition in tumors with neither *BRCA* mutations or HRD, the efficacy demonstrated in patients with tumors demonstrating HRD suggests that relying solely on germline and somatic *BRCA* mutation testing may miss a significant subset of patients who could benefit from PARP inhibitors. We expect future FDA approvals to reflect this broader population of patients who could be candidates for frontline PARP inhibitor therapy.

PROMISING EARLY PHASE STUDIES

Several Phase I and II studies have recently been published evaluating the use of PARP inhibitors in ovarian cancer patients, and many other trials are ongoing. The vast majority of these are evaluating novel treatment combinations that include PARP inhibitors. A selection of ongoing clinical trials is listed in Table 4.

One such class of drugs being investigated in combination with PARP inhibitors are the anti-angiogenic agents. In 2014, Liu et al published their initial Phase II data evaluating the combination of olaparib and the oral anti-angiogenic drug cediranib (Liu, et al., 2014). The study enrolled women with recurrent, platinum-sensitive high grade serous or endometrioid ovarian cancers. However, if women had a germline *BRCA* mutation, any high-grade ovarian cancer histology was eligible. Patients could have received prior anti-angiogenic drugs in the frontline setting only but could not have received prior PARP inhibitor therapy. Patients were randomized to olaparib alone or to the combination of olaparib and cediranib. In the updated survival information, the overall population showed an improvement in progression-free survival in the combination arm compared with the olaparib monotherapy arm (16.5 vs 8.2 months, HR 0.50, 95% CI 0.30–0.83) (Liu, et al., 2019). Interestingly, there was no significant progression-free survival difference in the women with *BRCA* mutations between the combination and single-agent arms. However, in the women who were *BRCA* wildtype or unknown, the combination arm was associated with a significantly longer progression-free survival (23.7 vs. 5.7 months, HR 0.31, 95% CI 0.15–0.66) and a trend to improved overall survival (37.8 vs. 23.0 months, HR 0.44, 95% CI 0.19–1.01) (Liu, et al., 2019). Multiple other trials are ongoing evaluating the combination of olaparib and cediranib in women with platinum sensitive (NRG-GY004, ICON9, NCT02345265) and platinum-resistant (NRG-GY005, NCT02889900, NCT02345265) tumors. Additionally, a study is ongoing evaluating the addition of cediranib to olaparib in patients who progressed after initial response to therapy with olaparib alone (NCT02681237).

More recently, results from the AVANOVA2 trial (NSGO-AVANOVA2/ENGOT-ov24) were published (Mirza, et al., 2019). This Phase II randomized open-label study evaluated niraparib versus the combination of niraparib and bevacizumab in patients with platinum-sensitive, recurrent high grade serous or endometrioid tumors. Prior bevacizumab was allowed as long as disease progression occurred more than three months after last bevacizumab treatment, but prior PARP inhibitor therapy was not permitted. HRD status was assessed using myChoice CDX (≥ 42; Myriad Genetics). Overall, progression-free survival was improved in the combination therapy arm, at 11.9 months versus 5.5 months (adjusted

HR 0.35, 95% CI 0.21–0.57). When limited to HRD positive tumors, median progression-free survival was 11.9 months for the combined group compared with 6.1 months with niraparib alone (HR 0.38, 95% CI 0.20–0.72). The HRD negative group also showed an improved progression-free survival in the combination arm, with a median progression-free survival of 11.3 months versus 4.2 months (HR 0.40, 95% CI 0.19–0.85) (Mirza, et al., 2019). A Phase III trial of this combination is anticipated.

The results of a GOG-9923, another study evaluating an anti-angiogenic and PARP inhibitor combination, were recently published (Armstrong, et al., 2019). In this Phase I trial, newly diagnosed Stage II-IV ovarian cancer patients were treated with one of three regimens: carboplatin and paclitaxel every three weeks, carboplatin every three weeks with weekly paclitaxel, or an intravenous/intraperitoneal cisplatin and paclitaxel regimen. All three regimens received bevacizumab starting cycle 2 and continuing as maintenance. Each of the three regimens were then administered either continuous or intermittent veliparib dosing during chemotherapy and as maintenance following. The recommended Phase II dose of veliparib was found to be 150 mg twice daily, and these data were used to develop the VELIA trial discussed above.

The combination of PARP inhibition and checkpoint inhibition is also of particular interest (Stewart, Pilie, & Yap, 2018). Preclinical data suggest that tumors with *BRCA* loss show an increase in immune cell infiltrates (Clarke, et al., 2009; McAlpine, et al., 2012), and that treatment with a combination of PARP inhibition and checkpoint inhibition may lead to improved responses (Higuchi, et al., 2015). Clinically, multiple studies investigating these combinations are completed or underway. The TOPACIO/KEYNOTE-162 study was a Phase I/II trial of the combination of niraparib and pembrolizumab in patients who could not receive additional platinum chemotherapy (Konstantinopoulos, Waggoner, et al., 2019). The objective response rate was 18%, but a significant number of patients who responded showed durable responses lasting more than six months. The MEDIOLA trial evaluated olaparib and durvalumab in patients with *BRCA* mutations and platinum-sensitive disease. Preliminary data demonstrated an overall response rate of 74% (Drew, et al., 2018). Several trials evaluating this combination in the recurrent setting are ongoing. ANITA (NCT03598270) is a Phase III trial studying to combination of platinum-based chemotherapy with and without niraparib and/or atezolizumab. ARIES (NCT03824704) is a Phase II evaluating the combination of rucaparib and nivolumab in platinum-sensitive recurrent ovarian cancer.

Other trials with more complex therapeutic arms are ongoing in the upfront setting. ATHENA (NCT03522246), DUO-O/ENGOT-ov46 (NCT03737643), GOG-3036/ENGOT OV-43/KEYLYNK-001 (NCT03740165), and the FIRST trial (ENGOT-OV44, NCT03602859) are Phase III studies of platinum-based chemotherapy with or without checkpoint inhibition and PARP inhibition as frontline and maintenance. JAVELIN Ovarian PARP 100 (NCT03642132) was terminated early, as JAVELIN 100 failed to show improvement with the addition of talazoparib and/or avelumab to chemotherapy compared with chemotherapy and bevacizumab.

The combination or PARP inhibition with other targeted therapies is also being evaluated. Several studies have investigated the combination of a PARP inhibitor with an inhibitor targeting aspects of the PI3K pathway, including AKT inhibitors and PI3K inhibitors (Konstantinopoulos, Barry, et al., 2019; Matulonis, et al., 2017; Westin, et al., 2017). Some Phase I data are promising, but Phase II trials of these combinations have not been completed. Preclinical data also suggest that the combination of a MEK inhibitor and a PARP inhibitor may result in synergistic efficacy (Sun, et al., 2017), and a Phase I expansion study of this combination is currently ongoing (Kurnit, et al., 2019). Preclinical studies have also investigated PARP inhibitors in combination with CDK4/6 inhibition (Yi, et al., 2019), BET inhibition (Karakashev, et al., 2017), WEE1 inhibition (EFFORT NCT02659241), and Chk1/2 inhibition (Brill, et al., 2017), among others. It is expected that some of these and other combination therapies will move to the early-phase clinical trial domain in the next several years.

Interestingly, the combination of a PARP inhibitor with traditional chemotherapy has been more difficult. Several Phase I studies have been completed (Lampert, et al., 2019; Lee, et al., 2017; Perez-Fidalgo, et al., 2019; Rivkin, et al., 2019; van der Noll, et al., 2019). However, several of these studies discuss concerns about tolerability, particularly related to myelosuppression (Lampert, et al., 2019; van der Noll, et al., 2019). This was true even when less traditional dosing regimens both for chemotherapy and for the PARP inhibitor were used. Study 41 was a Phase II study evaluating patients with platinum-sensitive recurrent, high grade serous ovarian cancer who had received up to three prior lines of chemotherapy (Oza, et al., 2015). Patients were randomized to the combination of carboplatin (AUC 4), paclitaxel (175 mg/m2), and olaparib (200 mg capsules twice daily) followed by olaparib maintenance (400 mg capsules twice daily) or carboplatin (AUC 6) and paclitaxel (175 mg/m2). Although PFS was longer in the olaparib group (12.2 vs 9.6 months, HR 0.52, 95% CI 0.34–0.77, p = 0.0015), 49% of patients in the olaparib group compared with 39% of patients in the control group had neutropenia, and were also more likely to have alopecia, gastrointestinal side effects (nausea, diarrhea, dyspepsia), and peripheral neuropathy) (Oza, et al., 2015). Another study demonstrated that the order in which the chemotherapy and PARP inhibitor is given may impact the amount of myelosuppression that is seen (Lee, et al., 2017), which leads to further questions about the optimal timing of drug administration both in terms of efficacy as well as tolerability. As discussed previously, the only PARP inhibitor to date that has successfully been evaluated in a Phase III study was veliparib, and some investigators posit that this is related to its weaker PARP trapping ability and decreased bone marrow toxicity (Hopkins, et al., 2019; Hopkins, et al., 2015). For this reason, most of the trials evaluating PARP inhibitors are using them either as single-agent, or in combination with non-cytotoxic regimens.

ONGOING QUESTIONS

Despite the rapid progress made as a field with PARP inhibitor treatment in ovarian cancer, many conceptual questions remain. One of the biggest questions is accurately predicting which patients are most likely to respond to PARP inhibitors. Currently, the best biomarker appears to be germline *BRCA1* or *BRCA2* mutations. But this accounts for a minority of patients with epithelial ovarian cancer, and thus other biomarkers have been evaluated as

well. Having a tumor with HRD appears to infer some increased responsiveness to PARP inhibition, but even the definition and diagnosis for HRD varies between studies. With next generation sequencing panels being used more frequently, many investigators have begun including patients with mutations in other HRD genes (e.g., *BRIP1*, *RAD51C*, *PALB2*) (Norquist, et al., 2018). The HRD evaluation included in many of these studies, though, did not use the simple presence or absence of a one of a prespecified set of genes. In ARIEL2, investigators calculated the percentage of genomic loss of heterozygosity (Swisher, et al., 2017), and in QUADRA, NOVA, PRIMA, and VELIA they used myChoice HRD CDX (Myriad Genetics) (Coleman, et al., 2019; Gonzalez-Martin, et al., 2019; Mirza, et al., 2016; K. N. Moore, et al., 2019). Of note, all of these tests are assessment at only one point in time. Thus, the test may remain "positive" even if resistance has developed. These data suggest that there is a clear need for real-time assessment of HRD. In addition to HRD, many but not all studies have specified that patients must be platinum-sensitive, suggesting that platinum-sensitivity may be an equally or more relevant biomarker (Coleman, et al., 2017; Fong, et al., 2010; Mirza, et al., 2016; Pujade-Lauraine, et al., 2017; Swisher, et al., 2017). However, there exists a subset of patients with platinum-resistant disease that respond to single-agent PARP inhibitor therapy, and thus restricting to platinum-sensitive disease may be too simplistic (Fong, et al., 2010; Kaufman, et al., 2015).

Next, as PARP inhibitors have an increasing number of frontline therapy indications, the question of whether retreatment with a PARP inhibitor might be beneficial becomes more important. All of the initial studies that served as the basis for the current FDA approvals for recurrent ovarian cancer patients excluded prior PARP inhibitor therapy. Thus, we do not yet know whether patients who responded the first time can still benefit from retreatment. At least two studies are currently underway to investigate this question (OREO (NCT03106987), MOLTO (NCT02855697)). Furthermore, the question of whether tumors that develop PARP resistance can be re-sensitized to respond to PARP inhibition again is intriguing. Preclinical data regarding methods for overcoming resistance mechanisms are promising (Rottenberg, et al., 2008; Xu, et al., 2015), but no clinical studies evaluating this question have been completed yet.

As more patients are treated with PARP inhibitors in the upfront setting, we will need to better understand the impact PARP inhibition may have on a tumor. To this point, although significant improvement was seen in progression-free survival after frontline treatment with PARP inhibitor maintenance in SOLO1 and PRIMA, we have yet to see this translate into an improvement in overall survival. This has led some to question whether we are trading a longer disease-free interval upfront for a shorter platinum-sensitive interval at recurrence. Additionally, some oncologists hypothesize that waiting to use PARP inhibitors until patients are further along in their disease course will provide a bigger benefit, although this has not yet been evaluated. As our primary therapies become more complex, we will need to better evaluate the molecular impact of these novel therapies on the evolution of the tumor.

Last, as more PARP inhibitors become clinically available, the decision about which PARP inhibitor to use becomes less straightforward. Currently, there are no trials that compare PARP inhibitors to each other, and it is unlikely that this will occur in the future. While several of the current indications for PARP inhibitor therapy are non-overlapping, the recent

Phase III data and anticipated new approvals is likely to change this to some extent. Clinically, many oncologists use side effects and individual patient considerations to help guide PARP inhibitor therapy choice, but as more data become available for a broader range of patients, identifying which PARP inhibitors work best in which patients and in which settings may be beneficial for optimizing outcomes.

CONCLUSIONS

PARP inhibitors have changed the landscape for ovarian cancer patients in the past 10 years, and more approvals are expected in the near future. As the indications for PARP inhibitor therapy continue to expand, determining which patients should be treated and the optimal timing of that treatment will continue to evolve. There is a need to continue to maximize biomarker testing to better clarify who receives the greatest benefit from this class of drug.

Acknowledgments

KCK served on an Advisory Board for LEAP Therapeutics through the GOG-Foundation. RLC is a consultant for AstraZeneca, Clovis Oncology, GSK/Tesaro, Novartis, Roche/Genentech, Eisai, Merck, Pfizer, Novocure, Genmab, Gamamab, Oncosec, Tarveda. RLC receives research funding from AbbVie, Genmab, Merck, AstraZeneca, Clovis Oncology, Roche/Genentech. SNW is a consultant for AstraZeneca, Circulogene, Clovis Oncology, Eisai, GSK/Tesaro, Merck, Novartis, Pfizer, and Roche/Genentech. SNW receives research support from ArQule, AstraZeneca, Bayer, Clovis, Cotinga Pharmaceuticals, Novartis, Roche/Genentech, and GSK/Tesaro.

Abbreviations:

(PARP)	Poly (ADP-ribose) polymerase
(FDA)	Food and Drug Administration
(PFS)	Progression-free survival
(LOH)	Loss of heterozygosity
CI	(confidence interval)
(HRD)	Homologous recombination deficiency

REFERENCES

Administration, U. S. F. a. D. (2019). FDA approves niraparib for HRD-positive advanced ovarian cancer. In (Vol. 2020).

Armstrong DK, Moore KN, Miller A, Bell-McGuinn KM, Schilder RJ, Fracasso PM, Walker JL, Duska LR, Mathews CA, Chen AP, O'Malley DM, Gray HJ, O'Cearbhaill RE, Guntupalli SR, Hagemann AR, & Aghajanian C. (2019). A phase I study of veliparib incorporated into front-line platinum based cheotherpy and bevacizumab in epithelial ovarian cancer (NCT00989651): A GOG/nrg trial. Journal of Clinical Oncology, 37, 5523–5523.

Berek JS, Matulonis UA, Peen U, Ghatage P, Mahner S, Redondo A, Lesoin A, Colombo N, Vergote I, Rosengarten O, Ledermann J, Pineda M, Ellard S, Sehouli J, Gonzalez-Martin A, Berton-Rigaud D, Madry R, Reinthaller A, Hazard S, Guo W, & Mirza MR (2018). Safety and dose modification for patients receiving niraparib. Ann Oncol, 29, 1784–1792. [PubMed: 29767688]

Brill E, Yokoyama T, Nair J, Yu M, Ahn YR, & Lee JM (2017). Prexasertib, a cell cycle checkpoint kinases 1 and 2 inhibitor, increases in vitro toxicity of PARP inhibition by preventing Rad51 foci

formation in BRCA wild type high-grade serous ovarian cancer. Oncotarget, 8, 111026–111040. [PubMed: 29340034]

Brody LC (2005). Treating cancer by targeting a weakness. N Engl J Med, 353, 949–950. [PubMed: 16135843]

Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, Kyle S, Meuth M, Curtin NJ, & Helleday T. (2005). Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature, 434, 913–917. [PubMed: 15829966]

Clarke B, Tinker AV, Lee CH, Subramanian S, van de Rijn M, Turbin D, Kalloger S, Han G, Ceballos K, Cadungog MG, Huntsman DG, Coukos G, & Gilks CB (2009). Intraepithelial T cells and prognosis in ovarian carcinoma: novel associations with stage, tumor type, and BRCA1 loss. Mod Pathol, 22, 393–402. [PubMed: 19060844]

Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, Okamoto A, Moore KN, Efrat Ben-Baruch N, Werner TL, Cloven NG, Oaknin A, DiSilvestro PA, Morgan MA, Nam JH, Leath CA 3rd, Nicum S, Hagemann AR, Littell RD, Cella D, Baron-Hay S, Garcia-Donas J, Mizuno M, Bell-McGuinn K, Sullivan DM, Bach BA, Bhattacharya S, Ratajczak CK, Ansell PJ, Dinh MH, Aghajanian C, & Bookman MA (2019). Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. N Engl J Med, 381, 2403–2415. [PubMed: 31562800]

Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Clamp A, Scambia G, Leary A, Holloway RW, Gancedo MA, Fong PC, Goh JC, O'Malley DM, Armstrong DK, Garcia-Donas J,Swisher EM, Floquet A, Konecny GE, McNeish IA, Scott CL, Cameron T, Maloney L, Isaacson J, Goble S, Grace C, Harding TC, Raponi M, Sun J, Lin KK, Giordano H, & Ledermann JA (2017). Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet, 390, 1949–1961. [PubMed: 28916367]

Drew Y, De Jonge M, Hong SH, Park YH, Wolfer A, Brown J, Ferguson M, Gore ME, Alvarez RH, Gresty C, Angell H, Meyer K, Learoyd M, Tang M, Lanasa M, Herbolsheimer P, & Domchek SM (2018). An open-label, phase II basket study of olaparib and durvalumab (MEDIOLA): Results in germline BRCA-mutated (gBRCAm) platinum-sensitive relapsed (PSR) ovarian cancer (OC). In Society of Gynecologic Oncology Annual Meeting on Women's Cancer. New Orleans, Louisiana.

Fong PC, Yap TA, Boss DS, Carden CP, Mergui-Roelvink M, Gourley C, De Greve J, Lubinski J, Shanley S, Messiou C, A'Hern R, Tutt A, Ashworth A, Stone J, Carmichael J, Schellens JH, de Bono JS, & Kaye SB (2010). Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol, 28, 2512–2519. [PubMed: 20406929]

Ford D, Easton DF, Bishop DT, Narod SA, & Goldgar DE (1994). Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet, 343, 692–695. [PubMed: 7907678]

Gonzalez-Martin A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, McCormick C, Lorusso D, Hoskins P, Freyer G, Baumann K, Jardon K, Redondo A, Moore RG, Vulsteke C, O'Cearbhaill RE, Lund B, Backes F, Barretina-Ginesta P, Haggerty AF, Rubio-Perez MJ, Shahin MS, Mangili G, Bradley WH, Bruchim I, Sun K, Malinowska IA, Li Y, Gupta D, & Monk BJ (2019). Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med, 381, 2391–2402. [PubMed: 31562799]

Higuchi T, Flies DB, Marjon NA, Mantia-Smaldone G, Ronner L, Gimotty PA, & Adams SF (2015). CTLA-4 Blockade Synergizes Therapeutically with PARP Inhibition in BRCA1-Deficient Ovarian Cancer. Cancer Immunol Res, 3, 1257–1268. [PubMed: 26138335]

Hopkins TA, Ainsworth WB, Ellis PA, Donawho CK, DiGiammarino EL, Panchal SC, Abraham VC, Algire MA, Shi Y, Olson AM, Johnson EF, Wilsbacher JL, & Maag D. (2019). PARP1 Trapping by PARP Inhibitors Drives Cytotoxicity in Both Cancer Cells and Healthy Bone Marrow. Mol Cancer Res, 17, 409–419. [PubMed: 30429212]

Hopkins TA, Shi Y, Rodriguez LE, Solomon LR, Donawho CK, DiGiammarino EL, Panchal SC, Wilsbacher JL, Gao W, Olson AM, Stolarik DF, Osterling DJ, Johnson EF, & Maag D. (2015). Mechanistic Dissection of PARP1 Trapping and the Impact on In Vivo Tolerability and Efficacy of PARP Inhibitors. Mol Cancer Res, 13, 1465–1477. [PubMed: 26217019]

Karakashev S, Zhu H, Yokoyama Y, Zhao B, Fatkhutdinov N, Kossenkov AV, Wilson AJ, Simpkins F, Speicher D, Khabele D, Bitler BG, & Zhang R. (2017). BET Bromodomain Inhibition Synergizes with PARP Inhibitor in Epithelial Ovarian Cancer. Cell Rep, 21, 3398–3405. [PubMed: 29262321]

Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, Mitchell G, Fried G, Stemmer SM, Hubert A, Rosengarten O, Steiner M, Loman N, Bowen K, Fielding A, & Domchek SM (2015). Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol, 33, 244–250. [PubMed: 25366685]

Kikuchi R, Lao Y, Bow DA, Chiou WJ, Andracki ME, Carr RA, Voorman RL, & De Morais SM (2013). Prediction of clinical drug-drug interactions of veliparib (ABT-888) with human renal transporters (OAT1, OAT3, OCT2, MATE1, and MATE2K). J Pharm Sci, 102, 4426–4432. [PubMed: 24122511]

Konstantinopoulos PA, Barry WT, Birrer M, Westin SN, Cadoo KA, Shapiro GI, Mayer EL, O'Cearbhaill RE, Coleman RL, Kochupurakkal B, Whalen C, Curtis J, Farooq S, Luo W, Eismann J, Buss MK, Aghajanian C, Mills GB, Palakurthi S, Kirschmeier P, Liu J, Cantley LC, Kaufmann SH, Swisher EM, D'Andrea AD, Winer E, Wulf GM, & Matulonis UA (2019). Olaparib and alpha-specific PI3K inhibitor alpelisib for patients with epithelial ovarian cancer: a dose-escalation and dose-expansion phase 1b trial. Lancet Oncol, 20, 570–580. [PubMed: 30880072]

Konstantinopoulos PA, Ceccaldi R, Shapiro GI, & D'Andrea AD (2015). Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. Cancer Discov, 5, 1137–1154. [PubMed: 26463832]

Konstantinopoulos PA, Waggoner S, Vidal GA, Mita M, Moroney JW, Holloway R, Van Le L, Sachdev JC, Chapman-Davis E, Colon-Otero G, Penson RT, Matulonis UA, Kim YB, Moore KN, Swisher EM, Farkkila A, D'Andrea A, Stringer-Reasor E, Wang J, Buerstatte N, Arora S, Graham JR, Bobilev D, Dezube BJ, & Munster P. (2019). Single-Arm Phases 1 and 2 Trial of Niraparib in Combination With Pembrolizumab in Patients With Recurrent Platinum-Resistant Ovarian Carcinoma. JAMA Oncol.

Korach J, Turner S, Milenkova T, Alecu I, McMurtry E, Bloomfield R, & Pujade-Lauraine E. (2018). Incidence of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in patients (pts) with a germline (g) BRCA mutation (m) and platinum-sensitive relapsed ovarian cancer (PSR OC) receiving maintenance olaparib in SOLO2: Impact of prior lines of platinum therapy. Journal of Clinical Oncology, 36, 5548–5548.

Kristeleit R, Shapiro GI, Burris HA, Oza AM, LoRusso P, Patel MR, Domchek SM, Balmana J, Drew Y, Chen LM, Safra T, Montes A, Giordano H, Maloney L, Goble S, Isaacson J, Xiao J, Borrow J, Rolfe L, & Shapira-Frommer R. (2017). A Phase I-II Study of the Oral PARP Inhibitor Rucaparib in Patients with Germline BRCA1/2-Mutated Ovarian Carcinoma or Other Solid Tumors. Clin Cancer Res, 23, 4095–4106. [PubMed: 28264872]

Kurman RJ, & Shih Ie M. (2010). The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol, 34, 433–443. [PubMed: 20154587]

Kurnit KC, Meric-Bernstam F, Hess K, Coleman RL, Bhosale P, Savelieva K, Janku F, Hong D, Naing A, Pant S, Rodon J, Yap TA, Sood AK, Soliman PT, Gershenson DM, Mills GB, & Westin SN (2019). Abstract CT020: Phase I dose escalation of olaparib (PARP inhibitor) and selumetinib (MEK Inhibitor) combination in solid tumors with Ras pathway alterations. Cancer Res, 79, CT020–CT020.

Lampert EJ, Hays JL, Kohn EC, Annunziata CM, Minasian L, Yu M, Gordon N, Sissung TM, Chiou VL, Figg WD, Houston N, & Lee JM (2019). Phase I/Ib study of olaparib and carboplatin in heavily pretreated recurrent high-grade serous ovarian cancer at low genetic risk. Oncotarget, 10, 2855–2868. [PubMed: 31080557]

Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, Scott C, Meier W, Shapira-Frommer R, Safra T, Matei D, Macpherson E, Watkins C, Carmichael J, & Matulonis U. (2012). Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med, 366, 1382–1392. [PubMed: 22452356]

Lee JM, Peer CJ, Yu M, Amable L, Gordon N, Annunziata CM, Houston N, Goey AK, Sissung TM, Parker B, Minasian L, Chiou VL, Murphy RF, Widemann BC, Figg WD, & Kohn EC (2017). Sequence-Specific Pharmacokinetic and Pharmacodynamic Phase I/Ib Study of Olaparib Tablets and Carboplatin in Women's Cancer. Clin Cancer Res, 23, 1397–1406. [PubMed: 27663600]

Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, Rimel B, Buss MK, Nattam S, Hurteau J, Luo W, Quy P, Whalen C, Obermayer L, Lee H, Winer EP, Kohn EC, Ivy SP, & Matulonis UA (2014). Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol, 15, 1207–1214. [PubMed: 25218906]

Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, Rimel BJ, Buss MK, Nattam SR, Hurteau J, Luo W, Curtis J, Whalen C, Kohn EC, Ivy SP, & Matulonis UA (2019). Overall survival and updated progression-free survival outcomes in a randomized phase II study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer. Ann Oncol, 30, 551–557. [PubMed: 30753272]

Matulonis UA, Wulf GM, Barry WT, Birrer M, Westin SN, Farooq S, Bell-McGuinn KM, Obermayer E, Whalen C, Spagnoletti T, Luo W, Liu H, Hok RC, Aghajanian C, Solit DB, Mills GB, Taylor BS, Won H, Berger MF, Palakurthi S, Liu J, Cantley LC, & Winer E. (2017). Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (ADP ribose) polymerase (PARP) inhibitor olaparib for the treatment of high-grade serous ovarian and breast cancer. Ann Oncol, 28, 512–518. [PubMed: 27993796]

McAlpine JN, Porter H, Kobel M, Nelson BH, Prentice LM, Kalloger SE, Senz J, Milne K, Ding J, Shah SP, Huntsman DG, & Gilks CB (2012). BRCA1 and BRCA2 mutations correlate with TP53 abnormalities and presence of immune cell infiltrates in ovarian high-grade serous carcinoma. Mod Pathol, 25, 740–750. [PubMed: 22282309]

Mirza MR, Avall Lundqvist E, Birrer MJ, dePont Christensen R, Nyvang GB, Malander S, Anttila M, Werner TL, Lund B, Lindahl G, Hietanen S, Peen U, Dimoula M, Roed H, Or Knudsen A, Staff S, Krog Vistisen A, Bjorge L, & Maenpaa JU (2019). Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol, 20, 1409–1419. [PubMed: 31474354]

Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, Fabbro M, Ledermann JA, Lorusso D, Vergote I, Ben-Baruch NE, Marth C, Madry R, Christensen RD, Berek JS, Dorum A, Tinker AV, du Bois A, Gonzalez-Martin A, Follana P, Benigno B, Rosenberg P, Gilbert L, Rimel BJ, Buscema J, Balser JP, Agarwal S, & Matulonis UA (2016). Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med, 375, 2154–2164. [PubMed: 27717299]

Monk BJ, Mirza MR, Vergote I, Li Y, Malinowska I, Gupta D, Graybill WA, Pothuri B, & Gonzalez-Martin A. (2019). A prospective evaluation of tolerability of niraparib dosing based upon baseline body weight and platelet count: Blinded pooled interim safety data from the ENGOT-OV26/PRIMA study. Gynecol Oncol, 154, 3–4. [PubMed: 30995961]

Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, Lisyanskaya A, Floquet A, Leary A, Sonke GS, Gourley C, Banerjee S, Oza A, Gonzalez-Martin A, Aghajanian C, Bradley W, Mathews C, Liu J, Lowe ES, Bloomfield R, & DiSilvestro P. (2018). Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med, 379, 2495–2505. [PubMed: 30345884]

Moore KN, & Monk BJ (2016). Patient Counseling and Management of Symptoms During Olaparib Therapy for Recurrent Ovarian Cancer. Oncologist, 21, 954–963. [PubMed: 27256873]

Moore KN, Secord AA, Geller MA, Miller DS, Cloven N, Fleming GF, Wahner Hendrickson AE, Azodi M, DiSilvestro P, Oza AM, Cristea M, Berek JS, Chan JK, Rimel BJ, Matei DE, Li Y, Sun K, Luptakova K, Matulonis UA, & Monk BJ (2019). Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol, 20, 636–648. [PubMed: 30948273]

Murai J, Huang SY, Das BB, Renaud A, Zhang Y, Doroshow JH, Ji J, Takeda S, & Pommier Y. (2012). Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. Cancer Res, 72, 5588–5599. [PubMed: 23118055]

Norquist BM, Brady MF, Harrell MI, Walsh T, Lee MK, Gulsuner S, Bernards SS, Casadei S, Burger RA, Tewari KS, Backes F, Mannel RS, Glaser G, Bailey C, Rubin S, Soper J, Lankes HA, Ramirez NC, King MC, Birrer MJ, & Swisher EM (2018). Mutations in Homologous Recombination Genes and Outcomes in Ovarian Carcinoma Patients in GOG 218: An NRG Oncology/Gynecologic Oncology Group Study. Clin Cancer Res, 24, 777–783. [PubMed: 29191972]

Oza AM, Cibula D, Benzaquen AO, Poole C, Mathijssen RH, Sonke GS, Colombo N, Spacek J, Vuylsteke P, Hirte H, Mahner S, Plante M, Schmalfeldt B, Mackay H, Rowbottom J, Lowe ES, Dougherty B, Barrett JC, & Friedlander M. (2015). Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol, 16, 87–97. [PubMed: 25481791]

Oza AM, Tinker AV, Oaknin A, Shapira-Frommer R, McNeish IA, Swisher EM, Ray-Coquard I, Bell-McGuinn K, Coleman RL, O'Malley DM, Leary A, Chen LM, Provencher D, Ma L, Brenton JD, Konecny GE, Castro CM, Giordano H, Maloney L, Goble S, Lin KK, Sun J, Raponi M, Rolfe L, & Kristeleit RS (2017). Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2. Gynecol Oncol, 147, 267–275. [PubMed: 28882436]

Penson RT, Valencia RV, Cibula D, Colombo N, Leath CA, Bidziński M, Kim J-W, Nam J-H, Madry R, Hernández CH, Mora PAR, Ryu SY, Milenkova T, Lowe ES, Barker L, & Scambia G. (2019). Olaparib monotherapy versus (vs) chemotherapy for germline BRCA-mutated (gBRCAm) platinum-sensitive relapsed ovarian cancer (PSR OC) patients (pts): Phase III SOLO3 trial. Journal of Clinical Oncology, 37, 5506–5506.

Perez-Fidalgo JA, Iglesias M, Bohn U, Calvo E, Garcia Y, Guerra E, Manso L, Santaballa A, & Gonzalez-Martin A. (2019). GEICO1601-ROLANDO: a multicentric single arm Phase II clinical trial to evaluate the combination of olaparib and pegylated liposomal doxorubicin for platinum-resistant ovarian cancer. Future Sci OA, 5, Fso370.

Plummer R. (2010). Perspective on the pipeline of drugs being developed with modulation of DNA damage as a target. Clin Cancer Res, 16, 4527–4531. [PubMed: 20823148]

Plummer R. (2011). Poly(ADP-ribose) polymerase inhibition: a new direction for BRCA and triple-negative breast cancer? Breast Cancer Res, 13, 218. [PubMed: 21884642]

Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, Korach J, Huzarski T, Poveda A, Pignata S, Friedlander M, Colombo N, Harter P, Fujiwara K, Ray-Coquard I, Banerjee S, Liu J, Lowe ES, Bloomfield R, & Pautier P. (2017). Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol, 18, 1274–1284. [PubMed: 28754483]

Ray-Coquard I, Pautier P, Pignata S, Perol D, Gonzalez-Martin A, Berger R, Fujiwara K, Vergote I, Colombo N, Maenpaa J, Selle F, Sehouli J, Lorusso D, Guerra Alia EM, Reinthaller A, Nagao S, Lefeuvre-Plesse C, Canzler U, Scambia G, Lortholary A, Marme F, Combe P, de Gregorio N, Rodrigues M, Buderath P, Dubot C, Burges A, You B, Pujade-Lauraine E, & Harter P. (2019). Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med, 381, 2416–2428. [PubMed: 31851799]

Rivkin SE, Moon J, Iriarte DS, Bailey E, Sloan HL, Goodman GE, BonDurant AE, Velijovich D, Wahl T, Jiang P, Shah CA, Drescher C, Fer MF, Kaplan HG, & Ellis ED (2019). Phase Ib with expansion study of olaparib plus weekly (Metronomic) carboplatin and paclitaxel in relapsed ovarian cancer patients. Int J Gynecol Cancer.

Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, Zander SA, Derksen PW, de Bruin M, Zevenhoven J, Lau A, Boulter R, Cranston A, O'Connor MJ, Martin NM, Borst P, & Jonkers J. (2008). High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci U S A, 105, 17079–17084. [PubMed: 18971340]

Satoh MS, & Lindahl T. (1992). Role of poly(ADP-ribose) formation in DNA repair. Nature, 356, 356–358. [PubMed: 1549180]

Staropoli N, Ciliberto D, Del Giudice T, Iuliano E, Cuce M, Grillone F, Salvino A, Barbieri V, Russo A, Tassone P, & Tagliaferri P. (2018). The Era of PARP inhibitors in ovarian cancer: "Class Action" or not? A systematic review and meta-analysis. Crit Rev Oncol Hematol, 131, 83–89. [PubMed: 30293710]

Stewart RA, Pilie PG, & Yap TA (2018). Development of PARP and Immune-Checkpoint Inhibitor Combinations. Cancer Res, 78, 6717–6725. [PubMed: 30498083]

Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, & Tucker MA (1997). The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med, 336, 1401–1408. [PubMed: 9145676]

Sun C, Fang Y, Yin J, Chen J, Ju Z, Zhang D, Chen X, Vellano CP, Jeong KJ, Ng PK, Eterovic AKB, Bhola NH, Lu Y, Westin SN, Grandis JR, Lin SY, Scott KL, Peng G, Brugge J, & Mills GB (2017). Rational combination therapy with PARP and MEK inhibitors capitalizes on therapeutic liabilities in RAS mutant cancers. Sci Transl Med, 9.

Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, Sun J, Konecny GE, Coleman RL, Tinker AV, O'Malley DM, Kristeleit RS, Ma L, Bell-McGuinn KM, Brenton JD, Cragun JM, Oaknin A, Ray-Coquard I, Harrell MI, Mann E, Kaufmann SH, Floquet A, Leary A, Harding TC, Goble S, Maloney L, Isaacson J, Allen AR, Rolfe L, Yelensky R, Raponi M, & McNeish IA (2017). Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol, 18, 75–87. [PubMed: 27908594]

van der Noll R, Jager A, Ang JE, Marchetti S, Mergui-Roelvink MWJ, de Bono JS, Lolkema MP, de Jonge MJA, van der Biessen DA, Brunetto AT, Arkenau HT, Tchakov I, Beijnen JH, De Greve J, & Schellens JHM (2019). Phase I study of intermittent olaparib capsule or tablet dosing in combination with carboplatin and paclitaxel (part 2). Invest New Drugs.

Venkitaraman AR (2002). Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell, 108, 171–182. [PubMed: 11832208]

Westin S, Litton J, Williams R, Soliman P, Frumovitz M, Schmeler K, Jazaeri A, Sood A, Lu K, Moulder S, Murthy R, Rodriguez A, Samuel C, Engerman L, Cyriac A, Rugman P, Lindemann J, McMurtry E, Mills G, & Coleman R. (2017). 391PPhase I expansion of olaparib (PARP inhibitor) and AZD5363 (AKT inhibitor) in recurrent ovarian, endometrial and triple negative breast cancer. Annals of Oncology, 28, mdx367.025-mdx367.025.

Xu G, Chapman JR, Brandsma I, Yuan J, Mistrik M, Bouwman P, Bartkova J, Gogola E, Warmerdam D, Barazas M, Jaspers JE, Watanabe K, Pieterse M, Kersbergen A, Sol W, Celie PHN, Schouten PC, van den Broek B, Salman A, Nieuwland M, de Rink I, de Ronde J, Jalink K, Boulton SJ, Chen J, van Gent DC, Bartek J, Jonkers J, Borst P, & Rottenberg S. (2015). REV7 counteracts DNA double-strand break resection and affects PARP inhibition. Nature, 521, 541–544. [PubMed: 25799992]

Yi J, Liu C, Tao Z, Wang M, Jia Y, Sang X, Shen L, Xue Y, Jiang K, Luo F, Liu P, & Cheng H. (2019). MYC status as a determinant of synergistic response to Olaparib and Palbociclib in ovarian cancer. EBioMedicine, 43, 225–237. [PubMed: 30898650]

Zibetti Dal Molin G, Westin SN, Msaouel P, Gomes LM, Dickens A, & Coleman RL (2020). Discrepancy in calculated and measured glomerular filtration rates in patients treated with PARP inhibitors. Int J Gynecol Cancer, 30, 89–93. [PubMed: 31792084]

Table 1:

PARP Inhibitor Use by FDA Designation

Primary Disease			
Agent	**Dose**	**Treatment Indication**	**Upfront Indication**
Olaparib (Lynparza)	300 mg BID (2 - 150mg tablets)	gBRCA/sBRCA mutant ovarian cancer	Platinum-sensitive ovarian, fallopian tube, peritoneal cancer after partial or complete response to initial platinum-based therapy
Secondary Disease			
Agent	**Dose**	**Treatment Indication**	**Recurrence Indication**
Olaparib (Lynparza)	300 mg BID (two 150mg tablets)	gBRCA mutant ovarian cancer	Ovarian cancer treated with three or more prior lines of chemotherapy
Rucaparib (Rubraca)	600 mg BID (two 300mg tablets)	gBRCA/sBRCA mutant ovarian cancer	Ovarian, fallopian tube, peritoneal cancer treated with two or more prior lines of chemotherapy
Niraparib (Zejula)	300 mg daily (three 100mg capsules)	gBRCA/sBRCA mutant ovarian cancer OR genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy	Ovarian, fallopian tube, peritoneal cancer treated with three or more prior lines of chemotherapy
Agent	**Dose**	**Treatment Indication**	**Maintenance Indication**
Olaparib (Lynparza)	300 mg BID (two 150mg tablets)	gBRCA/sBRCA mutant OR any patient with advanced, recurrent ovarian, fallopian tube, peritoneal cancer	Platinum-sensitive ovarian, fallopian tube, peritoneal cancer after partial or complete response to platinum-based therapy
Rucaparib (Rubraca)	600 mg BID (two 300mg tablets)	Advanced, recurrent ovarian, fallopian tube, peritoneal cancer	Platinum-sensitive ovarian, fallopian tube, peritoneal cancer after partial or complete response to platinum-based therapy
Niraparib (Zejula)	300 mg daily (three 100mg capsules)	Advanced, recurrent ovarian, fallopian tube, peritoneal cancer	Platinum-sensitive ovarian, fallopian tube, peritoneal cancer after partial or complete response to platinum-based therapy

Table 2

Comparison of select adverse events across single-agent, phase III maintenance drug trials.

Trial	Olaparib				Niraparib				Rucaparib	
Adverse event	S0L02		SOLOl		NOVA		PRIMA		ARIEL3	
N (treatment group)	195		260		367		484		372	
Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade
Any	36%	98%	39%	98%		100%	65%	96%	55%	100%
Nausea	3%	76%	1%	77%	3%	74%	1%	57%	14%	75%
Neutropenia	5%	19%	9%	23%	20%	30%	13%	26%	7%	18%
Fatigue	4%	66%	4%	63%	8%	59%	2%	35%	7%	69%
Anemia	19%	44%	22%	39%	25%	50%	31%	63%	19%	37%
Thrombocytopenia	1%	14%	1%	11%	34%	61%	29%	46%	5%	28%
Vomiting	3%	37%	< 1%	40%	2%	34%	1%	22%	4%	37%
Diarrhea	1%	33%	3%	34%	<1%	19%			1%	32%
Constipation	0%	21%	0%	28%	1%	40%	<1%	39%	2%	37%
Abdominal pain	3%	24%	2%	25%	1%	23%	1%	22%	2%	30%
Decreased appetite	0%	22%	0%	20%	<1%	25%			1%	23%
Insomnia					<1%	24%	1%	25%	0%	14%
Arthralgia	0%	15%	0%	25%	<1%	12%			1%	15%
Dizziness	1%	13%	0%	20%	0%	17%			0%	15%
Headache	1%	25%	<1%	23%	<1%	26%	<1%	26%	<1%	18%
Hypomagnesemia	0%	14%							<1%	11%
Dyspnea	1%	12%	0%	15%	1%	19%			0%	13%
Urinary Tract Infection	1%	9%			1%	10%				
Hypertension					8%	19%				
Creatinine	0%	11%							<1%	15%
AST ALT elevation									10%	34%

Table 3:

Summary of primary therapy studies at the European Society for Medical Oncology 2019 Meeting

Study	Patient Population	Treatment arms			Primary Outcome	Primary Results	Ref
PRIMA (PRIMA/ ENGO - OV26/ GOG-3012)	Stage III/IV; high grade serous or endometrioid; CR or PR after 6–9 cycles of chemotherapy; must have had residual disease or were inoperable	Niraparib maintenance	Placebo		Progression-free survival in patients with HRD tumors	HRD positive: 21.9 vs 10.4 months (HR 0.43, 95% CI 0.31–0.59, p < 0.001) favoring niraparib maintenance; Entire cohort: 13.8 vs 8.2 months (HR 0.62, 95% CI 0.50–0.76, p < 0.001) favoring niraparib maintenance	[1]
PAOLA-1 (PAOLA-1/ ENGOT-ov25)	Stage III/IV high grade serous or endometrioid; must have undergone tumor debulking (primary or interval), allowed complete resection; must have received at least 3 cycles of bevacizumab as part of treatment; must have had CR or PR to chemotherapy	Olaparib + bevaciz umab mainte nance	Placebo + bevaciz umab mainte nance		Progression-free survival	22.1 vs 16.6 months (HR 0.59, 95% CI 0.49–0.72, p < 0.001) favoring olaparib maintenance	[2]
VELIA (VELIA / GOG-3005)	Stage III/IV high grade serous; primary or interval tumor debulking with either complete resection or residual disease present; did not need to have a response to chemotherapy	Carboplatin, paclitaxel, veliparib + veliparib maintenance	Carboplatin, paclitaxel, veliparib + placebo maintenance	Carboplatin, paclita xel, placebo + placebo maintenance	Progression-free survival for patients who received veliparib (treatment and maintenanc e) vs. those that received placebo (treatment and maintenance)	Women with BRCA mutation: 34.7 vs. 22.0 months (HR 0.44, 95% CI 0.28–0.68, p < 0.001); Women with HRD tumors: 31.9 vs 20.5 months (HR 0.57, 95% CI 0.43–0.76, p < 0.001); intention to treat group: 23.5 vs 17.3 months (HR 0.68, 95% CI 0.56–0.83, p < 0.001) favoring the veliparib arm	[3]

Table 4:

Select ongoing Phase II and III clinical trials of PARP inhibitors in patients with ovarian cancer

Setting	Study Name	NCT number	Trial Phase	Treatment arms	Patient Population
Frontline	ATHENA	NCT03522246	III	maintenance therapy with: - rucaparib/nivolumab - rucaparib/placebo - placebo/nivolumab - placebo/placebo	newly diagnosed ovarian cancer patients with response to first line chemotherapy
	DUO-O/ ENGOT-ov46	NCT03737643	III	- platinum-based chemotherapy/ bevacizumab/durvalumab followed by maintenance bevacizumab/durvalumab/olaparib - platinum-based chemotherapy/ bevaciumab /durvalumab followed by maintenance bevacizumab/durvalumab/placebo - platinum-based chemotherapy/ bevaciumab /placebo followed by maintenance bevacizumab/placebo/ olap arib For BRCA cohort: - platinum-based chemotherapy/ bevaciumab /durvalumab followed by maintenance bevacizumab/ durvalumab/olpaarib (bevacizumab optional for this cohort)	newly diagnosed Stage III-IV ovarian cancer who are candidate for surgery (upfront or interval) with known somatic BRCA status
	GOG-3036/ENGOT-ov43/KEYLYNK-001	NCT03740165	III	- carboplatin/paclitaxel/pembrolizumab followed by pembrolizumab/olaparib maintenance - carboplatin/paclitaxel/pembrolizumab followed by pembrolizumab/placebo maintenance - carboplatin/paclitaxel/place bo followed by placebo/placebo maintenance. NOTE: Bevacizumab treatment and maintenance is allowed in all groups	newly diagnosed Stage III-IV ovarian cancer who are candidate for surgery (upfront or interval) without germline or somatic BRCA mutations
	FIRST (ENGOT-OV44)	NCT03602859	III	- platinum-based chemotherapy/ dostarlimab followed by maintenance dostarlimab/niraparib - platinum-based chemotherapy/ placebo followed by maintenance placebo/niraparib - platinum-based chemotherapy/ placebo followed by maintenance placebo/placebo	newly diagnosed Stage III who are receiving neoadjuvant therapy or are high risk, or all stage IV ovarian cancer
Recurrent	NRG-GY004	NCT02446600	III	- olaparib - olaparib/cediranib - cytotoxic chemotherapy (carboplatin/ paclitaxel, carboplatin/gemcitabine, carboplatin/liposomal doxorubicin)	platinum-sensitive recurrent ovarian cancer
	ICON9	NCT03278717	III	- maintenance olaparib - maintenance olaparib/cediranib	platinumsensitive recurrent ovarian cancer
		NCT02345265	II	- olaparib - olaparib/cediranib	platinum-sensitive or platinum-resistant recurrent ovarian cancer
	NRG-GY005	NCT02502266	II/III	- cytotoxic chemo (weekly paclitaxel, liposomal doxorubicin, topotecan) cediranib/olaparib - cediranib - olaparib. NOTE: Phase III does not include the olaparib only arm.	platinum-resistant or refractor recurrent ovarian cancer

Setting	Study Name	NCT number	Trial Phase	Treatment arms	Patient Population
	CONCERTO	NCT02889900	IIB	cediranib/olaparib	platinum-resistant, recurrent ovarian cancer, BRCA wildtype
		NCT02345265	II	cediranib/olaparib	platinumsensitive or resistant/refractory recurrent ovarian cancer
	ANITA	NCT03598270	III	- Atezolizumab/cytotoxic chemotherapy (carboplatin/paclitaxel, carboplatin/gemcitabine, carboplatin/liposomal doxorubicin) followed by atezolizumab/niraparib maintenance - Atezolizumab/cytotoxic chemotherapy (carboplatin/paclitaxel, carboplatin/gemcitabine, carboplatin/liposomal doxorubicin) followed by placebo/niraparib maintenance	platinum-sensitive recurrent ovarian cancer with known BRCA mutation status
	ARIES	NCT03824704	II	rucaparib/nivolumab	platinumsensitive recurrent ovarian cancer with either somatic BRCA mutatino or loss of heterozygosity
ReTreatment	OREO	NCT03106987	IIIB	- olaparib - placebo	platinum-sensitive recurrent ovarian cancer with known BRCA mutation status, previously treated with PARP inhibitor maintenance therapy
	MOLTO	NCT02855697	II (feasibility)	- maintenance olaparib for first maintenance - either olaparib or olaparib/cediranib for second maintenance	platinum-sensitive recurrent ovarian cancer (with and without prior PARP inhibitor maintenanc e), with germline BRCA mutations

1. Gonzalez-Martin, A., et al., Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med, 2019. 381(25): p. 2391–2402.

2. Ray-Coquard, I., et al., Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med, 2019. 381(25): p. 2416–2428.

3. Coleman, R.L., et al., Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. N Engl J Med, 2019. 381(25): p. 2403–2415.