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AN OVERVIEW OF PARP INHIBITORS IN BRCA 1/2 MUTATED OVARIAN CANCER

DR. DHARITRI G JOSHI[1], DR. G.L. PRABHUSHANKAR[2]

[1]Assistant Professor, Department of Pharmacy Practice, Bapuji Pharmacy College, Davangere

[2] Professor, HOD of Department of Pharmacy Practice, Bapuji Pharmacy College, Davangere

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Abstract:

Ovarian cancer being asymptomatic is leading to late diagnosis resulting in increased death rate worldwide. The development of platinum resistant ovarian cancer, research has paved the way for new class of drug called PARP inhibitors. PARP inhibitors [Poly (ADP-Ribose) polymerase inhibitors] are used in epithelial cell carcinoma, platinum resistant ovarian cancer, recurrent ovarian cancer etc. They act by inhibiting PARP proteins that are involved in DNA repair, finally resulting in cell death. Olaparib, Niraparib, Rucaparib, Talazoparib and Veliparib are the members that belong to the family of PARP inhibitors. These drugs vary in their route of administration, dose, toxicity profile, efficacy and pharmacokinetic parameters. This class of drugs majorly exhibits haematological and gastrointestinal adverse reactions. Most of these drugs causes Myelodysplastic syndrome/ Acute Myeloid Leukaemia and Embryo-foetal toxicity. These classes of drugs are contraindicated in lactating women, also these drugs shows wide changes in various laboratory parameters. Pharmacist plays a major role in monitoring the patient's laboratory values, thereby modifying the dose of the drug in toxicities. The main role of a clinical pharmacist is dose adjustment in renal and hepatic impairment patients. It is also hypothesized that, these drugs exhibit resistance through the efflux of drug by p-gp transporters. Another concern with this class of drugs is development of secondary malignancy. This review summarizes the characteristics and uses of various drugs that belongs to PARP inhibitors.

KEYWORDS: *Ovarian cancer, Epithelial cell carcinoma, PARP Inhibitors, Olaparib, Niraparib, Rucaparib.*

Corresponding author:

Dr.Dharitri G Joshi,

Assistant Professor,

Department of Pharmacy Practice,

Bapuji Pharmacy College,

Davangere-577004.

Email ID- dharitrijoshi96@gmail.com

Mobile Number- 8762742916, 7019157136.

QR code

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INTRODUCTION:

Epithelial Ovarian Cancer (EOC) is considered as the 18th leading cause of mortality worldwide. The high mortality rate is due to its asymptomatic nature, resulting in the delayed diagnosis of the disease or the diagnosis of the disease occurs in advance stage.[1] The 5-year survival of ovarian cancer is 94% when diagnosed in the early stage - Stage I, where only 15% of cases are diagnosed at this stage. Majority (62%) of cases are diagnosed in Stages III and IV. [2] By the end of 2020, India reported an estimate of 59,276 new ovarian cancer cases. By 2035, the annual incidence of ovarian cancer is expected to rise by 55% to 371,000 cases, with a death rate of 67 percent to 254,000 cases. [3] On the basis of tissue origin, ovarian cancer is categorized by World Health Organization (WHO) as: Epithelial surface tumour (65%), ovarian germ cell (15%), sex cord tumour (10%), metastatic ovarian tumour (5%), and miscellaneous ovarian tumour (5%).[4] The utmost incidence of ovarian cancer have various subtypes, namely, transitional (1%), mucinous (3%), mixed (6%), endometrioid (7–11%), clear cell (12–13%), and serous (68–71%).[5]

The predisposing factors for ovarian cancer are women of age group between 50-60 years, Obesity, Early menarche and late menopause, polycystic ovarian syndrome (PCOS), Pelvic Inflammatory Disease (PID), Endometriosis, Lynch Syndrome, Tubal ligation, smoking and alcohol consumption. Women who are on Hormonal therapy are also at greater risk of developing ovarian cancer. [4] Majority of ovarian cancers are due to genetic mutations of BRCA1 and BRCA2. These genes are typical and normal, they help to prevent cancer by producing proteins that protects the cells from abnormal multiplication. BRCA1 and BRCA2 genes act as tumour suppressor genes, mutations of these results in the increased risk of breast/ ovarian cancer. It is estimated that the chances of developing ovarian cancer is between 35% to 70% with BRCA1 mutation. [6] Debulking cytoreductive surgery followed by chemotherapy using platinum agents (paclitaxel and carboplatin) still remains the first line treatment for ovarian cancer. [7] The combination of paclitaxel (as a 3-hour infusion at 175 mg/m2) and carboplatin (dosed to AUC of 5 to 6 over 1 hour), administered once every 3 weeks for a total of 6 cycles, is the standard first line adjuvant chemotherapy regimen in advanced stage ovarian cancer.[8] Recently, the treatment alternatives that has been proposed for ovarian cancer is the neoadjuvant chemotherapy (NAC))with antiangiogenic agent like Bevacizumab with interval debulking surgery (IDS).[7] The latter one is not accepted as there is no sufficient evidence available.

PARP INHIBITORS

Genome instability is one of the attributing factors for ovarian cancer, more than half of the ovarian cancer shows defects in one or more of the DNA repair pathways and most of them are in Homologous Recombination DNA repair pathway.[29, 30]High mutation of HR genes in ovarian cancer has provided a unique opportunity for targeted therapy like PARP inhibitors. The present treatment options of debulking surgery followed by chemotherapy by using platinum containing compounds has shown high relapse rates of tumours. Unfortunately, the tumours of relapsed cases are likely to show resistance to the same platinum-based therapy or cross-resistant to the modified platinum agents. Even though the ovarian cancer cells are initially sensitive to chemotherapeutic drugs such as platinum analogues (carboplatin or cisplatin), they develop resistance to these drugs over time. [31] Thus, alternative therapeutic options such as PARP inhibitor therapy, will be beneficial in ovarian cancer patients.

PARP inhibitors are small molecules which are taken orally and showed promising responses towards the platinum resistant ovarian cancers. [10] The management of ovarian cancer has been added with PPAR [Poly (ADP-Ribose) polymerase inhibitors] by US-FDA, as the relapse rates are high. [9] PARP inhibitors, namely Olaparib and Niraparib, have recently become a standard of care for patients with recurrent BRCA-mutated ovarian cancer. [11] Currently, Niraparib, Olaparib and Rucaparib have been approved by the US –FDA and EMA for the treatment of ovarian cancer. [12-14]

List of Parp Inhibitors with their Indications and Dose: [15-23]

Drug	Approval	Agency	Indications	Clinical Setting	Dosing
Olaparib Capsule	December 2014	EMA, FDA	Platinum-sensitive relapsed OC, Advanced OC	Maintenance	400mg BID
Olaparib tablet	August 2017	FDA	Recurrent OC	Maintenance	300 mg BID
Rucaparib	December 2016 May 2018	FDA EMA	Advanced OC, Recurrent OC Platinum-sensitive relapsed OC	Third line	600 mg BID
Niraparib	March 2017 November 2017	FDA EMA	Recurrent OC Platinum-sensitive relapsed OC	Maintenance	300 mg BID
Veliparib	-	-	-	-	300 mg BID
Talazoparib	2018	FDA	Germline BRCA1/2 mutations, HER2 negative metastatic breast cancer patients	Maintenance	1.0 mg QD

The FDA granted an accelerated approval to Olaparib in 2014 for the treatment of ovarian cancer associated with specific *BRCA* genes. Olaparib was approved for maintenance therapy for recurrent, platinum-sensitive disease based on 2 clinical trials by FDA in 2017. Also, Niraparib was approved in 2017 for maintenance treatment of patients with recurrent ovarian cancer, regardless of *BRCA* status. [24- 26] In 2016, FDA approved Rucaparib which is indicated as both the third-line treatment for BRCA1/2 mutation-associated ovarian cancer and also for the maintenance treatment for recurrent ovarian cancer; whereas Niraparib is indicated only as the maintenance treatment for recurrent ovarian cancer. [10] The US-FDA has also approved Talazoparib in 2018, for the treatment of germline BRCA1/2 mutations, HER2 negative metastatic cancer patients.

MECHANISM OF ACTION OF PARP INHIBITORS

The PARP proteins contains two ribose and two phosphates moieties per unit polymer. Specifically, PARP1 and PARP2 are the enzymes that are involved in a DNA repair pathway for SSBs called BER. [27]The six major DNA repair pathways in humans are namely base excision repair (BER), single strand break repair (SSR), nucleotide excision repair (NER), non-homologous end joining (NHEJ), homologous recombination (HR), mismatch repair (MMR).[28]

The function of PARP in DNA repair: In cancer cells, the deficiency in one DNA repair pathway leads to inhibition of the second DNA repair pathway often leading to synthetic lethality [32, 33]. BRCA genes code for DNA repair enzymes that do not require the PARP pathway to function. Because both pathways to repair DNA are inhibited in cells with BRCA mutations, PARP inhibitors cause cell cycle arrest and apoptosis particularly in cells that has BRCA mutations.[63]PARP is a multi-function protein that is present in all the proliferating cells, that has a major role in DNA repair and genome integrity. There are currently eighteen members of the PARP family, with PARP-1 being the most essential and playing a key part in DNA repair pathways. PARP is known as an important protein that is meant for single strand break (SSB) repair and base excision repair (BER).[34] The main 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 plays a major role in recruitment of DNA repair protein at the damage sites. Therefore PARP inhibitors inhibit PARP proteins that are involved in DNA repair, thereby preventing the repair of SSB by BER. [35]As the DNA repairing is not done apoptosis of cell occurs, eventually leading to cell death.

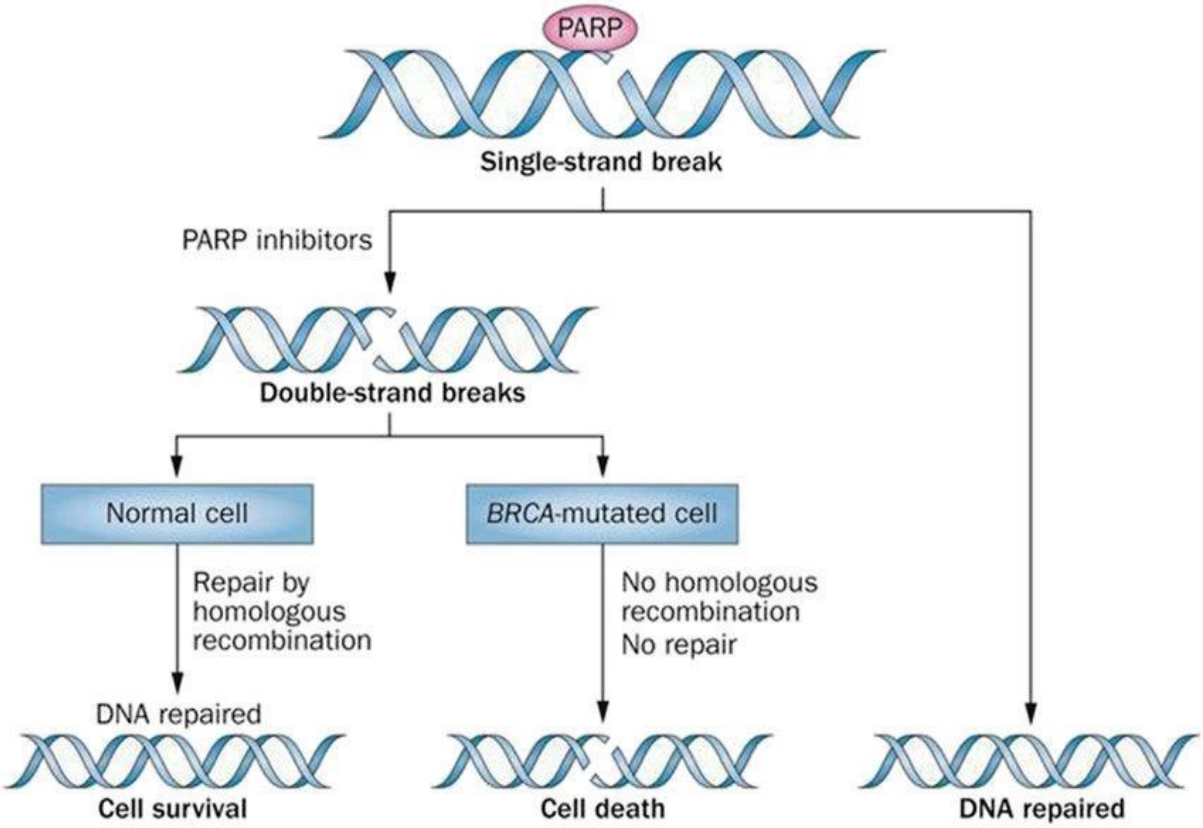

Image Courtesy: Adapted from Sonnenblick A et al. An update on PARP inhibitors-moving to the adjuvant setting. Nat Rev Clin Oncol. 2015 Jan; 12(1):27-41.Written permission has been given by Springer Nature. License number: 4381210949123.

Figure 1: Mechanism of action of PARP inhibitors and synthetic lethality: The proliferating cells will have frequent endogenous single-strand breaks (SSB), these SSB are repaired mostly by PARP-dependent base excision repair (BER) pathway. For the survival of a cell, these SSB have to be repaired. PARP inhibitors thus inhibit PARP proteins that are involved in DNA repair, thereby preventing the repair of SSB by BER. The unrepaired SSB will be converted to double-strand breaks (DSB) that are toxic to cells. The major pathway to repair lesions during cell replication is homologous recombination (HR). The cells which has efficient homologous recombination (HR) can repair DSB originated from SSB to maintain genome stability and cell survival, while the cells which are HR-deficient cannot repair those DSB undergo apoptosis and eventually cell death.[35]

The effect of PARP inhibitors on immune cells is mostly due to the immune system's response to dying cancer cells, and this immune response is partly mediated by a series of transcriptional factors and chemokines. The IFN-γ that is released by STING/TBK1/IRF3 signalling is a typical immune response that is induced by PARP inhibitors.[69] Nuclear Factor-κB (NF-κB) is known as an essential coactivator for PARP-1,studies has also shown that PARP-1 could interact with the NF-κB subunits, ultimately formatting the transcription complex, and influence NF-κB–dependent gene expression, that was independent of the enzymatic activity of PARP 1.[70,71] The studies also suggested that PARPs also regulated a series of cytokines, such as Th1 cytokines (interleukin [IL]-2, IFN-γ), Th2 cytokines(IL-4, IL-5, IL-10), transforming growth factor-β (TGF-β) and the chemokines CXCL10, CCL5, CCL4, and CCL9.[65-68] Therefore, the PARP inhibitors has shown notable antitumor efficacy in BRCA1/2 mutant tumours, specifically through catalytic inhibition- induced synthetic lethality and PARP trapping.[72,73]

DRUG PROFILE OF VARIOUS TYPES OF PARP INHIBITORS:

Olaparib [LYNPARZA®] – Approved by US-FDA and EMA. It is available as a tablet and capsule. The recommended dose of Olaparib tablet is 300 mg

taken orally twice daily with or without food. The available dose of Olaparib capsule is 400mg.

Indications: Ovarian cancer and Breast Cancer
Olaparib is used in the maintenance treatment of recurrent epithelial ovarian cancer, fallopian tube cancer and primary peritoneal cancer. It is also beneficial in patients who show complete or partial response to platinum-based chemotherapy. Olaparib is used to patients who have had three or more courses of chemotherapy and have deleterious or suspected harmful germline BRCA-mutated (gBRCAm) advanced ovarian cancer.

Pharmacokinetics: The absorption of Olaparib is quick and attains peak concentration after 1 -3 hours that ranges between 4.7 and 9.1 mcg/ml. The AUC of Olaparib after a dose of 200 mg is of 25.8 mcg h/L. The volume of distribution was 40.3 L.The plasma protein binding of Olaparib was found to be 82%. [37]Olaparib is extensively metabolized in the liver by the action of CYP3A isoenzymes. [38] The Half-life of Olaparib varies from 5-11 hours. The total clearance of Olaparib was reported to be 4.6 L/h. 70% of Olaparib is excreted unchanged form through urine and faeces.

Niraparib [ZEJULA®] – Approved by US-FDA. The PRIMA trials of Niraparib for maintenance therapy showed a progression free period of 6 months.[57]The available dose of Niraparib capsule is 100mg taken once daily with or without food.

Indications: Ovarian cancer & Primary Peritoneal Cancer
Ovarian cancer- Niraparib is used in the maintenance treatment of patients with recurrent epithelial ovarian cancer, fallopian tube cancer and primary peritoneal cancer. It is also believed to be responsive in patients with complete or partial response to platinum-based chemotherapy. [39]

Pharmacokinetics: Following oral administration, Niraparib can attain peak concentration within 3 hours. The AUC of Olaparib after a dose of 200 mg is of 25.8 mcg h/L. The volume of distribution was 40.3 L. Niraparib is 83% plasma-protein bound. [40] The average apparent volume of distribution of Niraparib was found to be 1074 L. Metabolism of Niraparib is carried out primarily by carboxylesterases (CEs) to form a major inactive metabolite, which subsequently undergoes glucuronidation. After multiple doses, the half -life is found to be 36 hours. The apparent total clearance is 16.2 L/hr in cancer patients. [41]

Rucaparib [Rubraca®] - It is approved by US-FDA. Available as a tablet of 200 mg, 250 mg and 300mg. The recommended dose of Rucaparib is 600 mg orally twice daily with or without food.

Indications - Ovarian cancer & Peritoneal Cancer
- Rucaparib is primarily used in the maintenance therapy of patients with recurrent epithelial ovarian cancer, as well as patients with cancers caused by the deleterious BRCA mutation, fallopian tube cancer, and primary peritoneal cancer who have received two or more chemotherapies. Patients who have also showed complete or partial response to platinum-based chemotherapy can also be treated with Rucaparib. [42,78]

Pharmacokinetics- The peak concentration of Rucaparib was attained after 1-2 hours and the absorption was found to be increased after a fat meal. The average apparent volume of distribution of Rucaparib was 113 L to 262 L after a single intravenous dose of 12 mg to 40 mg. The plasma protein binding of Rucaparib was found to be 70%. Rucaparib is metabolized in the liver by the action of CYP2D6, also to a lesser extent by CYP1A2 and CYP3A4. The Half-life of Olaparib varies from 17-19 hours. The total clearance of Olaparib was reported to range between 13.9- 18.4 L/h. [14, 20]

Talazoparib [Talzenna®] - Talazoparib is approved by US-FDA in the year 2018. The dose of Talazoparib is available as 1 mg capsule. The recommended dose is 1 mg, which is to be taken as a single dose, with or without food. In case of abnormal variations of laboratory parameters, the dose of the drug can be reduced to 0.25 mg per day.

Indications-Talazoparib is indicated for the treatment of patients with suspected deleterious germline BRCA-mutated (gBRCAm) and deleterious HER-2 negative locally advanced or metastatic breast cancer.

Pharmacokinetics- After oral administration, peak concentration of Talazoparib was attained between 1-2 hours and the presence of high –fat, high-calorie meal leads to decrease in absorption. The average apparent V_d of Talazoparib is 420 L. The plasma protein binding of Talazoparib is 74%. Talazoparib undergoes minimal hepatic metabolism. It is mostly metabolised by mono-oxidation, dehydrogenation, cysteine conjugation of mono-desfluoro-Talazoparib, and glucuronide conjugation. Large fraction of drug is excreted through urine. [49]

ADVERSE REACTIONS OF PARP INHIBITORS: PARP Inhibitors have varying degrees of toxicities. However, the severity of adverse reactions will depend upon the interaction and binding affinities to the sites of various PARP enzymes. [43, 45]

Hematologic: PARP inhibitors are known to exhibit hematologic toxicities, which occur shortly after treatment initiation and recover in a few months. [45]Anaemia is a common hematologic toxicity with all three PARP inhibitors; however, Niraparib maintenance therapy had the highest incidence (50%) followed by Olaparib (44%), and Rucaparib (37%). Severe grade of (grade 3 and 4) anaemia was also more prevalent with Niraparib (25%), followed by Rucaparib (19%) and Olaparib (19%). It is assumed that anaemia occurs as a result of PARP2 inhibition of erythrogenesis. [45]

Another haematological disorder is neutropenia that is associated with PARP inhibitors, ranging from 18% to 30%. Niraparib having the severe (grade 3 and 4) neutropenia (20%), followed by Rucaparib (7%) and Olaparib (5%). [45] The increase in the potency of PARP inhibition is thought to increase myelosuppression in patients. [45] Thrombocytopenia is another hematologic AE of PARP inhibitors. The incidence is greater with Niraparib (61%), 28% with Rucaparib and 14% with Olaparib. The severity of thrombocytopenia, is higher with Niraparib (34%) compared with Rucaparib (5%) and Olaparib (1%). [45]

It is recommended to perform complete blood count (CBC) prior to initiating therapy with a PARP inhibitor. [45] The FDA recommends patients undergo a weekly CBC in the first month of treatment, as the incidence of hematologic toxicities are higher with Niraparib. Thereafter it is recommended for monthly investigation, in the first year of treatment. [45, 46] It is recommended to monitor CBC monthly for Rucaparib and Olaparib while on therapy. [18-20]

Gastrointestinal: The occurrence of GI adverse reactions is nausea, which occurs in 74% to 76% of patients on PARP inhibitors. The other common AEs associated with the use of PARP inhibitors are constipation, vomiting, and diarrhoea are other common AEs (20%-40%). Dyspepsia and dysgeusia occur more frequently with Rucaparib compared with the other PARP inhibitors.[45]

Other AEs: The other common adverse reaction associated with PARP inhibitors is fatigue, which occurs in 59% to 69% of patients. Serum creatinine can also be elevated with the use of Rucaparib and Olaparib. Niraparib is not associated with any renal dysfunction.[45] Upper respiratory tract infection is common with Olaparib and Rucaparib. Hypertension, headache, rash, dyspnoea, cough, dizziness, acute kidney injury, urinary tract infection and hypomagnesemia occurs with Niraparib. [18, 20, 21] Notable adverse reactions of Talazoparib are fatigue, anaemia, nausea, neutropenia, headache, thrombocytopenia, vomiting, alopecia, diarrhoea, decreased appetite. [49]

ABNORMAL LABORATORY PARAMETERS: The noted laboratory abnormalities with Olaparib were decrease in haemoglobin, increase in mean corpuscular volume, decrease in lymphocytes, leukocytes, absolute neutrophil count and platelets. Olaparib also causes elevation in serum creatinine levels. [51]Niraparib can cause a decrease in haemoglobin, decrease in neutrophil count, and decrease in Leukocyte count and a reduction in magnesium levels in the body. [52] Rucaparib causes an increase in creatinine, increase in ALT, increase in AST, increase in alkaline phosphatase, decrease in haemoglobin, increase in cholesterol, decrease in platelets, leukocytes, lymphocytes and neutrophils. Monitoring of Liver function test and dosage adjustment in liver failure patients is recommended with the use of Rucaparib. [53]Talazoparib causes reduction in haemoglobin, platelets, neutrophils, lymphocytes, leukocytes, and calcium. Talazoparib is known to increase in the blood glucose and few liver enzymes like alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. [49]

WARNINGS/ PRECAUTIONS OF PARP INHIBITORS: Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) can occur in patients receiving Olaparib, Niraparib and Rucaparib. Embryo -fetal toxicity is common with Olaparib, Niraparib, Talazoparib and Rucaparib. Patients using Olaparib can encounter pneumonitis. Niraparib can cause bone marrow suppression, Posterior Reversible Encephalopathy Syndrome (PRES). BP and Heart rate after 2 weeks of starting Niraparib. [50] Talazoparib can cause Myelodysplastic syndrome (MDS) and Myelosuppression. [49]

DRUG- DRUG INTERACTIONS: Olaparib- Strong CYP3A4 inhibitors such as Itraconazole, Telithromycin, Clarithromycin, Ketoconazole, Voriconazole, Nefazodone, Posaconazole, Ritonavir, Lopinavir/Ritonavir, Indinavir, Saquinavir, Nelfinavir, Boceprevir, Telaprevir and moderate CYP3A4 inhibitors like Aprepitant ,Amprenavir, Ciprofloxacin, Atazanavir, Crizotinib,

Darunavir/Ritonavir, Diltiazem, Erythromycin, Fluconazole, Fosamprenavir, Imatinib, Verapamil should be avoided for concomitant use. These CYP3A4 inhibitors can increase the plasma concentration of Olaparib. In case the strong CYP3A4 inhibitors are to be used, the dose of Olaparib can be reduced, to prevent its toxicity.

On the other hand, the concomitant use of strong CYP3A4 inducers such as Phenytoin, Rifampicin, Carbamazepine, and St. John's Wort or moderate CYP3A4 inducers such as Bosentan, Efavirenz, Etravirine, Modafinil, and Nafcillin results in decreased efficacy of Olaparib. [47]**Rucaparib-** Avoid concomitant administration of Caffeine, Midazolam, Warfarin, Omeprazole and Digoxin. Consider monitoring the International normalized ratio (INR) when warfarin is administered. [48]**Niraparib-** No known interactions. **Talazoparib-** P-gp inhibitors and BCRP inhibitors must be avoided. In case of concomitant administration the dose of P-gp inhibitors should be reduced. Clarithromycin, Itraconazole, Amiodarone, Carvedilol, Verapamil, Gefitinib and Imatinib has known interactions with Talazoparib. [49]

DRUG –FOOD INTERACTION: Olaparib- Grapefruit, grapefruit juice, Seville oranges, and Seville orange juice have the potency to inhibit CYP3A4 enzymes, therefore these should be avoided during Olaparib treatment. [47]

CONTRAINDICATIONS: PARP Inhibitors are contraindicated in Pregnancy and Lactating women.

RESISTANCE TO PARP INHIBITORS: PARP inhibitors has also developed resistance. The deficiency of BRCA may be reversed by causing change in the mutational reading frame, ultimately resulting in the production of wildtype of BRCA protein. These changes can result in secondary mutation, compensatory mutations or crossovers. [54] This explanation tells why all BRCA mutation tumours respond to PARP inhibitors. [56] Therefore it becomes necessary to check for restoration of the HR in patients with BRCA mutation associated tumours. Single agent PARP inhibitor might not be a suitable choice to treat such patients. Another proposed mechanism is regarding the upregulation of the p-glycoprotein efflux pump reducing intracellular PARP inhibitor concentrations. [55]

ROLE OF PHARMACIST: The pharmacist should work as a clinical team member to monitor and treat the adverse reactions which might require dose adjustments of PARP inhibitors, based on laboratory values or by assessing the tolerance by the patient. Patients with renal dysfunction may require dose reduction for Olaparib and Talazoparib (creatinine clearance below 50 mL/min). On the other hand, dose reductions is not necessary for Niraparib and Rucaparib in renal dysfunction. Also no dose-reduction is required for any of the four PARP inhibitors in hepatic dysfunction. However, in case of mild hepatic dysfunction, Olaparib requires close monitoring. [18]

Other than dose adjustments, patient counselling regarding adherence to treatment is an important aspect in cancer patients for the success of the treatment. Educating the patient to take the missed dose at the time of next dose. It is important to instruct patient that the vomited doses should not be replaced. In concern with Olaparib educating the patient to avoid grapefruit, grapefruit juice, orange, orange juice is of utmost importance.

FUTURE OF PARP INHIBITORS: PARP inhibitors being one of the new class of agents that has shown efficacy for BRCA related, high grade serous ovarian cancer and also BRCA mutation breast cancer. The current research is going on to identify specific biomarkers of the tumours that are more likely to respond to PARP inhibitors and also for screening for resistance to PARP inhibitors. The PARP inhibitor that is under investigation is Veliparib, which has been tested & evaluated to treat patients with BRCA1/2 mutated recurrent epithelial ovarian cancer and primary peritoneal cancer. Phase II trial has shown promising response that has made the researchers to investigate further on Veliparib. Presently, many phase II and III trials are going on to evaluate this agent (Veliparib) in various tumour types, including gynaecologic malignancies. Antiangiogenic agents like bevacizumab are also being combined with PARP inhibitors. The AVANOVA trial is assessing the efficacy of Niraparib in combination with bevacizumab in women with platinum-sensitive ovarian cancer. [45]

Another perspective of therapy is combining PARP inhibitors with immunotherapy. A phase II trial of Olaparib in combination with Durvalumab had shown a promising results in patients with platinum-sensitive, recurrent ovarian cancer, with the majority of patients (63%) showing a complete or partial response (n = 34). [57] The phase II trial also showed that the patients achieved 62% partial response or stable disease looking at Niraparib in combination with pembrolizumab in the platinum-resistant setting (n = 29).[58]

Few recently approved PARP inhibitors have moved into the frontline maintenance based on recent phase III trials of PAOLA-1/ENGOT-OV25, SOLO-1, PRIMA/ENGOT-OV26, and VELIA/GOG-3005. [44] The VELIA trial tested Veliparib, combining chemotherapy with a PARP inhibitor in addition to the use of a PARP inhibitor as maintenance therapy. The trial arm was placebo with carboplatin/paclitaxel followed by placebo as maintenance. The second arm was Veliparib with carboplatin/paclitaxel followed by placebo. The third arm was Veliparib with carboplatin/paclitaxel followed by Veliparib maintenance. The result showed an increase in PFS in patients receiving a PARP inhibitor throughout. The median PFS was 23.5 months for Veliparib throughout when compared to the treatment with carboplatin and paclitaxel followed by placebo showed a survival free period (SFP) for 17.3 months. [58] As a result of all the trials, it was found that patients with BRCA mutations were most benefitted in these trials.[59] The Maintenance treatment with PARP inhibitors is currently able to delay the disease progression with manageable toxicity but not clear about its impact on the efficacy of subsequent therapies.[64]

As, this class of drug belongs to neoadjuvant chemotherapy, the probability of development of secondary malignancy is a concern. [60] PARP on the whole plays a major role in monitoring DNA mutations. [61] Secondary malignancy can occur as a result of long-term inhibition of PARP leading to continual inability to repair a normal process similar to a BRCA mutation. [62] The risk of developing a secondary malignancy can be assessed over the next few years. Overall, this class of drug has shown the most promising response towards the treatment of BRCA1/2 mutated metastasis.

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ABBREVIATIONS:

PARP – Poly (ADP-Ribose) polymerase inhibitors
EOC- Epithelial ovarian cancer
OC- Ovarian Cancer
WHO-World Health Organization
FDA- Food and Drug Administration
EMA- European Medicine Agency
SSB- Single Strand Break
DSB-Double Strand Break
BER- Base Excision Repair
NER- Nucleotide Excision Repair
SSR- Single strand break repair
HR- Homologous recombination
NHEJ-Non- homologous end joining
MMR-Mismatch repair
PCOS- Polycystic Ovarian syndrome
PID- Pelvic Inflammatory Disease
NAC-Neo Adjuvant Chemotherapy
IDS- Interval debulking surgery
gBRCAm- germline BRCA mutated
HRD- Homologous recombination deficiency
PRES- Posterior Reversible Encephalopathy Syndrome
CE's- Carboxylesterases
INR- International Normalized Ratio
MDS- Myelodysplastic Syndrome
PFS- Progression Free Survival
NF-κB - Nuclear Factor- κB
IL-2- Interleukin-2
IFN-γ- Interferon-γ
STING- Stimulator of interferon genes
TBK1- TANK binding kinase 1
IRF3- IFN regulatory factor 3
TGF-β- Transforming growth factor- β
CXCL10- Motif Chemokine ligand 10
CCL5- Motif Chemokine ligand 5
CCL4- Motif Chemokine ligand 4
CCL9-Motif Chemokine ligand 9

REFERENCES:

1. Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: epidemiology and risk factors. Int J Womens Health. 2019; 11: 287-99.
2. Danforth KN, Im TM, Whitlock EP. Addendum to screening of ovarian cancer: Evidence update Evidence Update for the US Preventive Services Task Force Reaffirmation Recommendation Statement. . Rockville, MD: AHRQ Publication No. 12-05165-EF4; 2012.
3. Shabir S, Gill PK. Global scenario on ovarian cancer – Its dynamics, relative survival, treatment, and epidemiology. Adesh Univ J Med Sci Res.2020;2(1):17-25.
4. Lima MA, Dos Santos L, Turri JA, Nonogaki S, Buim M, Lima JF, *et al*. Prognostic value of ADAMTS proteases and their substrates in epithelial ovarian cancer. Pathobiology.2016; 83:316-26.
5. Torpy JM, Burke AE, Golub RM. Ovarian cancer. J Am Med Assoc.2011; 305:2484-4.
6. Lefkowitz ES, Garland CF. Sunlight, Vitamin D, and ovarian cancer mortality rates in US women. Int J Epidemiol.1994; 23:1133-6.
7. Medina-Franco H, Mejía-Fernández L. Neoadjuvant chemotherapy and interval debulking surgery for advanced ovarian cancer, an alternative with multiple advantages. Chin Clin Oncol. 2018;7(6):57–.

8. Bhargav B. Consensus document for management of epithelial ovarian cancer. New Delhi: Division of Publication and Information on behalf of the Secretary DHR & DG, ICMR; 2019.
9. Bahena-González A, Toledo-Leyva A, Gallardo-Rincón D. PARP inhibitors in ovarian cancer: evidence for maintenance and treatment strategies. *Chin Clin Oncol*. 2020; 9(4):51-.
10. Jiang X, Li W, Li X, Bai H, Zhang Z . Current status and future prospects of PARP inhibitor clinical trials in ovarian cancer. *Cancer Manage and Res*.2019;11:4371–90.
11. Cortez JA, Tudrej P, Kujawa KA, Lisowska KM. Advances in Ovarian Cancer Therapy. Cancer Chemother. Pharmacol . 2018; 81:17-38. doi:https://doi.org/10.1007/s00280-017-3501-8.
12. Deeks ED. Olaparib: first global approval. Drugs. 2015; 75:231–40. doi:10.1007/s40265-015-0345-6.
13. Scott LJ. Niraparib: first global approval. Drugs. 2017; 77:1029–34. doi:10.1007/s40265-017-0752-y.
14. Syed YY. Rucaparib: first global approval. Drugs. 2017; 77:585–92. doi:10.1007/s40265-017-0716-2.
15. Lynparza 50 mg hard capsules [Internet]. EU summary of product characteristics. Astrazeneca; 2014 [cited 2021 Jul 15]. Available from: https://www.ema.europa.eu/documents/product-information/lynparza-epar productinformation_en.pdf
16. Lynparza (Olaparib) capsules, for oral use [Internet].US prescribing information. AstraZeneca Pharmaceuticals LP; 2014 [cited 2021 Jul 15] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206162s011lbl.pdf .
17. Lynparza (Olaparib) tablets, for oral use [Internet].FDA approved Olaparib tablets for maintenance treatment in ovarian cancer. AstraZeneca Pharmaceuticals LP; 2014[cited 2021 Jul 15] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s005lbl.pdf .
18. Lynparza 100 mg and 150 mg tablet [Internet]. EU CHMP post-authorisation summary of positive opinion for lynparza. AstraZeneca AB; 2018[cited 2021 Jul 15] Available from: https://www.ema.europa.eu/documents/smop/chmppost-authorisation-summary-positive-opinion-lynparza_en.pdf
19. Lynparza (Olaparib) tablets, for oral use [Internet]. US prescribing information. AstraZeneca Pharmaceuticals LP; 2018 [cited 2021 Jul 15]Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s006lbl.pdf.
20. Prescribing information for rubraca (Rucaparib) tablets, for oral use [Internet]. Clovis Oncology Inc; 2016[cited 2021 Jul 15] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209115s003lbl.pdf
21. Rubraca tablet [Internet]. EU CHMP summary of positive opinion for rubraca. Clovis Oncology Inc; 2018[cited 2021 Jul 15] Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/rubraca
22. Zejula(Niraparib)[Internet]: US prescribing information. Tesaro; 2017[cited 2021 Jul 15] Available from:https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208447lbl.pdf
23. Zejula 100 mg hard capsules [Internet]: EU summary of product characteristics.Tesaro; 2017[cited 2021 Jul 15]. Available from: https://www.ema.europa.eu/documents/product-information/zejula-epar-product-information_en.pdf .
24. Kaufman B, Shapira-Frommer R, Schmutzler RK et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol*. 2015; 33:244-50.
25. Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012; 366:1382-92.
26. Mirza MR, Monk BJ, Herrstedt J et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med*. 2016; 375:2154-64.
27. Rouleau M, Patel A, Hendzel MJ et al. PARP inhibition: PARP1 and beyond [J]. Nat Rev Cancer. 2010; 10(4):293-301.
28. Sancar A, Lindsey-Boltz L, Ünsal-Kaçmaz K, Linn S. Molecular Mechanisms of Mammalian DNA Repair and the DNA Damage Checkpoints. Annu Rev Biochem. 2004; 73(1):39-85.
29. Integrated genomic analyses of ovarian carcinoma. Nature.2011; 474(7353):609-615.
30. Bast R, Hennessy B, Mills G. The biology of ovarian cancer: new opportunities for translation. Nat Rev Canc. 2009;9(6):415-28.
31. Pignata S, Cannella L, Leopardo D, Pisano C, Bruni-Salvatore G, Facchini G. Chemotherapy in epithelial ovarian cancer.Cancer Lett.2011; 303(2):73–83.
32. Curtin JN. DNA repair dysregulation from cancer driver to therapeutic target, Nat Rev Cancer.2012; 12(12):801-17.

33. Brown J, O'Carrigan B, Jackson S, Yap T. Targeting DNA Repair in Cancer: Beyond PARP Inhibitors. Cancer Discovery. 2016; 7(1):20-37.
34. Liu C, Vyas A, Kassab M, Singh A, Yu X. The role of poly ADP-ribosylation in the first wave of DNA damage response. Nucleic Acid Res. 2017; 45(14):8129-41.
35. Sonnenblick A, Azambuja ED , Azim HA, Piccart M. An update on PARP inhibitors – moving to adjuvant setting. Nat Rev Clin Oncol. 2015; 12(1):27-41
36. Lynparza (Olaparib). Product Monograph including patient medication information. [Internet]. Mississauga, Ontario: AstraZeneca Canada Inc; 2021 [cited 18 July 2021]. Available from: https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/lynparza-tablets-product-monograph-en.pdf.
37. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza M et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. New Engl J of Med. 2019; 381(25):2391-402.DOI: 10.1056/NEJMoa1910962.
38. Antolin A, Ameratunga M, Banerji U, Clarke P, Workman P, Al-Lazikani B. The kinase polypharmacology landscape of clinical PARP inhibitors. Sci Rep.2020; 10: 2585. https://doi.org/10.1038/s41598-020-59074-4.
39. Van Andel, L., Rosing, H., Zhang, Z. *et al.* Determination of the absolute oral bioavailability of Niraparib by simultaneous administration of a 14C-microtracer and therapeutic dose in cancer patients. *Cancer Chemother Pharmacol*.2018; 81:39–46. https://doi.org/10.1007/s00280-017-3455-x
40. Drew Y, Kristeleit RS, Oaknin A, Ray-Coquard I, Haris NM, Swisher EM. Real-World Delivery of Rucaparib to Patients with Ovarian Cancer: Recommendations Based on an Integrated Safety Analysis of ARIEL2 and Study 10. *Oncologist*. 2020; 25(1):109-19. doi:10.1634/theoncologist.2019-0229.
41. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. *Science*. 2017; 355(6330):1152-58.
42. Mirza MR, Pignata S, Ledermann JA. Latest clinical evidence and further development of PARP inhibitors in ovarian cancer. *Ann Oncol*. 2018; 29(6):1366-76.
43. LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. *Lancet Oncol*. 2019; 20(1):15-28.
44. Zejula (Niraparib) [Internet]: Package insert. Waltham, MA: Tesaro; 2017[cited 2021 Jul 19]. Available from:https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf
45. Pilla Reddy V, Bui K, Scarfe G, Zhou D, Learoyd M. Physiologically Based Pharmacokinetic Modeling for Olaparib Dosing Recommendations: Bridging Formulations, Drug Interactions, and Patient Populations. *Clin Pharmacol Ther*. 2019; 105(1):229-241. doi:10.1002/cpt.1103.
46. Xiao JJ, Nowak D, Ramlau R, et al. Evaluation of Drug-Drug Interactions of Rucaparib and CYP1A2, CYP2C9, CYP2C19, CYP3A, and P-gp Substrates in Patients With an Advanced Solid Tumor. *Clin Transl Sci*. 2019;12(1):58-65. doi:10.1111/cts.12600.
47. Talzenna (Talaoparib) capsules for oral use [Internet]: Prescribing information. New York: Pfizer Inc; 2018[cited 2021 Jul 20].
48. O'Cearbhaill RE. Using PARP Inhibitors in Advanced Ovarian Cancer. *Oncology (Williston Park)*. 2018; 32(7):339-43.
49. Moore KN, Monk BJ. Patient counseling and management of symptoms during Olaparib therapy for recurrent ovarian cancer. *Oncologist*. 2016;21(8):954-63. doi:10.1634/theoncologist.2015-0268.
50. Patibandla NS, Monga DK. Niraparib - A promising drug with hematological toxicity. J Oncol Pharm Pract. 2019 Oct;25(7):1749-1753. doi: 10.1177/1078155218800156. Epub 2018 Oct 6. PMID: 30293481.
51. Coleman, Robert L et al. "Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial." *Lancet (London, England)* vol. 390, 10106 (2017): 1949-61. doi:10.1016/S0140-6736(17)32440-6.
52. Sakai W, Swisher EM, Karlan BY, et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2 mutated cancers. Nature.2008; 451(7182):1116-20.
53. Rottenberg S, Jaspers JE, Kersbergen A, et al. High sensitivity of BRCA1- deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum durgs [J]. PROC Natl Acad Sci USA, 2008,105(44):17079-84.
54. Chen A. PARP inhibitors: its role in treatment of cancer. Chin J Cancer.2011;30(7):460-71.
55. Drew Y, De Jonge M, Hong S-H, et al. 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). *Gynecol Oncol*. 2018; 149(1):246-47.
56. Konstantinopoulos PA, Munster P, Forero-Torez, et al. TOPACIO: preliminary activity and safety (pts) in patients with platinum-resistant ovarian cancer (PROC) in a phase 1/2 study of niraparib in combination with pembrolizumab. *J Clin Oncol*. 2018; 36(15 suppl):106-106.
57. PARP Inhibitors as Initial Treatment for Ovarian Cancer [Internet]. National Cancer Institute. 2021 [cited 28 July 2021]. Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2019/parp-inhibitors-ovarian-cancer-initial-treatment
58. Coleman RL, Fleming GF, Brady MF, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med.2019; 381: 2403–15.
59. K D, Armstrong. Use of PARP inhibitors for ovarian cancer. J Natl Compr Canc Netw. 2021; 19(5.5):636–8. doi: 10.6004/jnccn.2021.5013.
60. Nizialek E, Antonarakis ES. PARP inhibitors in metastatic prostate cancer:Evidence to date. Canc Mang Res. 2020;12: 8105-7.
61. Jang A, Sartor O, Barata P, Paller C. Therapeutic Potential of PARP Inhibitors in the Treatment of Metastatic Castration-Resistant Prostate Cancer. Cancers. 2020;12(11):3467.
62. Javle M, Curtin NJ. The role of PARP in DNA repair and its therapeutic exploitation. Br J Cancer. 2011; 105(8):1114-22.
63. Wiggans AJ, Cass GKS, Bryant A, Lawrie TA, Morrison J. Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer. *Cochrane Database of Systematic Reviews*.2015 [cited 28 July 2021], Issue 5. Art. No.: CD007929. Accessed from:https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007929.pub3/full
64. To C, Kim E, Royce D, Williams C, Collins R, Risingsong R et al. The PARP Inhibitors, Veliparib and Olaparib, Are Effective Chemopreventive Agents for Delaying Mammary Tumor Development in BRCA1-deficient Mice. Cancer Prev Res. 2014;7(7):698-707.
65. Nero C, Ciccarone F, Pietragalla A, Duranti S, Daniele G, Salutari V et al. Ovarian cancer treatments strategy: Focus on PARP inhibitors and immune check point inhibitors. *Cancers*. 2021; 13(6):1298.
66. Olabisi OA, Soto-Nieves N, Nieves E, et al. Regulation of transcription factor.NFAT by ADP-ribosylation. *Mol Cell Biol*. 2008;28:2860-71.
67. Ghonim MA, Pyakurel K, Ibba SV, et al. PARP inhibition by olaparib or gene knockout blocks asthma-like manifestation in mice by modulating CD4(+) T cell function. *J Transl Med*. 2015;13: 225.
68. Rosado MM, Bennici E, Novelli F, Pioli C. Beyond DNA repair, the immunological role of PARP-1 and its siblings. *Immunology*. 2013;139: 428-37.
69. Mulligan AM, Raitman I, Feeley L, et al. Tumoral lymphocytic infiltration and expression of the chemokine CXCL10 in breast cancers from the Ontario Familial Breast Cancer Registry. *Clin Cancer Res*. 2013;19: 336-46.
70. Xue C, Xu Y, Ye W, et al. Expression of PD-L1 in ovarian cancer and its synergistic antitumor effect with PARP inhibitor. *Gynecol Oncol*. 2020; 157: 222-33.
71. Zerfaoui M, Errami Y, Naura AS, et al. Poly(ADP-ribose) polymerase-1 is a determining factor in Crm1-mediated nuclear export and retention of p65 NF kappa-B upon TLR4 stimulation. *J Immunol*. 2010; 185: 1894-902.
72. Hassa PO, Covic M, Hasan S, Imhof R, Hottiger MO. The enzymatic and DNA binding activity of PARP-1 are not required for NF-kappa B coactivator function. *J Biol Chem*. 2001; 276:45588-97.
73. Lord CJ, Tutt AN, Ashworth A. Synthetic lethality and cancer therapy: lessons learned from the development of PARP inhibitors. *Annu Rev Med*. 2015; 66:455-70.
74. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res*. 2012; 72:5588-99.
75. Paradiso A, Andreopoulou E, Conte P, Eniu A, Saghatchian M. PARP Inhibitors in Breast Cancer: Why, How, and When?. Breast Care. 2018; 13(3):216-219.
76. Wu Z, Cui P, Tao H, Zhang S, Ma J, Liu Z et al. The Synergistic Effect of PARP Inhibitors and Immune Checkpoint Inhibitors. Clinical Medicine Insights: Oncology. 2021;15:117955492199628.
77. Nolan E, Savas P, Policheni AN, Darcy PK, Vaillant F, et al. Combined immune checkpoint blockade as a therapeutic strategy for BRCA1-mutated breast cancer. Sci Transl Med 2017;9:eaal4922.
78. Gien L, Mackay H. The Emerging Role of PARP Inhibitors in the Treatment of Epithelial Ovarian Cancer. J of Oncol. 2010; 2010:1-6.
79. Audebert M, et al. Involvement of poly (ADPribose) polymerase-1 and XRCC1/DNA ligase III in an alternative route for DNA double-

strand breaks rejoining. *J Biol Chem*.2004; 279(53):55117–126.
80. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oza AM, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet.2017;390: 1949-61.
81. Usmani H, Hussain SA, Sheikh A. PARP inhibitors: current status and implications for anticancer therapeutics. *Infe ag and canc*.2013:8:46.
82. Grewal K, Grewal K, Tabbar I. PARP Inhibitors in Prostate Cancer. Anticanc Res. 2021; 41(2):551-6.
83. Xie H, Wang W, Xia B, Jin W, Lou G. Therapeutic applications of PARP inhibitors in ovarian cancer. Biomed Pharmacother. 2020; 127:110204.