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Targeting BRCA: A Review of Olaparib's Efficacy and Safety

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ABSTRACT: -

Olaparib is a PARP (Poly-ADP Ribose Polymerase) Inhibitor. It is mainly used for the treatment of certain types of cancers. Olaparib is sold under the brand name Lynparza. In this article, we had explained about pharmacological and pharmacokinetic effect of Olaparib.

KEYWORDS: - Olaparib, Lynparza, PARP, Cancer.

Discovery and further history of drug Olaparib:-

PARP inhibitors are the group of biological enzymes which are responsible for transferring ADP-ribose to the target proteins. (1) PARP inhibitors are widely responsible for replication, recombination, transcription processes etc. They are been used from decades for the treatment of various types of cancers. (2) The most common PARP inhibitors used for inhibition of various types of cancerous cells is Olaparib. (3) Olaparib was firstly synthesized from small molecule of PARP inhibitor for treatment of BRCA-mutated (Breast Cancer gene) germline and ovarian cancer. Apart from many advantages of Olaparib, there are also some dis advantage of Olaparib such as, low solubility in aqueous and lipophilic solution, poor pharmacokinetics and Bioavailability. (4)(5)

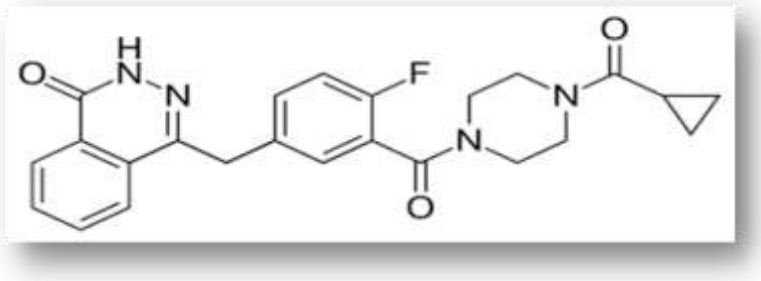
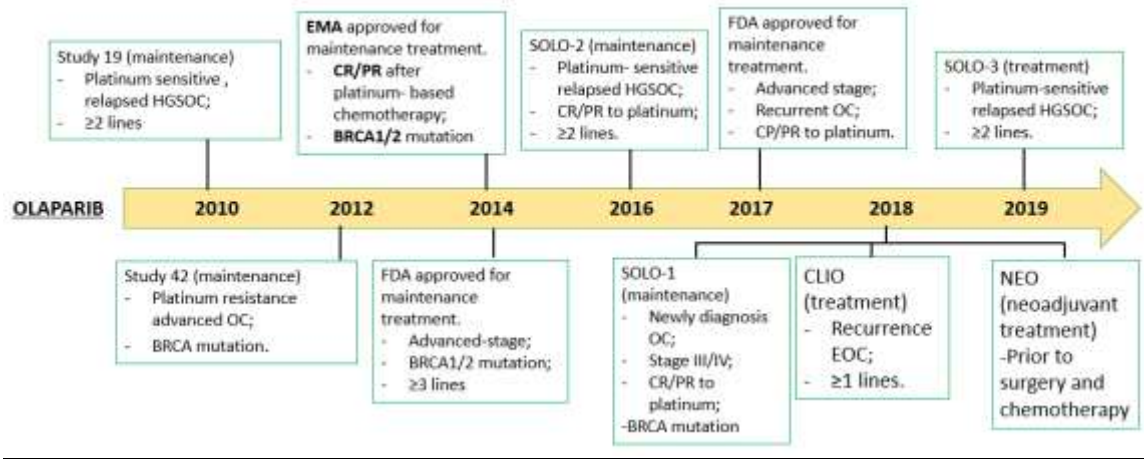


Figure.1. represents FDA approved PARP inhibitors utilized for the treatment of cancer.

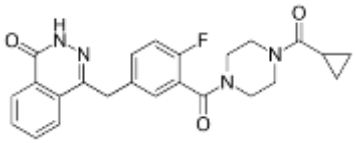
In order to improve the aqueous and lipo-solubility of Olaparib, structural modifications were made in the SAR (Structural Activity relationship) of Olaparib. The carbonyl group present into the Olaparib was reduced to Ch2. Substitution of cycloalkane formyl in piperazine causes increase in the potency and inhibitory activity of Olaparib. Swapping out of carbonyl group with methylene group between piperazine and phenyl ring it decreases the potency of PARP inhibitor. Potentially important factors that affect the potency of inhibitory enzymes include the binding of inhibitors to the active site of receptors. In order to determine the structural components that influence PARP1 inhibitory activity, the crystal structure of Olaparib in the active site of PARP1 was examined. (6)

Olaparib was developed and first dosed into patients by the UK-based biotechnology company, Kudos Pharmaceuticals that was founded by Stephen Jackson of Cambridge University, UK. (7) On 19th December 2014, FDA approves Olaparib as Lynparza for the treatment of ovarian cancer. (8) Professor Thomas Helleday, an a researcher in Sheffield resulted in development of new drug called as Lynparza (Olaparib) used by women's for certain types of cancers such as ovarian, fallopian, breast, etc.(9) In India, Olaparib is manufactured in headquarters of Hyderabad in Dr. Reddy's Laboratories. This laboratory is one of the leading global manufacturers and suppliers of Olaparib API (Active Pharmaceutical Ingredients). (10) In 2020, an adjuvant setting of Olaparib for the patients with BRCA-mutated was discovered.

Flow chart of history of drug Olaparib. (38)



Physiochemical Properties:-

Sr. no.	Physiochemical property	Value
1	Molecular formula	$C_{24}H_{23}FN_4O_3$
2	Molecular weight	434.46 g/mol
3	Chemical structure	
4	Solubility	Olaparib is sparingly soluble in water, but it exhibits good solubility in organic solvents such as dimethyl sulfoxide (DMSO) and ethanol.
5	Melting point	193-195 °C
6	Partition coefficient	octanol-water partition coefficient (Log P = 1.55)
7	UV spectrum	A 5 µL sample volume was administered, ultraviolet (UV) spectra ranging from 210 nm to 400 nm were recorded between 0 and 14 min, and the Olaparib monitoring wavelength was adjusted to 254 nm.[11]
8	IR spectrum	Olaparib compromise absorption peaks at 1.5 cm-1. [12]

Pharmacokinetic Properties:-

Sr. No.	Pharmacokinetic property	Inference
1	Biopharmaceutical classification system	It is a non-hydrolytic compound with a very poor solubility for aqueous solvents, and is categorised as Class 4 under the Biopharmaceutical classification system.
2	C-max	Following a single 300 mg tablet dose, the geometric average AUC and geometric average C max for Olaparib were 42.0 µg*h/mL and 5.8 µg/mL respectively (n = 204). Following 300 mg tablets twice daily, the geometric average geometric mean AUC (at steady state) and geometric mean C max (at baseline) were 49.0 µg*h/mL and 7.7 µg/mL, respectively (n = 227).

3	T-max	Olaparib at a 300 mg dose demonstrated a time-maximized plasma concentration of 1.5 hours.
4	T half	Olaparib was administered at a dose of 300 mg and the mean (±SDA) terminal plasma elimination half-life was 14.9 ±8.2 hand apparent plasma concentrations were 7.4 ±3.9 l/h after a single dose.
5	Absorption	absorption after oral administration Median peak plasma concentrations are typically reached 1.5 h after oral administration AUC average accumulation ratio (AUC) at steady state is 1.8 after multiple oral doses of 300mg tablets twice daily Single dose AUC increases approximately proportional with doses over 25mg to 450mg C-max increases slightly less than proportional with the same dose range
6	Distribution	The apparent volume of distribution for Olaparib following a single 300 mg dose was 158 ± 136 L (± standard deviation). Olaparib protein binding in vitro was approximately 82%.
7	Metabolism	Olaparib's Phase I metabolism was primarily mediated by the cytochrome P450 oxidase (CYP) family of enzymes, with the dominant metabolic enzymes being (CYP3A4 and (3A5). The major metabolic pathways were oxidation and hydroxylation, and many products underwent multiple metabolic transformations. Some minor products resulted from the Phase II metabolism of pre-existing Phase I products.[13]
8	Excretion	After a single 300mg dose, the mean terminal half-life in plasma is 14.9–8.2 hours, and apparent plasma concentrations are 7.4–3.9 liters/h. After a single dose, 86–88% of the dose is recovered within 7 days of collection, 44–42% via urine and 42–48% via feces, and most of the material is eliminated as metabolites.

Mechanism of working:-

Poly (ADP-ribose) polymerase (PARP) enzymes, such as PARP1, PARP2, and PARP3, are inhibited by Olaparib. Normal bodily functions which involve DNA transcription and DNA repair need PARP enzymes. DNA single-strand breaks (SSBs) are normally repaired by an error-free method involving poly (ADP-ribose) polymerase (PARP). Double strand breaks (DSBs) can happen during DNA replication when SSBs are present. These are preferentially repaired via homologous recombination, which is usually thought of as an error-free repair mechanism but which, according to recent research, may also be mutagenic. Olaparib prevents the PARP-mediated error-free repair of SSB, which causes synthetic lethality in cancer cells linked with the BRCA gene. As a result, DNA is repaired through more error-prone repair mechanisms, such as single-strand annealing and non-homologous end joining.

Large quantities of DNA damage, such as those caused by the use of genotoxic chemicals, exceed these alternative repair pathways. This leads to the accumulation of DSBs, damaged DNA, and ultimately cell death. [14] [15].

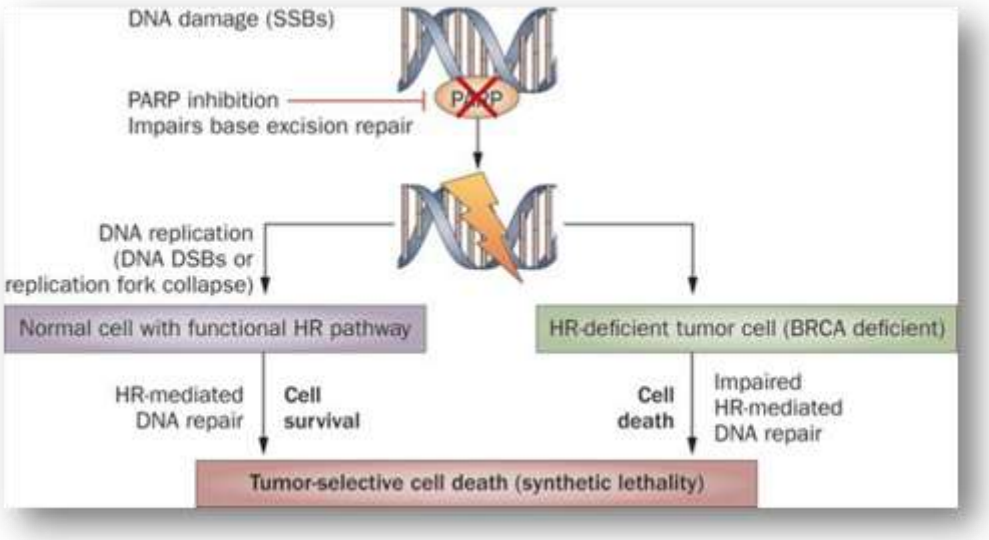
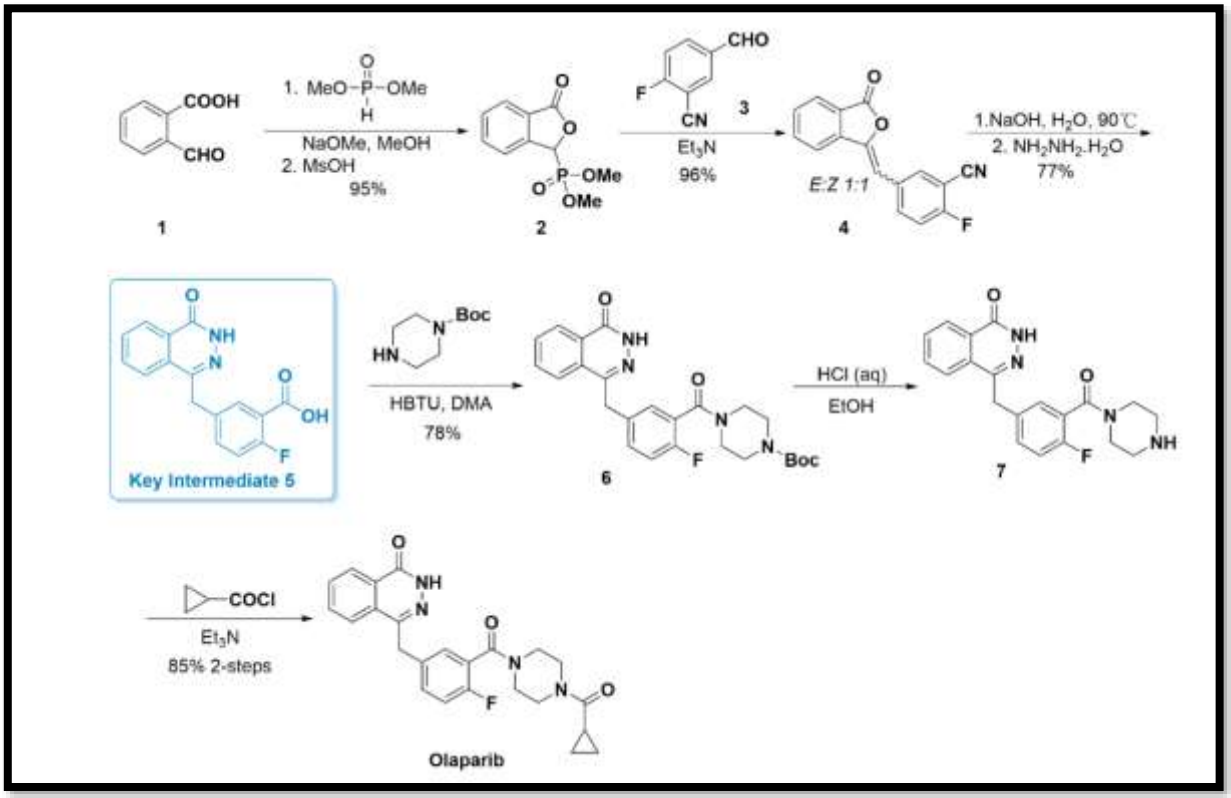


Figure.1 represents the effect of PARP inhibitor (Olaparib) in ovarian cancer by inhibiting the growth of cancerous cells. (26)

Method of synthesis:-



Olaparib's initial medicinal chemistry process involved six steps and a 46% yield {16}. First, 2-formylbenzoic acid (1) and dimethyl phosphite were used to produce phosphonate (2), which was subsequently produced in a Horner-Wadsworth-Emmons reaction with aldehyde (3) to create olefin (4) (E:Z = 1:1) in a 96% yield. In the same reaction system, compound (4) was hydrolysed to acid under alkaline conditions, then reacted with hydrazine hydrate to produce critical intermediate (5) with a total yield of 77%. By condensing compound (5) and N-Boc-piperazine under the conditions of 2-(1H-benzotriazol-1-yl)-1, 1, 3, 3-tetramethyluronium hexafluorophosphate, compound (6) was produced with a yield of 78%. Olaparib was produced with an 85% yield by removing the Boc group in hydrochloric acid and then reacting it with cyclopropane carbonyl chloride. [a][b][c][d].

Medicinal Uses:-

Olaparib tablets are most commonly used for the treatment of cancer. Olaparib is a drug that has been used to stop cell growth. They are been used as chemotherapy medication in treatment of cancer. They are been used in many types of cancer treatments such as:

- Ovarian Cancer
- Breast Cancer
- Pancreatic Cancer
- Prostate Cancer.
- Fallopian tube Cancer. (17)

Sometimes, when cancer has returned after treatment with another drug or when it has spread to untreated areas of the body, Olaparib may be used. (18) Olaparib is discerning and effective inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, PARP1 and PARP2. (19) PARP inhibitor symbolise a new class anti-cancer therapy and they function by exploiting a weakness in DNA repair in cancer cells with BRCA mutations and causing cell death. (20) Olaparib is additionally used to treat BRCA-associated tumours (BRCA1- and BRCA2-associated hereditary breast and ovarian cancer (HBOC) is characterized by an increased risk for female and male breast cancer, ovarian cancer (including fallopian tube and primary peritoneal cancers), and to a lesser extent other cancers such as prostate cancer, pancreatic cancer, and melanoma primarily in individuals with a BRCA2 pathogenic variant). (21)

Their main role in treatment of various types of cancer are as follows: -

- Ovarian Cancer-

Ovarian cancer is a common female cancerous mass with high mortality and morbidity. (22) Ovarian cancer patients are extremely sensitive to platinum-based chemotherapy drugs, and the majority of them recover from their illnesses within three years of starting treatment. This theory is crucial for getting more noteworthy results. The homologous recombination repair function of cancer cells is absent in about 50% of patients with serous ovarian cancer, leading to double stranded DNA damage that cannot be repaired. (23) Olaparib is recommended for adults with deleterious or suspected deleterious germ line mutations as a maintenance treatment. (24)

The first-line treatment for ovarian cancer includes platinum based chemotherapy treatment. In this therapy most commonly used platinum drugs are Cisplatin and Carboplatin. These medications create extremely reactive platinum complexes that bind to and crosslink DNA, a double-stranded molecule found in the cell's nucleus and responsible for regulating cellular activity. The chemical crosslinking in the DNA stops the growth of cancer cells and kills them. (25) Also Olaparib is used in combination with bevacizumab for maintenance of ovarian cancer as a first line treatment in platinum based chemotherapy. (24).

Figure.1. Represents the effect of PARP inhibitor (Olaparib) in ovarian cancer by inhibiting the growth of cancerous cells. (26)

- Breast Cancer-

Olaparib, a PARP inhibitor, has been shown to be an effective treatment for germ line BRCA1/2-mutated breast cancer; however, it is unknown whether this treatment is also effective for somatic BRCA1/2 mutations or mutations in genes involved in homologous recombination DNA repair. Olaparib can halt the spread of the illness in patient suffering from ovarian cancer. It has been found that the phase 2 study to assess the effectiveness of continuing Olaparib treatment in people with metastatic breast cancer. Patients with metastatic ER (+) Her2 (-) or triple-negative breast cancer are enrolled by the researchers. (25) Recently, the drug Olaparib was authorised for the adjuvant, or supportive, treatment of early breast cancer. There is a choice for patients with BRCA1/2 mutations who have HER2-negative breast cancer at significant risk of recurrence, previously managed with chemotherapy in addition to surgery.

- Pancreatic Cancer-

In ductal adenocarcinoma of the pancreas, the PARP inhibitor Olaparib was just authorised as a maintenance treatment in patients with germ line BRCA mutations reaching disease control after a platinum-based first line chemotherapy, proving significant benefit on progression free survival. (27) Recently, researchers have sponsored phase 3 trails which consist of 92 patients randomized by Olaparib and 62 placebo. (28)

- Prostate Cancer-

Olaparib is used in course of adult patients for repairing gene mutated metastatic castration-resistant prostate cancer (m-CRPC). They are been used in combination with hormone agents like enzalutamide or abiraterone. (29) Olaparib works by inhibiting the effects of PARP (poly (ADP-ribose) polymerase). The prostate cancer cells are more likely to die if PARP isn't present because the damaged DNA can't be repaired. Your prostate cancer won't be cured by Olaparib. (30)

The researchers have found that, among 14 men Olaparib prevents the generation of cancerous cells within 10 months on average, but among 33 men who had tumours, DNA repair remained unaltered. Only two of them have demonstrated the effectiveness of Olaparib and, on average, stopped the

development of cancerous cells for two months. (30) For the treatment of adult patients with metastatic castration-resistant prostate cancer (m-CRPC), Olaparib is also indicated in combination with abiraterone, prednisone, or prednisolone. (29).

- Fallopian tube Cancer- In Fallopian tube cancer, Olaparib is used in combination with bevacizumab (Avastin) to keep the reaction going. (17).

Adverse effects/ Side effects: -

Lynparza's (Olaparib) negative effects might range from minor to severe. Some of the most significant adverse effects that could happen while using Lynparza are listed in the lists below. These lists don't include every potential negative effect. (31)

Serious side effects of Lynparza include:

-Pneumonitis (inflammation in your lunges). Symptoms of Pneumonitis can include:

•Fever

•Cough

•Headache

•Chill

•Shortness of breath

•Fatigue (lack of energy)

-Blood clots, such as deep vein thrombosis or pulmonary embolism. Symptoms may include:

•Warmth, pain, or swelling in your arm or leg

•Trouble breathing

•Chest pain

-Hypertension (high blood pressure), which usually doesn't cause symptoms.

Very high blood pressure may cause:

•Headaches A

•Dizziness

•Blurred vision

-Severe blood disorders, including myelodysplastic syndrome/acute myeloid leukaemia.

Clinical trial experience:-

Because clinical trials are conducted under a variety of different circumstances, adverse reaction rates found in one drug's clinical trials cannot be directly compared to rates found in clinical trials of another treatment and may not accurately reflect rates seen in real-world settings.

Maintenance treatment of recurrent ovarian cancer:-

The safety of Lynparza for the maintenance treatment of patient sensitive gBRCAm ovarian cancer was investigated in solo-2. The study in which 294 patients received either Lynparza 300mg (2*150mg tablets) twice daily (n=195) until disease progression or unacceptable toxicity. The median duration of study treatment was 19.5 months for patients who received Lynparza. Dose interruptions due to an adverse reaction of any grade occurred in 45% of patients receiving Lynparza; dose reduction due to an adverse reaction occurred in 27% of Lynparza patients. The most frequent adverse reactions leading to dose interruption or reduction of Lynparza were anaemia (22%), neutropenia (9%), and fatigue/asthenia (8%). Discontinuation occurred in 11% of Lynparza patients. (33)

Table 1 summarizes the adverse reactions that occurred in at least 20% of patients who received Lynparza in SOLO-2.

Adverse reaction	**Lynparza tablets n=195**	
	Grades 1-4 %	**Grades 3-4 %**
Blood and lymphatic disorders		
Nausea	76	3
Vomiting	37	3
Diarrhea	33	2
Stomatitis	20	1
Infection and infestation		
Nasopharyngitis/URI/sinusitis/ Rhinitis/influenza	36	0
General disorders and administration site conditions		
Fatigue including asthenia	66	4
Fatigue including asthenia 66 4		
Decreased appetite	22	0
Musculoskeletal and connective tissue disorder		
Arthralgia/myalgia	30	0
Nervous system disorders		
Dysgeusia	27	0
Headache	26	1

- Treatment of overdose:-

There is no specific treatment in the event of Lynparza overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat the patient symptomatically. (33)

Contradictions:-

Haematological toxicity:-

Patients using Olaparib have reported experiencing haematological toxicity, which has included clinical diagnoses and/or test results of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia, and lymphopenia. Patients shouldn't begin Lynparza medication until their haematological toxicity from prior anticancer therapy has subsided (normal levels of haemoglobin, platelets, and neutrophils, or CTCAE grade 1 status). For the first 12 months of treatment, baseline testing, followed by monthly monitoring of total blood counts, is advised. Thereafter, periodic monitoring is advised to look for clinically significant changes in any parameter. Treatment with Lynparza should be stopped and the proper haematological testing should be started if a patient exhibits severe haematological toxicity or becomes dependent on blood transfusions. After stopping Lynparza for four weeks, blood cytogenetic testing and/or bone marrow testing are advised if the blood parameters are still clinically abnormal.

Myelodysplastic syndrome/Acute Myeloid Leukaemia: -

A rare number of patients who had Lynparza alone or in combination with other anti-cancer medications have been reported to have developed Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML); the majority of these cases have been fatal. Olaparib therapy in patients with MDS/AML lasted somewhere between six months and two years. The cases were characteristic of AML caused by subsequent MDS and cancer treatment. The majority of instances of MDS/AML were in people who carried the gBRCA mutation, and some patients also had a history of prior malignancy or bone marrow dysplasia. All patients had potential risk factors for the development of MDS/AML. All had previously undergone chemotherapy regimens that contained platinum, and many had also had radiation and other treatments that damage DNA. It is advised that the patient be given the proper care if MDS and/or AML are identified while they are receiving Lynparza treatment. If additional anticancer treatment is advised, Lynparza should be stopped and should not be administered in conjunction with additional anticancer treatment.

Pneumonitis-

Few people receiving Olaparib have experienced pneumonitis, and some cases have been deadly. There was no consistent clinical pattern in the reports of pneumonitis, and several predisposing factors (lung cancer and/or metastases, underlying pulmonary illness, smoking history, and/or prior chemotherapy and radiotherapy) complicated the situation. Patients should stop using Lynparza immediately and start an investigation if they have any new or worsening respiratory symptoms, such as dyspnoea, coughing up blood, or fever. If pneumonitis is identified, Lynparza therapy should be stopped and the patient should receive the proper care.

Embryo foetal toxicity-

Olaparib could harm a foetus if it is given to a pregnant woman because of its mode of action (PARP inhibition). Olaparib has been proven in nonclinical investigations to have negative effects on embryo foetal survival and to produce significant foetal abnormalities at exposures below those anticipated at the 400 mg twice daily dose for humans.

Pregnancy/contraception-

Pregnant women and women of reproductive potential who are not taking effective contraception during treatment and for one month after getting the final dose of Lynparza should not take it. (34)

Interactions-

Lynparza and other medications-

The list of drugs that may interact with Lynparza is provided below. Not all the medications that might interact with Lynparza are included in these lists. Consult with both your doctor and chemist before beginning Lynparza. Any prescription, over-the-counter, and other medications you use should be disclosed to them. Additionally, let them know whether you use any vitamins, herbs, or supplements. You can avoid potential interactions by disclosing this information. Ask your doctor or chemist if you have any queries regarding possible drug interactions that could impact you.

Lynparza and cancer drugs-

You have a higher risk of serious side effects if you combine Lynparza with other cancer medications that lower your immune system's capacity to fight infection. Serious infections are one of these adverse outcomes. However, in some circumstances, your doctor can suggest that you receive more than one cancer treatment at once. Discuss the safest treatment regimen with your doctor if you need to take more than one cancer medication at once.

Lynparza and antifungal drugs-

The amount of Lynparza in your bloodstream may rise if you take it along with specific antifungal medications (medicines used to treat fungal infections). This raises the possibility of experiencing Lynparza side effects.

Antifungal medications that can raise Lynparza levels include-

(Nizoral A-D, Extina) ketoconazole

Sporanox, Onmel, and itraconazole

(Vfend) voriconazole

Noxafil (posaconazole)

Diflucan (fluconazole)

Avoid using these antifungals while receiving Lynparza therapy, if at all possible. Your doctor will lower your Lynparza dosage if you have to take one of these medications along with it while you take the two medications.

Lynparza and HIV drugs-

Your risk of experiencing Lynparza side effects may rise if you combine it with specific HIV medications. This is due to the fact that some HIV drugs raise your body's Lynparza levels.

Lopinavir/ritonavir (Kaletra), indinavir (Crixivan), saquinavir (Invirase), nelfinavir (Viracept), atazanavir (Reyataz), and fosamprenavir (Lexiva) are a few examples of HIV medications that might raise Lynparza levels.

Your doctor will reduce the amount of Lynparza you take while taking the two medications together if you must use one of the medications on the above list.

Lynparza can work less effectively to treat your disease when used with specific HIV medications. Efavirenz (Sustiva) and etravirine (Intelence) are two examples of these medications. A different HIV medication than those mentioned above may be prescribed by your doctor if you need therapy for HIV while taking Lynparza. They might also keep a closer eye out for Lynparza side effects or diminished effectiveness.

Lynparza and antibiotics-

Your risk of experiencing adverse effects with Lynparza may rise if you take it along with some antibiotics. This is due to the fact that some antibiotics raise your body's level of Lynparza.

Antibiotics that can raise levels of Lynparza include:

Biaxin XL (clarithromycin)

Cipro (ciprofloxacin)

(EryPed) Erythromycin

If you need to take antibiotics while taking Lynparza, your doctor will probably suggest a different antibiotic from those on the above list. Your doctor will reduce the amount of Lynparza you are prescribed while taking the two medications together if you must take one of the antibiotics on the above list.

Additionally, the effectiveness of Lynparza in treating your disease may be diminished if you combine it with the antibiotic nafcillin. If an alternative to nafcillin is available, your doctor would probably prescribe it if you need to take an antibiotic along with Lynparza. The effectiveness of Lynparza will be continuously monitored by your doctor if you must combine it with nafcillin.

Lynparza and seizure drugs-

The effectiveness of Lynparza in treating your disease may be lessened if you take it along with specific anti-seizure medications. This is due to the fact that some medications used to treat seizures will cause your body's level of Lynparza to decrease.

Seizure medications that can lower Lynparza levels include:

(Dilantin, Phenytek) phenytoin

(Carbatrol, Equetro, Tegretol) carbamazepine

Oxcarbazepine (Trileptal, Oxtellar XR)

Phenobarbital-

Your doctor would probably suggest a different seizure drug from those mentioned above if Lynparza is required in combination with a seizure medication. Your doctor will most likely keep a closer eye on you than normal if you need to take one of the medications mentioned above in addition to Lynparza. They can then make sure Lynparza works to treat your disease effectively.

Lynparza and modafinil-

Taking Lynparza with the stimulant medication modafinil (Provigil) can lower Lynparza levels in your body. This can decrease how effective Lynparza is in treating your condition.

If you need to take Lynparza with modafinil, your doctor will monitor you closely for decreased effectiveness of Lynparza. Or they may even prescribe a stimulant drug other than modafinil for you. (35)

Marketed Preparations:-(36)

TYPES	BRAND NAMES	COMPANY NAME	DOSE	PRICE
1) Tablet	Lynparza	AstraZeneca	• 100mg • 150mg	
2) Tablet	Bracanat	Subhra Pharma Private Limited	• 150mg	
3) Tablets	Olanib	Vishaka Impex	• 150mg	

Lynparza (Olaparib) Tablet. (36)

Bacanat (Olaparib) Tablets. (36)

Olanib (Olaparib) Tablets. (36)

Patents:-

•Phthalazinone derivatives-

Patent 7,449,464

Issued: November 11, 2008

Inventor(s): Martin; Niall Morrison Barr & Smith; Graeme Cameron & Jackson; Stephen Philip & Loh; Vincent Junior M & Cockcroft; Xiao-Ling Fan & Matthews; Ian Timothy Williams & Menear; Keith Allan & Kerrigan; Frank & Ashworth; Alan

Assignee(s): Kudos Pharmaceuticals Limited May bridge Limited

Patent expiration dates: October 11, 2024

•Phthalazinone derivatives-

Patent 7,981,889

Issued: July 19, 2011

Inventor(s): Barr Martin; Niall Morrison & Smith; Graeme Cameron & Jackson; Stephen Philip & Loh; Vincent Junior M & Cockcroft; Xiao-Ling Fan & Williams Matthews; Ian Timothy & Menear; Keith Allan & Kerrigan; Frank & Ashworth; Alan

Assignee(s): Kudos Pharmaceuticals Limited May bridge Limited

Patent expiration dates: October 11, 2024

•DNA damage repair inhibitors for the treatment of cancer-

Patent 8,071,579

Issued: December 6, 2011

Inventor(s): Ashworth; Alan & Jackson; Stephen & Martin; Niall & Smith; Graeme

Assignee(s): The Institute of Cancer Research: Royal Cancer Hospital Kudos Pharmaceuticals Limited

Patent expiration dates: August 12, 2027

Patent use: maintenance treatment of deleterious or suspected deleterious GBRCA-mutated metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen

•Phthalazinone derivatives-

Patent 8,912,187

Issued: December 16, 2014

Assignee(s): Kudos Pharmaceuticals Limited

Patent expiration dates: March 12, 2024

Patent use: treatment of BRCA mutated ovarian cancer using PARP inhibitor

•Phthalazinone derivative-

Patent 8,247,416

Issued: August 21, 2012

Inventor(s): Menear; Keith Allan & Ottridge; Anthony Peter & Londesbrough; Derek John & Hallett; Michael Raymond & Mulholland; Keith Raymond & Pittam; John David & Laffan; David Dermot Patrick & Ashworth; Ian Woodward & Jones; Martin Francis & Cherryman; Janette Helen

Assignee(s): Kudos Pharmaceuticals Limited

Patent expiration dates: September 24, 2028

•Use of RNAI inhibiting PARP activity for the manufacture of a medicament for the treatment of cancer-

Patent 8,859,562

Issued: October 14, 2014

Assignee: The University of Sheffield

The present invention relates to the use of an agent that inhibits the activity of an enzyme that mediates repair of a DNA strand break in the manufacture of a medicament for the treatment of diseases caused by a defect in a gene that mediates homologous recombination.

Patent expiration dates: August 4, 2031. (37)

References:-

1) Krishnakumar, R., and Kraus, W. L. (2010). The PARP side of the nucleus: Molecular actions, physiological outcomes, and clinical targets. Mol. Cell 39 (1), 8–24. doi:10.1016/j.molcel.2010.06.017.

2) Coyne, G. O., Chen, A., and Kummar, S. (2015). Delivering on the promise: Poly ADP ribose polymerase inhibition as targeted anticancer therapy. Curr. Opin. Oncol. 27 (6), 475–481. doi:10.1097/Cco.0000000000000238.

3). Menear, K. A., Adcock, C., Boulter, R., Cockcroft, X. L., Copsey, L., Cranston, A., et al. (2008). 4-[3-(4-cyclopropanecarbonylpiperazine-1-carbonyl)-4-fluorobenzyl]-2H-phthalazin- 1-one: A novel bioavailable inhibitor of poly(ADP-ribose) polymerase-1. J. Med. Chem. 51 (20), 6581–6591. doi:10.1021/jm8001263.

4) Jackson, S. E., and Chester, J. D. (2015). Personalised cancer medicine. Int. J. Cancer 137 (2), 262–266. doi:10.1002/ijc.28940.

5) Gala, U. H., Miller, D. A., and Williams, R. O. (2020). Harnessing the therapeutic potential of anticancer drugs through amorphous solid dispersions. Biochimica Biophysica Acta-Reviews Cancer 1873 (1), 188319. ARTN 188319. doi:10.1016/j.bbcan.2019.188319.

6) Chen, Y. M., Jia, Y. P., Song, W. G., and Zhang, L. (2018). Therapeutic potential of nitrogen mustard based hybrid molecules. Front. Pharmacol. 9, 1453. ARTN 1453. doi:10.3389/fphar.2018.01453.

7) https://en.wikipedia.org

8) https://www,drugs.com

9) https://www.yokshirecancerreasearch.org.uk

10) https://api.drreddys.com

11) Pierre Daumar, Robin Dufour, Clémence Dubois, Frédérique Penault-Llorca, Mahchid Bamdad, et al.. Development and validation of a high-performance liquid chromatography method for the quantitation of intracellular PARP inhibitor Olaparib in cancer cells. Journal of Pharmaceutical and Biomedical Analysis, 2018, 152, pp.74-80. ff10.1016/j.jpba.2018.01.036ff. ffhal-03121699f

12) .Barbara NOVO, Jacopo BONANOMI, Stella De Fiore, Francesco Calogero. Crystalline and amorphous forms of Olaparib, 2017-06-28 https://patents.google.com/patent/EP3184513A1/en

13) European medicines agency. CHMP assessment report-Lynparza, INN-olaparib,2014

14) Feiyue Zheng , Yi Zhang, Shuang Chen , Xiang Weng , Yuefeng Rao , Hongmei Fang. Mechanism and current progress of Poly ADP-ribose polymerase (PARP) inhibitors in the treatment of ovarian cancer, Volume 123, March 2020, 109661

15) Br J Clin Pharmacol. Olaparib, 2016 Jan. PMCID: PMC4693566

16) https://pubs.acs.org/doi/10.1021/acsomega.1c06920

a. Martin N. M. B.; Smith G. C.; Jackson S. P.; Loh V. J. M.; Cockcroft X.-L. F.; Matthews I. T. W.; Menear K. A.; Kerrigan F.; Ashworth A.. Phthalazinone Derivatives. U.S. Patent Appl. 7449464 B2, November 11, 2008.

b. Martin N. M. B.; Smith G. C.; Jackson S. P.; Loh V. J. M.; Cockcroft X.-L. F.; Matthews I. T. W.; Menear K. A.; Kerrigan F.; Ashworth A.. Phthalazinone Derivatives. U.S. Patent Appl. 7981889 B2, July 19, 2011.

c. Martin N. M. B.; Smith G. C.; Jackson S. P.; Loh V. J. M.; Cockcroft X.-L. F.; Matthews I. T. W.; Menear K. A.; Kerrigan F.; Ashworth A.. Phthalazinone Derivatives. U.S. Patent Appl. 7981889 B2, December 16, 2014.

Medicinal Chemistry route summarized in the following review

d. Flick A. C.; Ding H. X.; Leverett C. A.; Kyne R. E.; Liu K. K. C.; Fink S. J.; O'Donnell C. Synthetic approaches to the 2014 new drugs. Bioorg. Med. Chem. 2016, 1937–1980. 10.1016/j.bmc.2016.03.004.

17) https://www.medicineplus.com

18) https://www.drugs.com

19) FDA Approved Drug Products: LYNPARZA (Olaparib) tablets, for oral use

20) Sachdev E, Tabatabai R, Roy V, Rimel BJ, Mita MM: PARP Inhibition in Cancer: An Update on Clinical Development. Target Oncol. 2019 Dec;14(6):657-679. doi: 10.1007/s11523-019-00680-2. (PubMed ID 31625002)

21) . https://www.ncbi.nlm.nih.gov ›

22) Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer Incidence and Mortality Patterns in Europe: Estimates for 40 Countries in 2012. Eur J Cancer (2013) 49:1374–403. doi: 10.1016/j.ejca.2012.12.027.

23) Poveda AM, Davidson R, Blakeley C, Milner A. Olaparib Maintenance Monotherapy in Platinum-Sensitive, Relapsed Ovarian Cancer Without Germline BRCA Mutations: OPINION Phase IIIb Study Design. Future Oncol (2019) 15:3651–63. doi: 10.2217/fon-2019-0343.

24) EMA Approved Drug Products: Lynparza (Olaparib) Oral Tablets (March 2023).

25) . https://clinicaltrials.gov.

26) Jemal, A. et al. Cancer statistics, 2009. CA Cancer J. Clin. 59, 225–249 (2009).

27) https://pubmed.ncbi.nlm.nih.gov

28) Kindler HL et al. Overall survival results from the POLO Trial: A phase III study of active maintenance Olaparib versus placebo for germline BRCA-mutated metastatic pancreatic cancer. J Clin Oncol 2022 Dec 1; 40:3929. (https://doi.org/10.1200/JCO.21.01604. opens in new tab)

29) FDA Approved Drug Products: LYNPARZA (Olaparib) tablets, for oral use.

30) https://prostratecanceruk.org

31) Healthline Media UK Ltd, Lynpraza (Olaparib), 2021 Dec 17

https://www.medicalnewstoday.com/articles/lynparza#side-effects

32) WebMD LLC, Olaparib (Rx)

https://reference.medscape.com/drug/lynparza-olaparib-999934#4

33) https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s001lbl.pdf

34) Eupropean medicine agency, Lynparza INN-Olaparib

https://ec.europa.eu/health/documents/community-register/2016/20160331134533/anx_134533_en.pdf

35) Healthline Media UK Ltd, Lynpraza (Olaparib), December 17, 2021

https://www.medicalnewstoday.com/articles/lynparza#interactions

36) https://idir.indiamart.com

37) Drugs.com, Generic Lynpraza Availability,2023

https://www.drugs.com/availability/generic-lynparza.html

38) Hongyu Xei, Wenjie Wong, Bairong Xia, Wei Lin Jin. Therapeutic applications of PARP inhibitors in ovarian cancer, May 2020, Biomedicine & Pharmacotherapy 127(1)