# "Latest Advancements in Ovarian Cancer: The Role of Olaparib in Management".

## Module II

## Mechanism of Action: How Olaparib in Ovarian Cancer

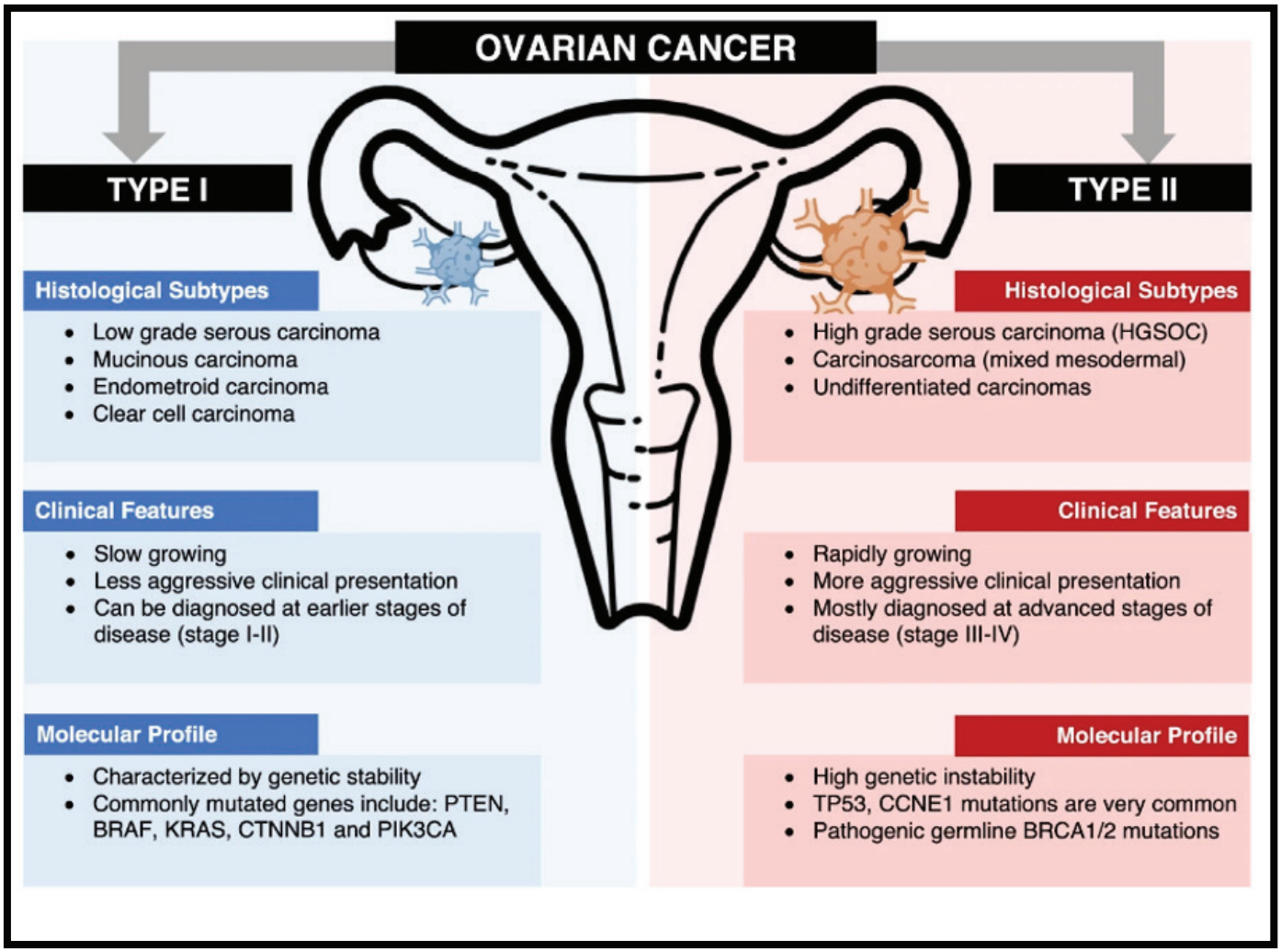
# CONTENT

# Introduction

Ovarian cancer is the seventh most common cancer in women worldwide and is the leading cause of death from gynecologic cancers in high-income countries. The five-year survival rate in the United States is 48% and the proportion of women dying from their disease has not improved substantially over time as compared to other prevalent cancers. Standard treatment for newly diagnosed advanced ovarian cancer consists of cytoreductive surgery and platinum-based chemotherapy with or without concurrent and maintenance bevacizumab, a vascular endothelial growth factor (VEGF) A inhibitor. The majority of women with epithelial ovarian cancer respond well to first-line platinum-based chemotherapy however there is a high rate of recurrence with a chemotherapy-free interval before disease progression ranging from 10 to 26 months. Response to subsequent therapies is variable and often short-lived, underscoring the need for novel effective treatment options to improve long-term disease control for women with ovarian cancer. Homologous recombination (HR) is a DNA repair process crucial for the accurate repair of DNA damage. BRCA1/2 mutations are known to lead to defective HR and ultimately results in risk for malignant transformation of cells. BRCA mutations, both germline and somatic, are thought to occur in up to 25% of patients with newly diagnosed serous ovarian cancer. While BRCA1/2 mutations were initially thought to be responsible for the majority of hereditary epithelial ovarian cancers, further investigation has shown that compromise of the HR pathway can occur by several other potential mechanisms. Thus, it is thought that approximately 50% of high-grade serous ovarian cancers have a deficiency in HR. There have been several studies investigating the role of maintenance therapy in ovarian cancer which until recently have not been found to significantly prolong survival. However, poly (ADP-ribose) polymerase (PARP) inhibitors have shown significant promise with several clinical trials demonstrating a survival improvement in women with newly diagnosed and recurrent ovarian cancer without a substantial increase in adverse effects. The antitumor effects of PARP inhibitors rely on an exploitation of the defective DNA damage repair in cancer cells with dysfunctional HR. Olaparib is a PARP inhibitor that has several approved indications for use in ovarian cancer and has demonstrated a progression-free survival (PFS) advantage in several trials. Here, we review the use of olaparib as maintenance treatment for ovarian cancer. We will summarize the evolution of its use, current approved indications, and evidence with respect to its clinical safety and efficacy. Finally, we will provide guidance on treatment decisions with olaparib for patients with ovarian cancer as well as commentary regarding ongoing research and future directions.

# Ovarian Cancer

Ovarian cancer is one of the most common cancers in women with a high mortality rate. According to Global Cancer Observatory (GCO), there were an estimated 239,000 new cases of ovarian cancer each year, which account for 152,000 deaths worldwide. In the United States, ovarian cancer occurs 11.4 per 100,000 women per year and the number of deaths was currently 7.0 per 100,000 women per year, and there were an estimated 229,875 women living with ovarian cancer (Cancer Stat Facts, NIH). The overall 5-year survival rate of all ovarian cancer is 47.6 %, while distant/late staged ovarian cancer has a 5-year survival of only 29.2 % in the US (Cancer Stat Facts, NIH). Ovarian cancer is a highly heterogenous disease, which has a few subtypes determined by tumor origination, pathogenesis, molecular alterations and prognosis. Ovarian can be grouped into three major groups: epithelial ovarian cancer, germ cell ovarian cancer, and stromal cell ovarian cancer, which are named after the type of cells that the cancer is originated. Most cases of malignant ovarian tumors (90 %) are epithelial in origin, in which serous carcinoma is the most common histotype. Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy and the fifth most lethal women's cancer in the United States. Genome instability is a hallmark of ovarian cancer, with almost half of the ovarian cancers harbor defects in one or more of the DNA repair pathways, and most of them are in HR DNA repair pathway. The high mutation rate of HR genes in ovarian cancer provided a unique opportunity for targeted therapy. The current standard care for ovarian cancer patients is debulking surgery followed by platinum-based chemotherapy. Despite high rate of initial regress of the cancer after chemotherapy, 70 %–80 % of the patients eventually experience relapse and readmitted to hospitals. When readmitted, a second round of chemotherapy with the same or modified platinum agents will be prescribed to the patient. Unfortunately, the relapsed tumors often develop resistance to the same platinum-based therapy or cross-resistant to the modified platinum agents. Even though ovarian cancer cells are initially sensitive to chemotherapeutic drugs such as platinum analogues (carboplatin or cisplatin), they become resistant to these drugs over time. Thus, alternative therapy options to platinum-based chemotherapy, such as PARP inhibitor therapy, will greatly benefit ovarian cancer patients.




Schematic representation of ovarian cancer classification into Type I and Type II tumours based on histology, clinical features, and molecular profile with commonly associated mutations. Type I tumours tend to be slow growing, less aggressive, and more likely to be diagnosed at earlier stages of disease associated with genetic stability. Type II tumours usually present with more aggressive, rapid growing disease that is diagnosed in more advanced stages, and are associated with a higher degree of genetic instability.

# Epidemiology and Risk Factors

## Epidemiology

Ovarian cancer was estimated to be the third most common cancer among Indian women and eighth overall as per the Globocan 2018 Fact sheet, constituting 3.44% (36170) of all cancer cases. It is also a leading cause of death from cancer in Indian women, with 3.34% (24015) of all cancer deaths in India in the same year. While 5-year survival from ovarian cancer is 94% when diagnosed in Stage I, only 15% of cases are diagnosed at this stage. Most (62%) of cases are diagnosed in Stages III and IV, when 5-year survival is only 28%. Advanced stage ovarian cancer has a dismal prognosis, with the highest casefatality ratio amongst all gynaecological cancers globally. The estimated age-adjusted incidence varies from 0.9 – 8.4 per 100,000 women in various populationbased cancer registries in India. The incidence of ovarian cancer increases with age. The age specific incidence rate (ASIR) increases from age 35 years and peaks between the ages of 55-64 years. Most population-based cancer registries have documented a gradual increase in the incidence of ovarian cancer over the years. Since the population prevalence is low, the specificity of any screening strategy must therefore be high in order to achieve an acceptable positive predictive value (PPV), particularly since the follow-up testing associated with screen positive results is quite invasive. Many western countries have reported a trend towards reduced incidence and mortality, which may be attributed to preventive measures like wider utilization of oral contraceptives, reduced use of postmenopausal hormone replacement therapy and increase in the risk-reduction surgeries. Many studies report ovarian cancer, fallopian tube cancer and primary peritoneal cancer as one group, though some will also identify independent sub-groups, with the latter two comprising 15-20% of cases.

## Risk Factors

According to IARC, there is sufficient evidence that epithelial ovarian cancer is caused by oestrogen hormone replacement therapy (HRT), tobacco smoking and exposure to asbestos. There is limited evidence regarding perineal use of tac-based body powder and exposure to X-radiation and gammaradiation. A long oestrogen window (early menarche and late menopause) also correlates strongly with risk of ovarian cancer. Nulliparity and older age at first childbirth (more than 35 years) confers an increased risk of developing ovarian cancer There is a strong genetic predisposition for ovarian cancer. A family history of ovarian cancer in 2 or more first-degree relatives increases risk and is also associated with an early onset disease. A personal history of breast cancer prior to 40 years of age, or a personal history of breast cancer prior to 50 years of age with a family history of breast or ovarian cancer also increase the risk. Women of Eastern European (Ashkenazi) Jew descent are a special category at high risk. Women with an inherited gene mutation have the highest risk, i.e. presence of BRCA1/BRCA2 gene mutations (associated with breastovarian cancer syndrome) or presence of a mismatch repair gene mutation associated with hereditary non-polyposis colorectal cancer (HNPCC)/ Lynch syndrome. The estimated lifetime risk of developing ovarian cancer is 26-54% in carriers of BRCA1 mutation and 10-23% in carriers of BRCA2 mutation.

However, these factors are present in only about 15% patients of ovarian cancer. Studies on other potential risk factors, such as obesity, infertility, endometriosis, sedentary lifestyle, smoking and alcohol consumption have conflicting results. Obesity is generally believed to be associated with the less aggressive types of ovarian cancer. Post-menopausal hormone therapy may actually increase the risk of ovarian cancer. Certain fertility drugs have also been implicated in the aetiology of ovarian cancer. Risk of low malignant potential ovarian cancer may be increased after ovarian stimulation for in-vitro fertilization. Recent data suggests that pelvic inflammatory disease may increase the risk of ovarian cancer . A recent meta-analysis of published studies of tubal ligation reported 60% risk reduction in the risk of high-grade serous carcinoma including the high-risk population (BRCA 1 & 2 mutation carriers) (12,13) Factors found to be protective against ovarian cancer include younger age (less than 25 years) at pregnancy and first childbirth (30-60% decreased risk of cancer), high parity, use of combined oral contraceptives for more than 5 years, and, possibly, breast feeding, hysterectomy and tubal ligation. The odds ratio for cancer of the ovary among women who use oral contraceptives for more than 5 years is 0.44-0.54. Conversely, nulliparity or older age at first pregnancy confers an increased risk of ovarian cancer. Tubal ligation reduces the risk of developing ovarian cancer by 29% overall, with the greatest risk reduction in endometrioid and clear cell histology. This risk reduction by tubal ligation has been observed in high-risk populations of BRCA1 & 2 mutation carriers.

**Table I** Factors related to ovarian cancer in the world

| Factors | | Protective | Predisposing | Controversial |
|---|---|---|---|---|
| **Demographic** | Age | | ✓ | |
| **Reproductive** | Menstrual-related factors | | ✓ | |
| | Age of menarche and menopause | | | ✓ |
| | Parity | ✓ | | |
| | Pregnancy characteristics | | | ✓ |
| | Higher age of childbirth | ✓ | | |
| **Gynecologic** | Pelvic inflammatory disease | | | ✓ |
| | Endometriosis | | ✓ | |
| **Hormonal** | Contraceptive methods | ✓ | | |
| | Hormone Replacement Therapy (HRT) | | | ✓ |
| | Infertility treatments | | | ✓ |
| **Genetic** | Family history | | ✓ | |
| | BRCA mutations | | ✓ | |
| | Lynch syndrome | | ✓ | |
| **Lifestyle** | Nutrition and Diet | | | ✓ |
| | Obesity and physical activity | | | ✓ |
| | Alcohol, caffeine and cigarettes | | | ✓ |
| **Other** | Lactation | ✓ | | |
| | Lower socioeconomic status | | ✓ | |

# Background: Homologous Recombination and PARP Inhibitors

HR is a high-fidelity DNA repair process for double-strand DNA breaks and BRCA1 and BRCA2 are key proteins required for the formation of the repair complex at the site of DNA damage. Germline or somatic mutations in the BRCA1 and BRCA2 genes results in dysfunction of their protein product, which creates genetic instability and thus a predilection of affected cells for malignant transformation. Other genetic aberrations can occur in the HR pathway including mutations in other homologous recombination genes and epigenetic changes such as inactivation of BRCA1/2 or methylation of promoters. PARP enzymes are involved in detecting single-strand DNA breaks and act as signal transducers via catalytic activity to recruit DNA repair proteins. Ultimately, PARP enzymes are released from the site of single-stranded breaks and repair ensues. PARP inhibitors are theorized to work by two potential mechanisms: 1) allowing the persistence of spontaneously occurring single-strand breaks due to a loss of enzymatic function, and 2) preventing the release of PARP from DNA (termed PARP trapping). Both mechanisms lead to persistent singlestrand breaks, collapsed replication forks, and resultant double-strand breaks. Repair of double-strand breaks can occur by either homologous recombination or nonhomologous end-joining (NHEJ). Homologous recombination repairs DNA with high-fidelity while NHEJ is an error-prone repair process that causes genetic instability. In normal cells with intact HR pathways, PARP inhibition is inconsequential given the accurate repair of double-stranded breaks with homologous recombination. In cells with BRCA1/2 mutations or other abnormalities in HR, PARP inhibition results in a process termed "synthetic lethality" whereby two mechanisms of DNA repair are functionally terminated leading to a reliance on NHEJ and subsequently, cell death. In this way, PARP inhibitors are unique in that they exploit an underlying defective process in cancer cells. PARP inhibitors are the first Food and Drug Administration (FDA)-approved therapy for ovarian cancer based on the underlying mechanism of malignancy. There are currently three PARP inhibitors FDA-approved for use in women with ovarian cancer: olaparib, rucaparib, and niraparib. Their FDA-approved indications are listed in Table 1.

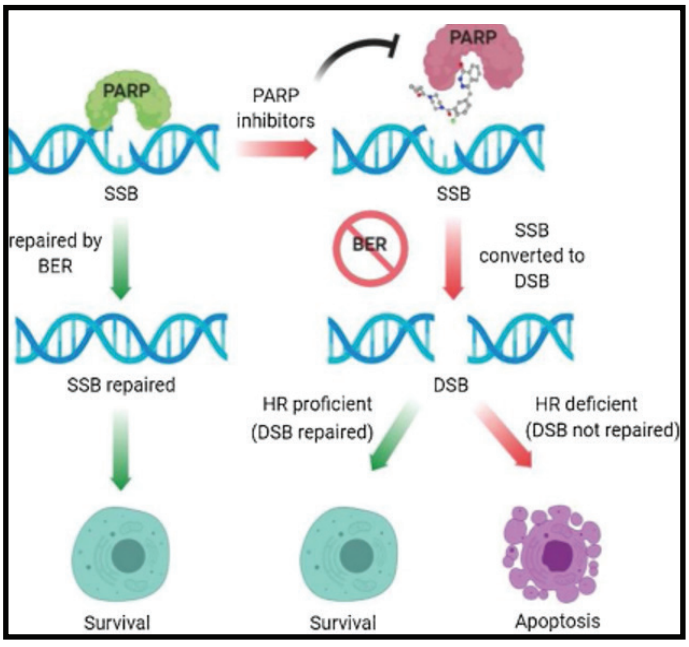



Fig. 1. The mechanism of action of PARP inhibitors. Endogenous single-strand breaks (SSB) occur frequently in proliferating cells, and SSB are repaired mostly by PARP-dependent base excision repair (BER) pathway. Efficient SSB repair is essential for the survival of cells. PARP inhibitors inhibit PARP and thus the repair of SSB by BER. The unrepaired SSB can be converted to double-strand breaks (DSB) that are toxic to cells, and homologous recombination (HR) is the major pathway to repair such lesion during cell replication. HR-proficient cells can repair DSB originated from SSB to ensure genome stability and cell survival, while HR-deficient cells that cannot repair those DSB undergo apoptosis and eventually cell death.

## The function of PARP in DNA repair

There are six major DNA repair pathways in humans, namely base excision repair (BER), nucleotide excision repair (NER), single strand break repair (SSR), homologous recombination (HR), non-homologous end joining (NHEJ), mismatch repair (MMR). Cancer cells are frequently mutated in one of their DNA repair pathways, which provided the Achilles heel of cancers for targeted therapy: In cancer cells with deficiency in one DNA repair pathway, inhibition of the second DNA repair pathway often creates a synthetical lethality. PARP is a multi-function protein that plays roles in DNA repair and genome integrity. Eighteen members have been identified in the PARP family so far, among which PARP-1 is the most important member and plays dominant roles in DNA repair pathways. It been known for a long time that PARP is critical for single strand break (SSB) repair and base excision repair (BER) pathways. The key enzymatic activity of PARP is to add ADP-ribose to substrate protein via cleavage of NAD + and release of nicotinamide. This parylation activity is activated by DNA strand breaks, which leads to addition of Par to PARP1 itself and other DNA repair enzymes; thus, PARP is critical for the recruitment of DNA repair proteins to the damage sites. The mechanism underneath the recruitment function has become a hot topic in both biology and biophysics fields. Studies show that many proteins can be recruited to DNA damage sites via PARP dependent manner, which include DNA ligase I, XRCC1 and DNA polymerase theta (POLQ). Despite its well-known function in SSR and BER, increasing evidences show that PARP can also modulate DSB repair. For instance, PARP recruits DSB repair enzymes MRE11 and NBS1, which are critical players in HR. PARP also regulate the expression of important HR genes BRCA1 and RAD51 at transcription level. A new function of PARP has been discovered in microhomology-mediated end-joining (MMEJ) of double-strand break (DSB) repair. The MMEJ pathway utilizes microhomology flanking the DSB sites and requires the trans-lesion polymerase POLQ, which is mechanistically different from the classic non-homologous end-joining (NHEJ) pathway. Both PARP1 and POLQ are required for the MMEJ pathway, and POLQ is recruited to DNA damages in a PARP-dependent manner.

# Mechanism Of Action Of Parp Inhibitors

The mechanism of action of the PARP inhibitors have been widely studied. In 2005, PARP was first reported to be synthetic lethality in BRCA mutations [25,26]. The authors proposed the idea that PARP inhibitor prevents the repair of SSB, which are subsequently converted to DSB. It was later discovered that PARP inhibitor can also trap PARP at SSB and prevent its repair. Since cells lacking BRCA1 are deficient in HR, the accumulation of DSB eventually leads to cell death via apoptosis (Fig. 1). This synthetic lethality relation has been tested to hold. However, other studies disagree with the idea that DSB converted from SSB is the causes of cell death in HR deficient cells, mainly for two reasons. First, PARPi does not increase the SSB in either wild type or BRCA-deficient cells. SSB level is normal in PARP1-/- or siRNA depleted cells without DNA damage agents. Second, DSBs are not significantly increased after PARPi treatment. Nevertheless, it is commonly accepted that PARP inhibitor suppress a second DNA repair pathway and create synthetic lethality in cancer cells with defects in homologous recombination repair. Different mechanisms of how PARPi inhibitors inhibit the enzymatic activity have been revealed, and those can be separated grossly into two groups. A PARPi can either bind to the active site of PARP and inhibit the enzymatic activity, or it can bind to the PARP-chromatin complex and such trap the enzyme in a non-effective state at chromatin, which can be tested biochemically in vitro. For example, olaparib is mostly an active site binder, while talazoparib is a much potent trapping compound. Choosing different PARPi based on their mechanism of action should be considered, using patient’s genotype as an important guide.

# The Current Status Of Parp Inhibitors In Cancer Treatment

PARP inhibitors have been wildly studied both in laboratories and in clinical trials in the past decade, and results are highly promising. In fact, the results from multiple clinical trials were so positive that it is believed that this new line of drugs will transform the trajectory of ovarian cancer treatment. As a result, three PARP inhibitors have been approved by FDA to be used in ovarian cancers, namely Olaparib (Lynparza), Rucaparib (Rubraca), Niraparib (Zejula). The clinical status of the PARP inhibitors prior to May 2018, and detailed dosing, dissociation constant, and relative trapping capacity of the PARP inhibitors have been previously reviewed by Jiang et al. A more upto-date summary of approval history, indications, clinical usage, and associated clinical studies. in this review, and we will discuss each drug in detail below. Before elaborating PARP inhibitors in clinical studies, it is important to understand that PARPi can be prescribed under two categories, for treatment or for maintenance. A treatment therapy is an initial use of the drug in an attempt to shrink the current tumor. For example, the current backbone chemotherapy treatment for ovarian cancer is platinum-based chemotherapy, and carboplatin-doxorubicin combination for recurrent ovarian cancer. Maintenance therapy is the continuation of treatment after completion of standard round of chemotherapy. It is used to avoid or slow down the return of cancers, thus it may or may not have an end-point.

# Olaparib: Mechanism Of Action, Pharmacokinectic And Other Properties

## Background

Olaparib Olaparib (Lynparza®) is an oral PARP inhibitor developed by AstraZeneca Pharmaceuticals LP. Based on available data, the standard dosing of olaparib is 300 mg tablet twice daily or 400 mg twice daily in capsule form. The primary adverse events noted in these trials include nausea, fatigue, vomiting, and anemia. A summary of grade 3–4 adverse events is provided in Table 2. Rare but serious adverse events associated with olaparib use include a risk of developing a secondary malignancy such as myelodysplastic syndrome, acute myeloid leukemia (AML), or chronic myelomonocytic leukemia (CML). Trials have shown that 30% with olaparib monotherapy in a heavily pretreated patient population. Around the same time as the initial FDAapproval for olaparib in 2014, the European Medicines Agency (EMA) approved olaparib as maintenance monotherapy for patients with platinum-sensitive relapsed (PSR) BRCA1/2-mutated high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, based on Study 19 which will be discussed in detail below. In 2017, the FDA broadened its approval of olaparib to include maintenance monotherapy for patients with platinum-sensitive recurrent ovarian cancer regardless of BRCA mutation status. The EMA followed suit shortly thereafter with an approval that matched these indications in 2018. And most recently, olaparib was approved for front-line maintenance therapy after a phase III trial (SOLO1) showed significant improvement in PFS among women with germline or somatic BRCA mutations who received olaparib maintenance therapy following platinumbased chemotherapy when compared to placebo (HR 0.30, 95% CI 0.23–0.41). In the remainder of this article, we will review evidence for current approved indications for olaparib as maintenance treatment for ovarian cancer and comment on critical ongoing trials that have the potential to expand its use in this arena. Olaparib Maintenance Monotherapy for Platinum-Sensitive Recurrent Ovarian Cancer Following the initial FDA-approval in 2014 for olaparib as monotherapy for recurrent gBRCAm ovarian cancer, several studies sought to demonstrate benefit in the maintenance setting. Study 19 and its subsequent analyses found that olaparib maintenance monotherapy significantly improved PFS in women with platinum-sensitive recurrent ovarian cancer who had received two or more platinum-based regimens and had a complete or partial response demonstrated to the most recent platinum-based chemotherapy, particularly in patients with germline and somatic BRCA mutations. In this randomized, double-blind, placebo-controlled phase II study, 256 women were enrolled including 129 in the placebo group and 136 in the olaparib group. Patients randomly assigned to the olaparib group received 400 mg twice daily (capsule formulation). Results showed a median PFS advantage of 8.4 months with olaparib versus 4.8 months with placebo (p6–12 months versus >12 months). There were 196 patients randomly assigned to receive olaparib and 99 to receive placebo. The median PFS was significantly longer for women treated with olaparib compared to placebo (19.1 months versus 5.5 months, $p<0.0001$) Secondary endpoints including time to first subsequent therapy and median time to second progression were significantly improved in the olaparib group when compared to placebo. Additionally, quality of life measures showed no appreciable difference for patients receiving olaparib compared with those receiving placebo. The most common adverse event in the olaparib group was anemia.

The rate of serious adverse events was 18% in patients receiving olaparib versus 8% in patients in the placebo group. The PFS benefit seen in SOLO2 substantially exceeded that seen in Study 19 and provided additional data confirming a manageable safety profile of olaparib. Olaparib maintenance monotherapy has also been studied after using it in combination with chemotherapy irrespective of BRCA1/2 status. In a phase II trial by Oza et al, women with platinum-sensitive recurrent high-grade serous ovarian cancer who had received up to three previous courses of platinum-based chemotherapy were randomized to receive olaparib in combination with chemotherapy followed by olaparib maintenance monotherapy versus chemotherapy alone. Patients in the combination group (n=81) received paclitaxel (175 mg/m2 on day 1) and carboplatin (AUC 4 mg/mL per min on day 1) plus olaparib (200 mg twice daily on days 1–10 of each 21-day cycle), followed by olaparib monotherapy (400 mg twice daily). Patients in the chemotherapy only group (n=75) received paclitaxel (175 mg/m2 on day 1) and carboplatin (AUC 6 mg/mL per min on day 1) and then no maintenance treatment. The combination chemotherapy and maintenance group had a significantly improved PFS compared to the chemotherapy only group, 12.2 months versus 9.6 months (p=0.0012). However, it is important to note that patients in the combination chemotherapy group had more frequent adverse events during treatment. Thus, it is not clear based on these results whether there is any benefit to adding olaparib to cytotoxic chemotherapy prior to olaparib maintenance therapy. Additional investigation would be warranted before this strategy could be recommended as standard of care. To summarize, these studies demonstrated the efficacy and safety of olaparib as maintenance monotherapy for platinum-sensitive recurrent ovarian cancer irrespective of BRCA mutation status but with a more substantial benefit in patients with BRCA-mutated ovarian cancer (see Table 3 for a summary). Study 19 and SOLO2 were the basis for the 2017 FDA approval for olaparib for platinum-sensitive relapsed ovarian cancer regardless of BRCA mutation status. Given the positive results of these studies and the progression free survival advantage olaparib conferred, new studies sought to evaluate the efficacy of olaparib as maintenance therapy in other settings such as women with newly diagnosed advanced ovarian cancer.

## Indication

Olaparib is indicated in adult patients with high-grade serous epithelial ovarian, fallopian tube and primary peritoneal cancer. The European Medicines Agency has approved olaparib for maintenance treatment of tumours that are both BRCA mutated and platinum sensitive (currently in response to last platinum therapy and ≥6-month duration of progressionfree survival after penultimate platinum therapy.

## Pharmacodynamic properties of olaparib

In vitro, olaparib inhibits PARP-1, -2, and -3 with IC50 5, 1, and 4 nM, respectively. It also has weak activity against PARP-5a (tankyrase 1 [TNKS1]) with IC50 1,500 nM (Table 1)
Similarly to other PARPis, olaparib acts through the mechanism of "synthetic lethality," as it inhibits PARP enzymes, causing the accumulation of DNA damage. In the case of HRD, this inhibition leads to apoptosis. Moreover, olaparib causes cytotoxic and pro-apoptotic PARP-DNA trapping. In pre-clinical models, these effects seemed additive or synergistic with the cytotoxicity exerted on DNA by chemotherapeutic agents, with even more contribution to DNA fragmentation and cell apoptosis than olaparib alot. Among resistance mechanisms, BRCA reversion mutations that restore the HR function are the main findings in olaparib-resistant cells.

Moreover, the occurrence of somatic mutations which restore the open reading frame of HRR genes, defects in non-homologous end-joining, increased drug efflux [e.g., with mutations of P-glycoprotein (P-gp)], or loss of 53BP1, have been found.

## Pharmacokinetic properties of olaparib

At the daily dosage of 600 mg tablets divided into two administrations (BID), olaparib's mean maximum plasma concentration (Cmax) is 7,700 ng/mL, reached in a median time (Tmax) of 1.5 h, and the half-life is 14.9 h. Olaparib is available as capsules or tablets. The two formulations are not equivalent: as evidenced by different studies, the 300 mg tablets had a 13% higher mean relative exposure at the steady state than the 400 mg capsules. In the case of 400 mg BID, Cmax is around 9,300 ng/mL, and Tmax is around 2 h (Table 1). Cytochromes P450 (CYP)3A4 and -5 mainly metabolize olaparib, forming three principal metabolites: M12 (ring opened hydroxy-cyclopropyl) M15 (mono-oxygenated), and M18 (dehydrogenated piperazine), with the potency to inhibit the growth of BRCA1-mutant cells and PARP-1 30-fold, 30-fold and 4-fold lower than olaparib, respectively. The use of potent inhibitors of CYP3A, such as clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal, and grapefruit, increases the Cmax of olaparib of 42% [90% confidence interval (CI), 33%–52%] and the median area under the curve (AUC) of 170% (90% CI, 144%–197%). Thus, co-administration is not recommended unless the dose of olaparib is reduced to 100 mg or 150 mg BID if a potent or moderate inhibitor is used, respectively. Olaparib also weakly inhibits CYP3A4 in vitro and CYP3A in vivo, thus possibly increasing the exposure to CYP3A substrates, which could be important for drugs with a narrow therapeutic window, such as simvastatin, cisapride, ciclosporin, ergotamine alkaloids, fentanyl, pimozide, sirolimus, tacrolimus e quetiapine. Furthermore, it has been demonstrated that the use of potent inducers of CYP3A, such as apalutamide, carbamazepine, enzalutamide, fosphenytoin, lumacaftor, lumacaftor-ivacaftor, mitotane, phenobarbital, phenytoin, primidone, rifampin (rifampicin) and St. John's wort might substantially decrease olaparib efficacy, reducing its median Cmax of 71% (90% CI, 76%–67%) and the median AUC of 87% (90% CI, 89%–84%); thus the co-administration should be avoided. The efficacy of hormonal contraceptives might be reduced, as olaparib slightly induces CYP1A2 and 2B6 in vitro. The liver metabolizes olaparib: after the drug administration, 44% is recovered in urine (of which 15% is unaltered, M15 representing the main metabolite) and 42% in feces (6% unaltered, M12 and M15 being among the most abundant metabolites) (Table 1)

## Olaparib in special populations

Renal and liver impairment

In patients with renal impairment, olaparib pharmacokinetic properties are altered, significantly increasing AUC and Cmax. Therefore, a higher exposure might eventually increase toxicity. In clinical studies, no relevant increase in exposure to olaparib was found in case of mild renal impairment. In the NCT01894256 phase I trial, patients received olaparib if they had normal renal function or mild to moderate renal impairment. In patients with moderate reduction of renal function, exposure to olaparib could increase up to 44%; therefore, dose adjustments (e.g., 200 mg twice daily) should be used. In case of severe renal dysfunction, without specific evidence, it is not safe to recommend olaparib.

On the contrary, hepatic dysfunction did not alter olaparib pharmacokinetics, therefore not requiring dose adjustments, except in patients with severe liver impairment, for which no dedicated studies exist; hence, olaparib should not be recommended.

Older patients

Although most OCs develop after age 65, only around 1 out of 3 patients is aged ≥65 in the major clinical trials of olaparib. In an ancillary analysis of ≥65 patients included in olaparib trials, no differences in adverse events (AEs), even those of severe grade, were detected between the older and the younger patients. The discontinuation rate of the two groups stood around 44.7%–64.7% of patients but was not significantly different between the age subgroups. We recently performed a meta-analysis, showing no differences in efficacy between older and younger patients, both with single agents and in combination with bevacizumab. Moreover, no increased risk of hematologic toxicity emerged in ≥65 women. However, only SOLO1, SOLO2, and PAOLA-1 trials published data explicitly focusing on older patients. Therefore, even if the evidence did not limit the use of full-dose olaparib in the old population, considering the high median age at diagnosis of mOC and the aging population in the next years, trials explicitly focusing on the elder age subgroups should be designed.

# Therapeutic Properties

## Therapeutic efficacy of olaparib

## Advanced BRCA mutant OC after 3 or more lines of chemotherapy

In December 2014, the FDA approved olaparib for treating women with deleterious or suspected deleterious gBRCAm advanced OC who have been previously treated with three or more lines of chemotherapy, based on the results of the phase II trial Study 42 (NCT01078662). The study treated 298 germline BRCA mutant (gBRCAm) cancers, of whom 193 (65%) had OC, with olaparib. They had received at least three lines of CHT, with 39 patients defined as platinum-sensitive (PS), 81 platinum-resistant (PRes), and 14 platinum-refractory (PRef) if the time from completion of last platinum CHT to study start was >6 months, <6 months or <2 months and progressive disease (PD) was the best response to last platinum, respectively. There was no prespecified primary endpoint, but the overall response rate (ORR) and median duration of response (mDoR) were collected first. The overall ORR was 34%. The PS subgroup reached the highest ORR (46%) while in the PRes group, ORR was 30%. The lowest ORR was reached by the PRef subgroup (14%). mPFS was 6.7 months, ranging from 5.5 to 9.4 months in the PRes and the PS groups, respectively (Table 2)

TABLE 1 Pharmacokinetics and pharmacodynamics of olaparib.

| | Dose (mg) | Cmax (ng/mL) | Tmax (h) | T1/2 (h) | IC50 (nM) | Metabolism | Cytocrome metabolism |
|---|---|---|---|---|---|---|---|
| Olaparib | 300/12 h | 7,700 | 1.5 | 11.9 | PARP1: 5, PARP2: 1, PARP3: 4, PARP5a: 1500 | Liver (42% recovered in feces), kidney (44% recovered in urine) | CYP 3A4/5 with 3 metabolites: M12 (ring opened hydroxy-cyclopropyl), M15 (mono-oxygenated), M18 (dehydrogenated piperazine) |
| | 400/12 h | 9,300 | 2 | | | | |

CYP3A4/5, cytochrome P 3A4/5; PARP1/2/3, Poly (ADP-ribose) polymerase 1/2/3.

## Olaparib as First-Line Maintenance Therapy

As olaparib maintenance therapy was found to benefit women in the setting of platinum-sensitive relapsed ovarian cancer, use in the frontline setting was investigated. SOLO1 was a phase III randomized, placebo-controlled, double-blind study that sought to evaluate the efficacy of olaparib as maintenance monotherapy in patients with high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer and a BRCA1/2 mutation (germline or somatic) who had a complete or partial response to platinum-based chemotherapy. Patients were assigned in a 2:1 ratio to receive olaparib tablets 300 mg twice daily or placebo. This study demonstrated a substantial PFS benefit with the use of olaparib maintenance therapy. The risk of disease progression or death was 70% lower with olaparib than with placebo after a median follow-up of 41 months (hazard ratio for disease progression or death, 0.28; 95% CI, 0.20 to 0.39; p<0.0001).

While the median PFS was not yet met for the olaparib group, a sensitivity analysis of investigator-assessed PFS was performed to assess for attrition bias and showed that the median PFS was approximately 36 months longer in the olaparib group compared to the placebo group. Moreover, the median PFS was 13.8 months in the placebo group, which is consistent with other studies of women with BRCA1/2 mutations with newly diagnosed advanced ovarian cancer who received only carboplatin and paclitaxel, thus indicating that the magnitude of PFS benefit is not exaggerated by the poor performance of the placebo group. Interim analysis also demonstrated favorable findings for other secondary end points. The median time to first subsequent therapy or death was 51.8 months in the olaparib group and 15.1 months in the placebo group. The estimate of the rate of freedom from the use of second subsequent therapy and from death at three years was 74% in the olaparib group and 56% in the placebo group (hazard ratio for the use of a second subsequent therapy or death, 0.45; 95% CI, 0.32 to 0.63). Measures of health-related quality of life were similar among the olaparib and placebo group. The most common adverse events that occurred during the trial intervention or up to 30 days after discontinuation included nausea, fatigue, vomiting, and anemia. Anemia was the most common serious adverse event, occurring in 7% of patients in the olaparib group compared to no patients in the placebo group. SOLO1 has provided evidence that PFS advantage can be achieved after frontline therapy particularly in women with BRCA1/2 mutated ovarian cancer. Future research will focus on confirming this benefit and demonstrating efficacy among other populations. PAOLA-1 (NCT02477644/ENGOT-ov25) is the second phase III trial evaluating the efficacy of olaparib as frontline maintenance therapy and also provides insight regarding concomitant use of olaparib with bevacizumab. Participants received first-line platinum chemotherapy plus bevacizumab and were randomized to maintenance placebo or olaparib plus maintenance bevacizumab regardless of BRCA status. Preliminary results demonstrated a median PFS of 22.1 in the olaparib and bevacizumab group versus 16.6 months in the placebo and bevacizumab group ($p<0.0001$). Of note, sub-analyses showed that the PFS benefit was only demonstrated in those with BRCA mutations or homologous recombination deficiency. Unfortunately, no trial arm evaluated olaparib maintenance therapy without bevacizumab, therefore the additional benefit of adding bevacizumab remains unclear. Ongoing Research and Future Directions Here we have provided the evidence to date supporting the use of olaparib as first-line maintenance treatment for women with BRCAm ovarian cancer as well as maintenance therapy following treatment for platinum-sensitive recurrent disease. In addition to olaparib, rucaparib and niraparib have FDA and EMA indications for use for maintenance treatment for ovarian cancer. Studies involving other PARP inhibitors including veliparib and talazoparib have shown promising clinical results and may lead to approvals in the near future (NCT01472783, NCT02470585, NCT01540565, NCT01286987). The role of olaparib in ovarian cancer continues to expand and there are many questions left to be answered about how to optimize its use. Ongoing studies are evaluating the role of olaparib as maintenance therapy in patients without germline or somatic BRCA mutations, in patients previously treated with a PARP inhibitor, in combination with other targeted therapies, and in the setting of PARP resistance. BRCA mutations result in homologous recombination deficiency (HRD) and confer sensitivity to PARP inhibition. While only about a quarter of patients with ovarian cancer have germline or somatic BRCA mutations, studies have demonstrated that approximately half have homologous recombination deficient tumors. This suggests that the population that may derive benefit from olaparib could extend beyond those with BRCA mutations. Data from Study 19 indicate there is likely a benefit, albeit less than for BRCA-mutated patients. This concept is also supported by data from the NOVA trial demonstrating a 9 month improvement in PFS with the use of niraparib as maintenance therapy after treatment for platinum-sensitive recurrent ovarian cancer in non-gBRCA patients with HRD.

Phase III studies on olaparib maintenance monotherapy in nonBRCAm patients are ongoing (OPINION/NCT03402841). The advancement of olaparib into front-line maintenance also raises questions regarding the role of subsequent PARP treatment, or the role of PARP after PARP. While trials are ongoing to assess the efficacy of a PARP after prior PARP therapy (OReO, NCT03106987), small retrospective studies have shown that some patients may experience a partial response or stable disease from repeat PARP.40 There is also great interest in the potential benefits of olaparib in combination with other targeted therapies in an effort to overcome PARP resistance and exploit opportunities for additive efficacy. Tumors with BRCA mutations or homologous recombination deficiencies exhibit significantly higher mutational and neoantigen loads and higher PD-L1 expression than BRCA1/2 wild-type or homologous recombination repair intact tumors. As such several trials are investigating the role of checkpoint inhibitors in combination with PARP inhibitors. DUO-O (NCT03737643) is an actively-recruiting phase III trial evaluating durvalumab (an anti-PD-L1 antibody) in combination with chemotherapy and bevacizumab followed by maintenance durvalumab, bevacizumab and olaparib. While not a study of olaparib maintenance therapy, MEDIOLA is a phase I/II trial investigating durvalumab in combination with olaparib in a platinum-sensitive BRCAm population (NCT02734004). Emerging clinical data will help establish the efficacy of combination therapy with olaparib and immune check point inhibitors in women with and without BRCA or homologous recombination deficiencies. The combination of olaparib and anti-angiogenesis therapy is also being explored. It has been theorized that hypoxia leads to downregulation of homologous recombination repair genes. As previously discussed, results from PAOLA-1 demonstrated a PFS benefit in women who received olaparib and bevacizumab for frontline maintenance as compared to those who received placebo and bevacizumab. Given that no arm evaluated olaparib maintenance therapy without bevacizumab, its contribution to the PFS benefit is unclear. ICON9 (NCT03278717) is actively recruiting and aims to compare olaparib maintenance treatment with and without cediranib in platinum-sensitive relapsed ovarian cancer. Table 4 lists the active phase III trials utilizing olaparib maintenance therapy. While no phase III trials are directly evaluating the role of PARP inhibitors in platinum-resistant disease, early studies show there may still be a role for PARP treatment in this population. A dose-escalation phase 1b study of alpelisib (a PI3K inhibitor) and olaparib demonstrated that among 28 women with epithelial ovarian cancer, 82% of whom had platinum-resistant disease, 36% had a partial response (median 5.5 months) and 50% had stable disease. It should be noted that this was not the primary endpoint of the study. However, these results indicate that the applications of PARP inhibitors, especially in combination with other targeted therapies, may play an important role in an even broader cohort of patients with ovarian cancer. Ongoing Phase II studies including ROLANDO and BAROCCO (NCT03161132, NCT03314740) are investigating the role of combination therapies in platinum-resistant ovarian cancer with olaparib and pegylated liposomal doxorubicin and olaparib, paclitaxel, and cediranib, respecitvely. Future studies could focus on maintenance treatment in this group. Increased utilization of PARP inhibitors portends a need to better understand PARP inhibitor resistance. The most widely accepted mechanism of PARP inhibitor resistance is the restoration of BRCA function or HR activity via secondary mutations. Therefore, many strategies for overcoming or preventing PARP inhibitor resistance focus on therapies that downregulate BRCA function or increase the degree of HR deficiencyIt is likely that studies on the horizon will continue to evaluate targeted and combination therapies that increase tumor sensitivity to PARP inhibition. Additionally, efforts to understand characteristics and mechanisms involved in patients with durable responses to olaparib are also underway and will likely provide valuable information (OLALA/NCT02489058).

# Summary Points

1. The advent of PARP inhibitors is an unprecedented advancement in the treatment of women with ovarian cancer.

2. Current FDA approved indications for olaparib use include maintenance for BRCA-mutated ovarian cancer in both the recurrent and front-line setting, as well as for treatment of gBRCAm ovarian cancer in patients who have received multiple prior lines of chemotherapy.

3. With the publication of the results from SOLO1 and SOLO2, the role of olaparib maintenance therapy for women with gBRCAm has been solidified.

4. Importantly, olaparib is the only PARP inhibitor FDA approved for front-line maintenance therapy in BRCA-mutated patients. Ongoing studies will further delineate the role of olaparib in ovarian cancer and likely expand indications for use

# Figures

**Table 1** PARP Inhibitor FDA Indications for Ovarian Cancer

| Drug Name | FDA Indications |
|---|---|
| Olaparib | 1. Maintenance treatment in germline or somatic *BRCA*-mutated epithelial ovarian cancer with complete or partial response to first-line platinum-based chemotherapy<br>2. Maintenance treatment for recurrent epithelial ovarian cancer with complete or partial response to platinum-based chemotherapy<br>3. Treatment of germline *BRCA*-mutated advanced ovarian cancer with three or more prior lines of chemotherapy |
| Rucaparib | 1. Maintenance treatment for recurrent epithelial ovarian cancer with complete or partial response to platinum-based chemotherapy<br>2. Treatment of germline or somatic *BRCA*-mutated epithelial ovarian cancer with two or more prior lines of chemotherapy |
| Niraparib | 1. Maintenance treatment for recurrent epithelial ovarian cancer with complete or partial response to platinum-based chemotherapy<br>2. Treatment of advanced ovarian cancer treated with three or more prior lines of chemotherapy whose cancer is associated with homologous recombination deficiency positive status |

**Note:** All indications are for epithelial ovarian cancer, fallopian tube, and primary peritoneal cancer.

**Table 2** Percentage of Patients Experiencing G3-4 Toxicities in Phase III Studies of Olaparib

| | Olaparib | Placebo |
|---|---|---|
| Anemia | 20–22 | 2 |
| Neutropenia | 5–9 | 4–5 |
| Fatigue | 4 | 2 |
| Nausea/Vomiting | 1–6 | 1 |
| Diarrhea | 2–3 | 0 |
| Thrombocytopenia | 1 | 1–2 |
| Abdominal Pain | 0–2 | 0–1 |

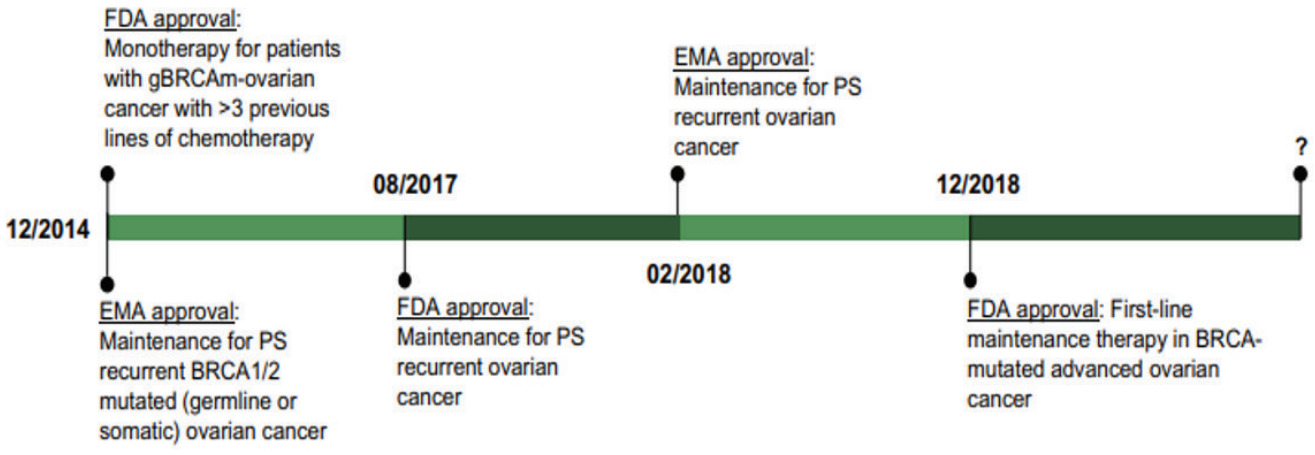



**Figure 1** Olaparib timeline of approval.

**Table 3** Published Trials Evaluating Olaparib Maintenance Therapy

| | Study Clinical Trial Phase Year | BRCA Status | Olaparib Use | Design Drug/Dose | Median Progression Free Survival (Olaparib versus Placebo) | Median Overall Survival (Olaparib versus Placebo) |
|---|---|---|---|---|---|---|
| PSR | Study 19[19] Phase II 2012 | *BRCA* mutation not required | Maintenance monotherapy | Randomized, double-blind Olaparib capsule 400 mg orally twice daily | 8.4 versus 4.8 months ($p< 0.001$) | 29.7 versus 29.9 months, NS |
| PSR | Study 19 retrospective interim analysis[20] 2014 | Germline or somatic *BRCA1/2* mutation | Maintenance monotherapy | Randomized, double-blind Olaparib capsule 400 mg orally twice daily | BRCAm: 11.2 versus 4.3 months ($p< 0.001$); BRCAwt: 7.4 versus 5.5 months, ($p=0.0075$) | Overall: 29.8 versus 27.8 months; BRCAm: 34.9 versus 30.2 months; BRCAwt: 24.5 versus 26.6 months. Did not meet the required threshold for statistical significance of $p<0.0095$ (71% maturity) |
| PSR | Oza et al[37] Phase II 2015 | *BRCA* mutation not required | Combination with chemotherapy then maintenance monotherapy | Randomized, open-label Olaparib capsule 200 mg orally twice daily on days 1–10 of chemotherapy cycle, then olaparib capsule 400 mg orally twice daily | 12.2 versus 9.6 months ($p< 0.0012$) | 33.8 versus 37.6 months, NS |
| PSR | SOLO2[22] Phase III 2017 | Germline or somatic *BRCA1/2* mutation | Maintenance monotherapy | Randomized, double-blind Olaparib tablet 300 mg orally twice daily | 19.1 versus 5.5 months ($p< 0.0001$) | Medians not reached, 23% of patients experienced event versus 27%, NS (24% maturity) |
| Front-line maintenance | SOLO1[21] Phase III 2018 | Germline or somatic *BRCA1/2* mutation | Maintenance monotherapy | Randomized, double-blind Olaparib tablet 300 mg twice daily | 70% lower risk of disease progression or death with olaparib compared to placebo | Rate of freedom from death at 3 years was 84% versus 80%, NS (21% maturity) |

**Table 4** Active Phase III Clinical Trials Utilizing Olaparib as Maintenance Therapy

| NCT Number | Trial Name | Phase | Purpose | Status | Sites |
|---|---|---|---|---|---|
| NCT03106987 | OReO: A Study to Examine Olaparib Maintenance Retreatment in Patients With Epithelial Ovarian Cancer | IIIb | Olaparib maintenance re-treatment in BRCA1/2 + and - patients | Active, recruiting | Belgium, Canada, Denmark, France, Spain, Germany, Israel, Italy, Norway, Poland, Spain, United Kingdom |
| NCT03278717 | ICON9: Study Evaluating the Efficacy of Maintenance Olaparib and Cediranib or Olaparib Alone in Ovarian Cancer Patients | III | Olaparib maintenance treatment ± cediranib in platinum-sensitive relapsed ovarian cancer | Active, recruiting | Australia, United Kingdom |
| NCT03737643 | DUO-O: Durvalumab Treatment in Combination With Chemotherapy and Bevacizumab, Followed by Maintenance Durvalumab, Bevacizumab and Olaparib Treatment in Advanced Ovarian Cancer Patients | III | Durvalumab in combination with standard of care platinum based chemotherapy and bevacizumab followed by maintenance durvalumab and bevacizumab or durvalumab, bevacizumab and olaparib in patients with newly diagnosed advanced ovarian cancer | Active, recruiting | United States (Florida, Georgia, Illinois, Maryland, New York, Ohio, Oklahoma, Pennsylvania, Utah), Austria, Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, Hungary, Italy, Japan, Korea, Poland, Romania, Spain, Turkey |
| NCT03740165 | MK-7339-001/KEYLYNK-001/ENGOT-ov43: Study of Chemotherapy With Pembrolizumab (MK-3475) Followed by Maintenance With Olaparib (MK-7339) for the First-Line Treatment of Women With BRCA Non-mutated Advanced Epithelial Ovarian Cancer | III | Carboplatin/paclitaxel + pembrolizumab and maintenance olaparib in women with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. | Active, recruiting | Belgium, Canada, Chile, Colombia, Czechia, France, Hungary, Israel, Italy, Japan, Korea, Poland, Russian Federation, South Africa, Spain, Taiwan, Turkey, Ukraine |
| NCT03402841 | OPINION: Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed Non gBRCAm Ovarian Cancer Patients | III | Olaparib maintenance in patients with non-BRCAm PSR HGSOC | Active, not recruiting | |
| NCT03534453 | L-MOCA: An Open Label, Single Arm, Multicentre Study to Assess the Clinical Efficacy and Safety of Lynparza (Olaparib) Tablets Maintenance Monotherapy in Platinum Sensitive Relapsed Ovarian Cancer Patients Who Are in Complete or Partial Response Following Platinum Based Chemotherapy | III | Olaparib maintenance in patients with PSR high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer | Active, not recruiting | |
| NCT02477644 | PAOLA-1: Randomized, Double-Blind, Phase III Trial Olaparib vs Placebo Patients With Advanced FIGO Stage IIIB-IV High Grade Serious or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer Treated Standard First-Line Treatment | III | Olaparib + bevacizumab as front-line maintenance therapy after first-line platinum-based + bevacizumab chemotherapy irrespective of *BRCA* status | Active, not recruiting | |

## Clinical Pearls

Normal cells, however, have a good pathway (the homologous recombination pathway) to repair double strand breaks. Some types of tumor cells have a deficiency in this homologous recombination pathway. Robertson said the best example of this phenomenon is the deficiencies that can occur in BRCA1 and BRCA2.

- Olaparib is a PARP inhibitor
- Inhibiting PARP causes cumulative DNA damage and cell death
- Some types of tumor cells have a deficiency in the homologous recombination pathway

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