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Review Article

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BRCA Mutations and PARP Inhibitors in Breast and/or Ovarian Cancer Patients

Abdulrahim Gari[1, 2]*, Ghufran Rawas[3], Ahmad Mufti[4], Omima Elemam[5, 6]

[1]Department of Obstetrics and Gynecology, College of Medicine, Faculty of Medicine, Umm-Al-Qura University, Makkah, Saudi Arabia.
[2]Department of Obstetrics and Gynecology, King Faisal Specialty Hospital and Research Center, Jeddah, Saudi Arabia.
[3]Senior Pharmacist, King Abdullah Medical City, Makkah, Saudi Arabia.
[4]Department of Medical Genetics, Faculty of Medicine, Umm-Al-Qura University, Makkah, Saudi Arabia.
[5]Department of Medical Oncology, King Abdullah Medical City, Makkah, Saudi Arabia.
[6]Department of Medical Oncology, Faculty of Medicine, Mansoura University, Egypt.

***Email:** gari_umq@yahoo.com*

ABSTRACT

BRCA (BReast CAncer gene) mutations are considered strong risk factors in females and males cancers, these include breast, male breast (although rare), ovarian, prostate, pancreatic, and melanoma skin cancers. This paper reviews the literature concerning the association between BRCA and the response rate to poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi) in breast and ovarian cancer patients. Recent evidence shows that PARPi can be utilized as a base for monotherapy strategies and a broad spectrum of molecular cancers. BRCA1/BRCA2 mutations enhance the risk for developing ovarian and breast cancer, amongst others that are caused either by somatic or germline mutations. PARPi begins the repair pathway of the single-stranded DNA breakage, which is considered the most common form of damage, with the help of certain key PARP enzymes. Olaparib was the first approved PARPi drug by the European Medicine Agency (EMA) and the American Food and Drug Administration (FDA) to treat patients with recurrent BRCA-mutated epithelial ovarian cancer after receiving three or more previous chemotherapies. Furthermore, the FDA approved olaparib to manage patients with HER2-negative, BRCA-mutated, and metastatic breast cancers managed previously through chemotherapy. The studies show that using olaparib for maintenance treatment results in a significantly longer progression-free survival and a slightly better overall survival rate among breast and ovarian cancer patients. Certain studies have shown that olaparib maintenance treatment was mostly prosperous and well-endured among advanced BRCA-mutated ovarian cancers.

Key words: *Breast cancer, Ovarian cancer, BRCA1/BRCA2, Poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi), Genes associated with breast cancer, Olaparib*

INTRODUCTION

Cancer begins when cells grow in a way that could be described as being ‘out of control’. Recognizing breast cancer begins possibly by feeling a lump or by detecting an x-ray after a consultation with a doctor. It is more likely to affect females than males. Some people experience a non-cancerous breast tumor, which is considered benign abnormal growth that does not spread further than the breast. However, these are non-life-threatening, but the developing risk can be advanced into malign breast cancers with some types of benign breast lumps. Breast cancer can spread if the tumor cells leak into the blood or lymph, then they can travel to other parts of the body,

which is a process called metastasis. Types and grades of breast cancer are measured once a biopsy is taken; breast cancer cells are then tested for proteins called progesterone receptors, estrogen receptors, and *HER2* (Human Epidermal growth factor Receptor 2). Together, the type and grade of cancer can help to decide treatment options [1]. The behavior and biology of the particular breast cancer affect the treatment plan. Treatment options include surgery, which is generally followed by radiation therapy; moreover, hormonal or endocrine therapy is often used effectively for malign tumors with progesterone or estrogen receptors. Alternatively, immunotherapy or biologic therapy aim to improve the natural defenses of the body for fighting cancer [2].

Ovarian carcinoma is a complex neoplasm that often affects middle age but mostly postmenopausal women over 65 years [3]. The ovarian cancer patients' 5-year survival rate (~45%) has increased by 30% to 50% over the last 20 years. New standards for targeted therapies were proposed when developing guidelines for genetic changes. Antibody therapy, combinatorial immunotherapy, adoptive cell T therapy, vaccine therapy, and checkpoint therapy are also used to treat ovarian carcinoma [4-6]. In 2011, the National Institute for Health and Care Excellence (NICE) suggested symptom-triggered testing with sequential CA125 and ultrasonography for ovarian cancer. Simple or unilocular cysts (fluid-containing cysts) measuring less than 5cm on ultrasonography are reassuring in that they are linked with a less than 1% chance of malignancy. Routine *BRCA* testing can be given to all women who have been diagnosed with high-grade serous ovarian cancer [7].

The literature search has been guided primarily via Trip Database, Google Scholar, Science Direct, and PubMed advanced search builder with the following keywords: BRCA1, BRCA2, Breast, Ovarian, Cancer, PARP inhibitors, and Olaparib. The search was limited to English language, human, and full text. Moreover, the search was limited to recent studies from 2015 to 2021 on the subject. The relevant articles have been included in this review. However, literature was scarce regarding the recent updates and studies on PARPi and olaparib's impact, particularly for treating breast and ovarian cancers, so the researchers depended on the available literature.

Epidemiology

Breast cancer is considered the most commonly diagnosed cancer in the United States (US), with approximately 268,600 new cases among women in 2019 (15.2% to 30% of all cancer cases), with around 2,670 cases newly diagnosed among men (<1% of all cancer cases). It is the second leading cause of cancer death after lung cancer [8, 9]. In the Kingdom of Saudi Arabia (KSA), the cancer statistics differ from the US in terms of the patient's age and disease stage when the cancer is discovered. It usually affects women over the age of 52 years in KSA in contrast to 65 years in the US [10]. With a total of 27,885 cancer cases newly diagnosed in 2020 in KSA, 3,954 (14.2%) were found to be breast cancer, as shown in **Figure 1**. **Figures 2 and 3** show the number of new cases at all ages in females and males [11].

Ovarian cancer is ranked the seventh most common female cancer worldwide. In 2020, the United States had assessed 21,750 new ovarian carcinoma cases and 13,940 deaths [12]. Women have a 1 in 75 chance of contracting ovarian cancer during their lifetime and a 1 in 100 chance of dying from it [13, 14]. In KSA, breast cancer is ranked nineteenth, with 444 (1.6%) new ovarian cancer cases diagnosed in 2020 and 281 (2.2%) deaths due to this fatal disease [11].

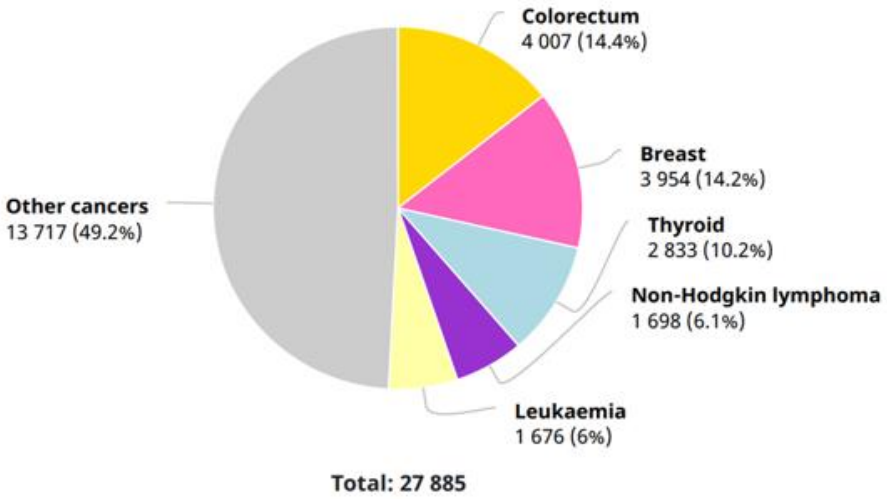

Figure 1. New cancer cases discovered in KSA in 2020, all ages, both sexes [11]

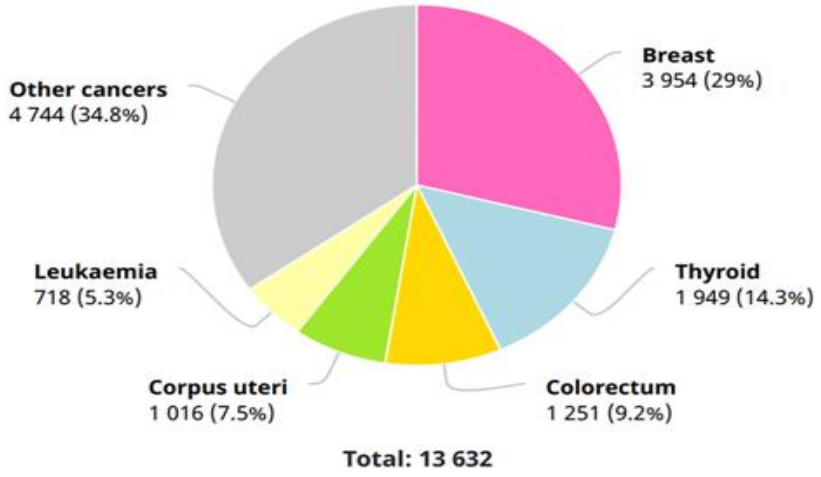

Figure 2. New cancer cases discovered in KSA in 2020, all ages, females [11]

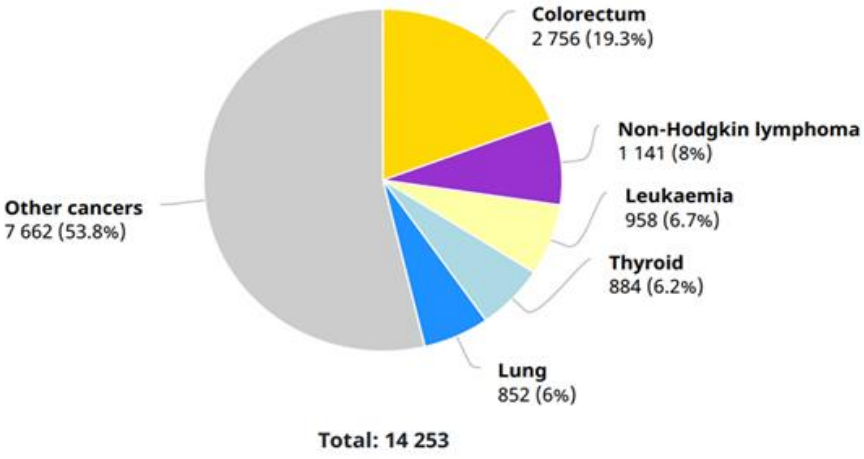

Figure 3. New cancer cases discovered in KSA in 2020, all ages, males [11]

Genes associated with breast/ovarian cancer

On certain genes mutations more risk of breast cancer occurs. About 0.25% of the population carries a mutated breast cancer gene (*BRCA1* or *BRCA2*). Some people have a higher chance of carrying this mutation due to their family history, potentially increasing the likelihood by 50%. Other genes that may enhance the cancer risk include *PALB2* (localizer and partner of *BRCA*2), that is considered the third most prevalent gene for breast cancer after *BRCA1* 1 and *BRCA2*. At the age of 70 years, an estimated 35% of women with a mutant *PALB2* gene will develop breast cancer. *CHEK2* (checkpoint kinase 2) forms a protein that helps to suppress tumor growth. Having a mutation doubles the risk in women and increases it ten-fold in men. The *CDH1* (cadherin 1) gene helps cells to stick together, forming organized tissues. Its mutation causes the common lobular breast cancer, enabling the cancer cells to break off from the breast tumor and metastasize [15]; *TP53* (tumor protein p53) recognizes and repairs DNA damage. When mutated, the cell will grow with the damaged DNA without repairing itself, allowing the cancer cells to develop. The *PTEN* gene (phosphatase and tensin homolog) helps to prevent tumor growth by controlling the cell division rate.

Furthermore, it causes a self-destruct mechanism for the damaged cells before they become cancerous. Similar to *CDH1*, this gene also helps the cells to stick together, preventing them from spreading. Finally, *STK11* (serine/threonine kinase 11) is another tumor suppressor, and when mutated, it causes Peutz-Jeghers syndrome, which carries a higher risk of cancer, including breast cancer [16].

Molecular genetics of BRAC1/2 genes

In 1994 and 1995, the tumor-suppressor genes *BRCA1* and *BRCA2* were discovered (located in the chromosomes 17 and 13, respectively, as shown in **(Figure 4)**) [17]. The *BRCA1* gene consists of 24 exons and 1,863 amino acids, with exon 10 being the largest; *BRCA2* is composed of 27 exons and 3,418 amino acids, with exon 11 being the largest [18]. *BRCA1/2* genes play an essential role in responding to DNA damage as well as maintaining DNA repair in different phases of the cell cycle [19]. It has a fundamental role in repairing double-stranded DNA breaks through its function in the recombination repair pathway (HRR) [18]. The large exons within the BRAC1/2 genes contain the majority of the identified mutations. Most of these mutations are frameshift mutations resulting in non-functional or missing proteins [17].

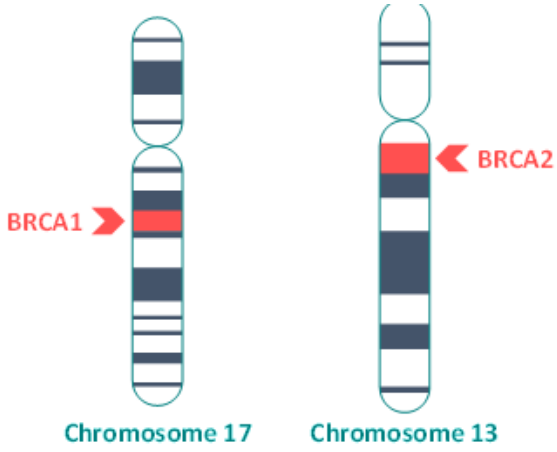

Figure 4. *BRCA*1 and *BRCA*2

Genetic polymorphisms within the BRAC1/2 genes

It is estimated that around 5-10% of all breast and ovarian cancers are due to an inherited predisposition [20]. Most of the mentioned hereditary cases have been related to mutations within the *BRCA1/2* genes. Until now, more than 3,000 genetic variants of *BRCA1/2* genes identified have been linked to breast and ovarian carcinoma development. In 2003, Rostagno *et al.* performed a mutational investigation of the *BRCA1* gene in 140 families with breast and ovarian cancer background in southeast France. They found five distinct truncating mutations that produce a non-functional protein product. Four of the identified mutations were deleteriously, consisting of frequent frameshifts in the nucleotide sequence. Two *BRCA1* missense mutations, T243C and A120G were reported to modify the initiation codon and have severe results on the function and structure of the BRCA1 protein product by altering the interaction of cysteine ligands. They also found that *BRCA1* gene alteration was more common in families with breast-ovarian cancer history than breast cancer families alone [20].

In another study conducted in Chile, a sample of 64 high-risk ovarian and breast carcinoma families were screened for exon-intron boundaries of BRCA1/2 genes and germline mutations in the coding region using conformation-sensitive gel electrophoresis and direct DNA sequencing techniques. Jara and his colleagues identified a total of 13 different pathogenic variants in *BRCA* genes with two novel mutations (2606delTT and 6504delTT) in the *BRCA1* gene and one novel mutation (c.5667delT) in the *BRCA2* gene [21]. They also noticed the presence of nine genetic variations of unknown biological importance, 5 in the *BRCA1* gene and 4 in the *BRCA2* gene. They suggest that their findings indicate the heterogeneous spectrum of *BRCA* gene mutations in the Chilean people which has a famous admixture of Amerindian-Caucasian descendants. They conclude that screening the entire *BRCA1/2* coding regions could provide an insightful understating of the Chilean high-risk ovarian and breast cancer patients.

Carriers of BRCA1/2 mutations have a greater than 50% chance of developing breast and ovarian cancers in their lifetime [22]. In a large association study, Wang and his colleagues identified 350 SNPs from 3451 *BRCA1* and 2006 *BRCA2* mutation carriers. Most identified SNPs were significantly associated with breast cancer risk (P(trend) <0.01). They suggest that these identified SNPs, together with other genetic and environmental factors, may improve breast and ovarian cancer risk assessment in these carrier patients [22].

BRCA gene mutations associated with breast/ovarian cancer

Past studies have confirmed a relation between *BRCA1*/*BRCA2* mutations of germline and the initial development of breast and ovarian cancers caused by either somatic or germline mutations [23]. It has been stated for many

decades that *BRCA* mutations enhance the venture of developing ovarian and breast cancers. Based on a recent report, the *BRCA1*/*BRCA2* mutation carriers' cumulative breast cancer incidence at the age of 80 was as high as 69% and 72%, respectively [24].

BRCA gene mutations can be inherited as a germline mutation in an autosomal dominant character or acquired as a somatic mutation where the mutation could remain silent or expressed. Germline or inherited mutations happen in germ cells, allowing for the transmission of a detrimental mutation to progeny in an autosomal dominant fashion, affecting all the body cells with the mutation, such as somatic and germ cells [25]. The majority of pathogenic variants are protein-truncating variants, such as frameshift or stop-gain variants, which cause function loss. *BRCA* mutations have an increased venture of pancreatic, cholangiocarcinoma, gastric, and esophageal carcinomas; only carriers of mutations of *BRCA*1 have an elevated risk for colorectal neoplasm. Gastric cancer was the commonest site for cancer across carriers of *BRCA* mutations, following ovarian and breast cancers within the Korean population [26].

Testing germline for *BRCA*1/*BRCA*2 is recommended routinely for patients with severe malignancies, depending on the proposed criteria via different organizations, such as the National Comprehensive Cancer Network (NCCN) [27]. Recently, four PARPi, including olaparib, niraparib, talazoparib, and rucaparib, have been confirmed as monotherapy via the Food and Drug Administration (FDA) for severe *BRCA*-mutated or specific deficiency of homologous recombination-positive ovarian or breast/ovarian cancers [28].

As *BRCA* mutated cells have increased carcinogenic potential, and their carriers are at higher risk of developing different cancers, as previously mentioned. They remain highly connected to breast and ovarian cancer [29], and this can be explained through the relationship between *BRCA* mutations and sex hormone alterations. *BRCA1* has been known to reduce sex hormone transcription by interacting with the receptors of estrogen and progesterone, which increases the chance of hormone-sensitive tissue deficiency in *BRCA1* activity to developing tumorigenesis in the breast, ovary, and fallopian tube [30].

Germline *BRCA* mutation is associated with high-grade epithelial ovarian cancer, and the behavior of these tumors is clinically characterized by visceral metastasis at an earlier age, and it has an improved survival rate [31]. Furthermore, ovarian tumors without germline *BRCA* mutation have homologous recombination of DNA repair defects, which is termed *BRCA*ness [32]. This is proven to be relevant due to the use of PARP inhibitors (PARPi), which has shown that its effects extend to such cases; somatic *BRCA* mutation has become significant due to its prevalence and being sensitive to platinum regimens and PARPi [33]. Although advancement in the treatment and management of breast cancer has increased substantially with improvements in Overall Survival (OS), 30% of cases will proceed to metastasis [34].

Most hereditary breast cancer cases have *BRCA1* and *BRCA2* mutations [35]; for ovarian cancer, the *BRCA* mutations cause disturbances in the Homologous Recombination (HR) DNA repair pathway, thus leading to tumorigenesis in younger populations; moreover, the chances of developing breast cancer at 70 years of age with germline *BRCA* mutations are 87%, and they mostly cause triple-negative breast cancer [36].

Therapeutic approaches for breast/ovarian cancer patients

Cancer treatment requires a multidisciplinary team to decide the best treatment options. The behavior and biology of breast and ovarian cancers affect the treatment plan. The existence of inherited breast or ovarian cancer genes with known mutations, such as *BRCA1* or *BRCA2*, tumor subtypes, including hormone receptor status (ER, PR), *HER2* status, tumor stage, nodal status, genomic markers, and patient's status, including age, general health, and menopausal status, all are factors that affect treatment plans, which need to be tailored to the individual [2]. Furthermore, if cancer cells migrate to lymph nodes, the disease can spread to other areas of the body. Hence, finding cancer in one or more lymph nodes affects the decisions related to treatment [1].

Treatment options include surgery (lumpectomy or mastectomy), which is usually accompanied by radiation therapy, involving the use of high-energy x-rays or other particles to destroy cancer cells (External-Beam Radiation Therapy (EBRT), Intraoperative Radiation Therapy (IORT), or brachytherapy). Additionally, systemic therapies may be used to destroy cancer cells throughout the body, which include chemotherapy given before surgery to minimize the risks (neoadjuvant chemotherapy) or after operation to decrease the recurrence of cancer (adjuvant chemotherapy); it includes capecitabine, cisplatin, doxorubicin, fluorouracil, methotrexate, amongst others. For tumors that are test positive for progesterone or estrogen receptors, hormonal or endocrine therapy is efficient. The treatment includes tamoxifen, aromatase inhibitors (AIs), and ovarian suppression.

Targeted therapy targets cancer proteins, certain genes, or the tissue environment that leads to carcinoma survival and growth. *HER2*-targeted therapy was approved for *HER2*-positive breast cancer and included trastuzumab,

pertuzumab, neratinib, and T-DM1 (ado-trastuzumab emtansine). Bone modifying drugs (bisphosphonates and denosumab) can cure cancer that has spread to the bone or inhibit cancer from relapsed in the bone; for metastatic breast cancer, alpelisib, lapatinib, and talazoparib are used. Immunotherapy or biologic therapy improves the natural defenses of the body for fighting cancer, including atezolizumab and pembrolizumab [2]. Lately, Poly (ADP-ribose) polymerase inhibitors (PARPi) are considered to be a new approach in breast and ovarian cancer treatment. PARPis are a family of enzymes that catalyze the transfer of ADP-ribose to target proteins (poly ADP-ribosylation) [37]. Different PARPi drugs that targets the BRCA1/2 signaling pathways have been studied and include olaparib, rucaparib, niraparib, and talazoparib.

PARP enzymes

Mechanisms of PARP enzymes in DNA repair

Several studies suggest that PARP plays an essential role in the DNA repair pathway. PARP is mainly involved in Base Excision Repair (BER) in response to Single-Stranded DNA Breaks (SSBs) [38]. Both PARP-1 and PARP-2 undergo activation by the damaged DNA. Particularly, PARP-1's molecular sensor roles include binding the zinc N-terminal finger domains to DNA single-strand breaks through enhancing its activity and catalyzing the ADP-ribose transfer into targeted proteins via their catalytic C-terminal domain. PARPs form polymer poly ADP-ribose chains after activating the nicotinamide adenine dinucleotide, which play an important role in recruiting intermediates for DNA repair pathways. PARP-1 attaches poly ADP-ribose chains to different proteins covalently, within a process known as PARylation.

PARP inhibition and synthetic lethality

PARP inhibition is accountable for the process known as synthetic lethality. This process includes various events which when considered together, can lead to cell death. In breast or ovarian cancer cells with mutated BRCA1/2 genes, DNA repair deficiency can lead to genomic instability and uncontrolled cell growth. More specifically, since single-stranded DNAs can also be damaged, their reparation is managed by PARP enzymes using the base-excision repair mechanism. When the PARP action stops that pathway, the single-stranded DNA breakage becomes irreversible and converts to a double-stranded breakage. In patients with a deficiency in the homologous recombination pathway and as carriers of *BRCA* mutations, a double-stranded breakage cannot be repaired as well. Thus, the cells accumulate genetic changes, which result in their death [39].

Biological association between PARP and angiogenesis prevention

Extensive empirical data have stated an association between angiogenesis and PARP enzymes. Angiogenesis is a significant driver of the progression and development of epithelial ovarian cancer, and it is the main anti-tumor treatment target [40]. Since 2011, anti-vascular endothelial growth factor treatment, in association with bevacizumab, paclitaxel, and carboplatin, has been the principal therapy by using monoclonal antibodies for patients with metastatic and locally advanced epithelial ovarian cancer [41, 42].

Through hypoxia-inducible factor-1α, the PARP1 pathway is capable of controlling gene expression and managing angiogenesis. Key studies have shown that mice deficient in PARP have been observed to have reduced levels of hypoxia-inducible factor-1α. This transcription agent is mainly involved in inducing tumor angiogenesis and is a subunit of hetero-dimer hypoxia-inducible factor-1 and hypoxia-inducible factor-1β. Hypoxia-inducible factor-1β is a nuclear protein expressed constitutively, which is not controlled by the level of oxygen. Hypoxia-inducible factor-1α, on the other hand, is a cytoplasmic protein; its activation is depended to oxygen concentration [43].

Particularly, within microenvironmental oxygenated conditions, hypoxia-inducible factor-1α constitutes hydroxylated via prolyl-hydroxylases, which is on its prolyl-residues during the degradation domain and based in oxygen. This event results in its linking to the von Hippel-Lindau protein before being degraded through the ubiquitin-proteasome pathway. In fact, prolyl-hydroxylase is inactivated at low oxygen tension, leading to the stabilization of hypoxia-inducible factor-1α, enabling its nuclear migration. It binds to hypoxia-inducible factor-1β, forming the hypoxia-inducible factor-1 complex. This complex focuses on hypoxia's reaction element within the promoter of pro-angiogenic various genes, particularly the vascular endothelial growth factor, initiating their transcription [44].

PARP-1 overexpression has been observed to possess a pro-angiogenic obvious effect within epithelial ovarian cancer through upregulation of vascular endothelial growth factor-A. Anti-angiogenic treatments are well-known to stimulate hypoxia within cells, resulting in a down-regulation of gene repairing homologous recombination,

such as *BRCA1*, *BRCA2*, and RAD51 increasing sensitivity of PARPi. Hypoxia is also associated with the upregulation of hypoxia-inducible factor-1α, which is regarded as a common mechanism of insistence to angiogenesis suppressors. Surprisingly, PARP-1 can have a vital effect on the consolidation of hypoxia-inducible factor-1α [45]. Using PARPi can evade its buildup and signaling, resulting in hypoxic targeted cell death if the mechanism of resistance is overcome [46].

PARP inhibitors (PARPi)

In various cancers, targeting the PARP pathway has proven to be a promising new therapeutic strategy. PARP inhibitors act as an effective trap for PARP on DNA and are able to stop the DNA-repair machinery in cells from functioning. **Figure 5** illustrates the PARP inhibitor mechanism of action [47]. Importantly, to accurately repair the resulting Double-Strand Breaks (DSB), the HRR pathway is required. DSB repair is imprecise in HRR-deficient cells, potentially due to the loss of *BRCA1/2*, resulting in DNA damage accumulation and cell death. Identifying patients with HRR deficiency in their tumors that are likely to respond to PARPi will improve treatment response rates [47]. Recent evidence shows that PARPi has the capacity to be utilized as a base for monotherapy treatment as well as for a broad spectrum of molecular cancers. While PARPi is a class that represents various similarities, significant structural differences can be translated to tolerability differences and anti-tumor activities, which have substantial applications practically [48].

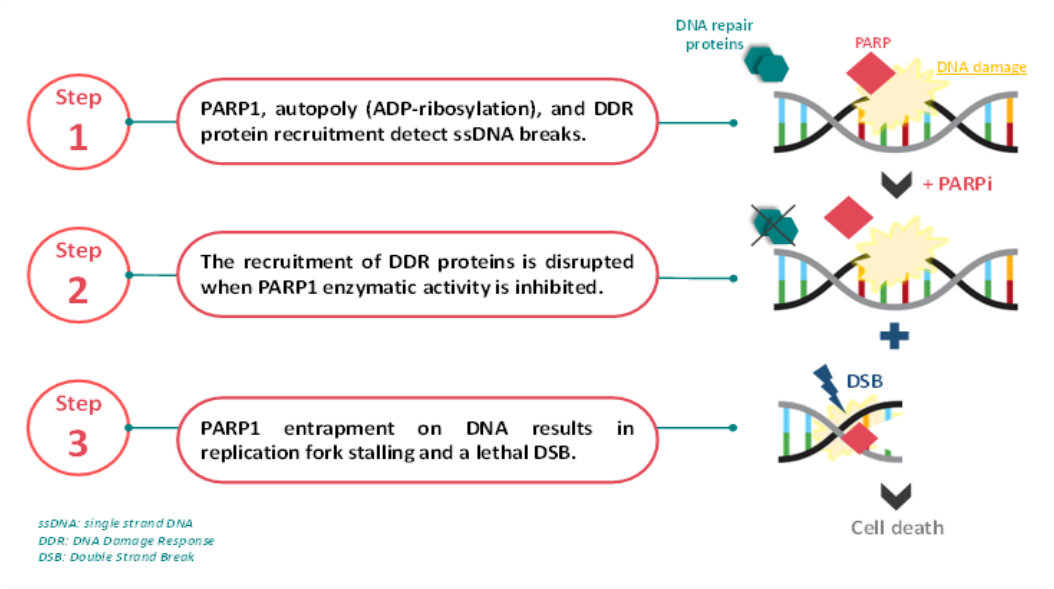

Figure 5. PARP inhibition mechanism of action [47]

At present, four PARP inhibitors have been given marketing permission in Europe and the US Olaparib was the first approved drug in the PARPi class in 2014. The American FDA has approved it and the European Medicine Agency (EMA) for germline *BRCA* mutated ovarian tumors in patients that have undergone three different chemotherapy cycles, or that have serous epithelial ovarian and fallopian tumors, triple-negative breast cancers, and with the application as a monotherapy or maintenance therapy in platinum-sensitive tumors [48, 49]. The Saudi FDA also approved the use of olaparib in 2016; Rucaparib reaches approval in 2016 for recurrent (or advanced) epithelial ovarian, primary peritoneal cancer, fallopian tube, and castration-resistant prostate cancer [50]. This was followed by the approval of niraparib in 2017 as a maintenance treatment for patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer and for patients with previously platinum-based chemotherapy and a total or partial response [51]. Recently, in 2018, talazoparib was approved as a monotherapy for treating *HER2*-negative metastatic or locally advanced breast carcinoma in adult patients with germline *BRCA1/2* mutations [52].

Recent trials test the capacity of new 17 PARPi in advanced and early breast cancers, including olaparib for those in phase III and with *BRCA* germline mutated breast cancers; veliparib for phase III in a neoadjuvant context standard or alongside carboplatin in breast triple-negative cancers; niraparib for phases II to III in combination treatment in *BRCA*-mutated germline breast cancers; talazoparib for phases II to III in various contexts in *BRCA*-mutated germline breast cancers; and rucaparib for phase II in *BRCA*-mutated solid germline breast cancers.

Olaparib received approval from the FDA in 2014, and rucaparib received approval in December 2016. Strategies for expanding PARP treatments beyond ovarian and breast cancers are currently studied [53]. Previously, the mixture of surgery and platinum-based chemotherapy was the first-line therapy for patients with newly diagnosed cancer. In 2018, a paradigm shift in the management had been seen with PARPi, in the four randomized phase III trials (SOLO-1, PAOLA-1, PRIMA, VELIA) in the first line settings [54-57].

Solo-1 trial in 2018 firstly reports the effects of first-line maintenance therapy with olaparib for two years extended Progression-Free Survival (PFS), which leads to setting a new standard of care. In 2019, with adding a PARPi to first-line treatment, phase III trials stated a considerable betterment in PFS in patients with *BRCA1/2* mutation: PRIMA (niraparib) [56], PAOLA-1 (olaparib plus bevacizumab) [55], and VELIA (veliparib with chemotherapy, followed by maintenance) [57].

These trials assessing PARP inhibitors within the first-line settings with an end primary point of PFS have shown that there are significant variations between them, especially in comparison with the control groups 'placebo' (in terms of susceptibility to platinum induction and the severity of the residual illness), the initiating time of PARPi (in conjugation with the chemotherapy against only maintenance therapy), as well as the planned period of therapy using PARPi [54, 56-58].

Each trial was intended with a particular hypothesis in mind, revealing differences in clinical development and drug target populations. Equally, each trial has restrictions in terms of applicability and generalizability, which are discussed further below.

Iniparib

Despite there being a great deal of concern about the novel medication iniparib, the most advanced PARPi in clinical trials, in 2011, it failed to improve survival rates in triple-negative breast cancer patients during phase III [59]. Since 2013, the failure has been linked to resistance to certain events. For the PARPi drug resistance, it was linked to the evolution of a *BRCA*2 secondary mutation. Following the synthetic lethality method, the mutation would most likely recover the protein's wild-type function [46, 47, 60].

Cediranib

The exploratory post-hoc analysis demonstrated enhanced activity of cediranib, a tyrosine-kinase oral inhibitor of VEGF-receptor, combined with olaparib, and compared to using olaparib alone among the patient's subgroup having a *BRCA* wild type or unknown population. Among the group of patients with *BRCA* mutations, there existed a lesser trend toward enhancing the activity for the combination medications group, with increased PFS from 16.5 to 19.4 months (cediranib with olaparib). Significantly, adverse events such as hypertension, fatigue, and diarrhea of any grade took place within the combination medications group, leading to reductions of doses in over 75% of the patients [61].

Phase III clinical trials are recently taking place for validating combination treatments within various settings. The GY004 trial goal aimed to compare prescribing olaparib alone with using cediranib and olaparib in combination against using standard chemotherapy based on platinum among patients having recurrent fallopian tube/ovarian cancers, which are sensitive to platinum chemotherapy. Moreover, the ICON 9 trial examines maintenance treatment using cediranib combined with olaparib or using olaparib only for maintenance following chemotherapy based on platinum among high-grade patients with recurrent ovarian cancer, which is sensitive to platinum chemotherapy [46, 60].

Niraparib

The phase III PRIMA/ENGOT-OV26/GOG-3012 trial assessed niraparib compared to placebo for 733 women with advanced ovarian carcinoma after reaction to platinum-based chemotherapy. Eligible criteria were patients with BRCA mutations and any Homologous Recombination Deficiency (HRD) status, obtaining a full response to platinum first-line chemotherapy with or without bevacizumab. Patients reviving niraparib as a maintenance therapy show a significant OS and longer PFR (22.1 vs. 10.9 months for placebo in HRD/BRCA-mutated population; 19.6 vs. 8.2 months in HDR/BRCA-wild type population; 8.1 vs. 5.4 months in HDR-proficient population) [62].

Veliparib

VELIA/GOG-3005 study evaluating PFS for patients with previously untreated stage III or IV high grade serous ovarian cancer after the addition of veliparib into the first-line chemotherapy with paclitaxel and carboplatin then

continued as maintenance monotherapy. The results show an improvement of PFS from 22 months in the control group to 34.7 in the veliparib group. A higher incidence of anemia was shown with veliparib alongside thrombocytopenia, nausea, and fatigue when given together with chemotherapy. It is still not clear for the independent value of adding veliparib while induction therapy without veliparib maintenance [57].

Talazoparib

The American and Saudi FDA has recently approved Talazoparib. Based on the findings of the EMBRACA trial, the drug shows a three-month improvement in median PFS in adults with germline *BRCA1/2*-mutant, *HER2*-negative locally metastatic or advanced breast carcinoma. With talazoparib, the median PFS was 8.6 months (95% CI, 4.2-6.7) versus 5.6 months (95% CI, 4.2-6.7) with chemotherapy (HR, 0.54; 95 % CI, 0.41-0.71; P.0001). Both predetermined patient subgroups benefited from talazoparib in terms of PFS [63].

Patients in the EMBRACA study (n=287) were given 1mg of oral talazoparib daily or gemcitabine, capecitabine, vinorelbine, or eribulin, in constant 21-day cycles (n=144). The qualified patients (≥ 18 years, had either advanced or metastatic breast carcinoma, or had a deleterious or suspected deleterious germline *BRCA1/2* mutation) had received therapy with a taxane, anthracycline, or both, unless contraindicated, and had taken no more than three prior cytotoxic regimens for advanced breast cancer. The median OS between the talazoparib and chemotherapy arms shows no statistical significance (19.3 vs. 19.5 months; 95% CI, 0.670-1.073; HR, 0.848; P=.17). Talazoparib had an analogous impact without considering *BRCA* condition.

After 324 deaths, the investigators ran the final report of OS using the intent-to-treat population. After 44.9 months for talazoparib median follow-up and 36.8 months for chemotherapy, 216 patients had died in the talazoparib group and 108 in the chemotherapy group. Totally, 59.7% of patients in the control group and 48.4% of patients in the experimental group received more PARPi or platinum-based chemotherapy treatment. Platinum therapy was administered to 46.3% of those who received talazoparib and 41.7% of those who received chemotherapy.

According to Litton [63], adjusting for post-study therapy reduced the confidence interval upper bound and the hazard ratio. The median OS difference within patients who received PARPi and/or platinum treatment (19.3 vs. 17.4 months, respectively; 95% bootstrap CI, 0.503-1.029; HR, 0.756), or PARP inhibition alone (19.3 vs. 19.1 months, respectively; 95% bootstrap CI, 0.617-1.047; HR, 0.820), shows no statistical significance when compared to chemotherapy. When compared to chemotherapy (-5.7; 95% CI, -10.0 to -1.4), the approximate alteration in baseline global health status/quality of life (QoL) in talazoparib patients (2.1; 95% CI, 0.1-4.1) was statistically significant [63].

Talazoparib was also well tolerated by the patients. Around 35% of patients experienced major side effects in the experimental arm, compared to 31% in the chemotherapy arm. Severe and drug-related adverse effects, and grade 3/4 serious adverse effects were reported at comparable rates in both arms. Researchers found that those given talazoparib had less adverse events than those given chemotherapy, which resulted in irreversible drug discontinuation (7.7% vs. 9.5%, respectively) [64].

The most common side effects (≥ 20%) were fatigue, nausea, headache, vomiting, anemia, neutropenia, alopecia, thrombocytopenia, and decreased appetite. For Laboratory abnormalities, talazoparib showed decreases in hemoglobin, leukocytes, lymphocytes, neutrophils, platelets, and calcium, and an increase in glucose, aspartate aminotransferase, and alkaline phosphatase, and alanine aminotransferase. When given to pregnant women, it has the potential to damage the fetus. During treatment and for at least 7 months after the last dose, women with reproductive potential should be recommended to use effective contraceptives. Because of the risk of severe adverse effects in breastfeeding babies, women must not breastfeed when taking the drug and for at least one month after the last dose [65].

Talazoparib has a convenient once-daily dosing schedule. 1mg orally once a day, with or without food, is the recommended starting dose. The 0.25mg capsule may be used to reduce the dose. Patients should be treated before their condition progresses or if they experience intolerable toxicity [66]. The minimum dosage for patients with mild renal dysfunction is 0.75mg once daily. The minimum dosage for patients with serious renal failure is 0.5mg once daily. Patients with moderate renal dysfunction do not require any dosage adjustments [65].

Olaparib

The SOLO-1 trial compared olaparib to placebo as maintenance treatment in patients diagnosed newly with advanced ovarian carcinoma with a *BRCA*1/*BRCA*2 mutation. All, except three patients, had germline *BRCA*1/*BRCA*2 mutations. Following chemotherapy, the majority of the patients showed no signs of disease, had a normal level of cancer antigen-125, and were in good health [54]. A clear restriction to general SOLO-1 outcome

applicability is the eligibility restriction to patients having tumors with mutated *BRCA* genes. The outcomes did not provide information regarding the patients having non-mutated *BRCA* tumors. Besides, the trial lacked therapy which includes bevacizumab, and previously bevacizumab was not allowed.

In the PAOLA-1/ENGOT-OV25 trial, both treatment groups used bevacizumab. The lack of a single olaparib arm is a drawback because it is difficult to know how much bevacizumab helps the combination regimen's operation. Olaparib was maintained for about two years or more, but bevacizumab was stopped following 15 months of usage [58]. Despite the design relating to the recently approved bevacizumab usage, the BOOST/AGO-OVAR 17 trial results compared 15 months of bevacizumab to 30 months within the first-line settings may impact interpretation and application of the PAOLA-1/ENGOT-OV25 outcomes. In terms of generalizability, the results are not applicable to the patients who were classed as ineligible for bevacizumab [67].

Olaparib, the first approved drug in the PARPi class, is administered orally in the form of a capsule of 400mg twice daily; a new 300mg tablet has been approved due to better bioavailability. This formulation has also simplified drug administration [68]. Olaparib has been approved for triple-negative breast, serous epithelial ovarian and fallopian tumors, primary peritoneal tumors which are platinum-sensitive, and castration-resistant prostate cancer under certain conditions, as well as its approval to be used in patients with ovarian carcinoma recurrence and a *BRCA* mutation as it is beneficial in these patients [49].

Apart from being a single-use drug, olaparib can also be used as a chemo- and/or radiosensitizer, which ensures enhancing the cytotoxic effects of these drugs [49]. Combining olaparib with the platinum agents for the treatment shows a significant positive outcome in cases of *BRCA1* and *BRCA2* mutated ovarian and breast tumors, and whether it was in combination or as a maintenance therapy post platinum agent, a decrease in tumor size and/or a prolonged stable disease were observed [69]. Olaparib can further sensitize the damage that the DNA of tumor cells undergo. Its use as a radiosensitizer is hypothesized to be effective with lower toxicity and side effects [70].

Olaparib is extremely tolerable when given in the appropriate doses (400mg twice daily). The most common side effects ($\geq$20%) that arise in single drug trials were fatigue (including asthenia), nausea, vomiting, diarrhea, headache, mouth sores, back pain, myalgia, and decreased appetite. 40% of patients that suffered from side effects needed a dose adjustment and modification of treatment [71]. In pregnancy, caution must be taken. Olaparib can cause embryo-fetal toxicity and may cause loss of pregnancy (miscarriage). For nursing mothers, olaparib must be discontinued or discontinue breastfeeding. Study findings have shown that olaparib affects an increase in creatinine, a decrease in hemoglobin, a mean corpuscular volume elevation, a decrease in platelets, a decrease in absolute neutrophil count, and a decrease in lymphocytes [72].

The most significant side effects occurred when olaparib is combined with platinum agents and other chemotherapies, such as neutropenia, Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), and pneumonitis. However, most cases with these severe side effects had already undergone multiple cycles of DNA damaging chemotherapies, such as platinum agents [73].

The only sensitivity biomarker for PARPi is currently the *BRCA* mutations in breast and ovarian cancers; Olaparib is effective in germline *BRCA* mutations in breast and ovarian tumors. On the other hand, it also shows better response chances in somatic *BRCA* mutation tumors [74]. The exploration of a homologous recombination defect being an independent sensitivity biomarker other than *BRCA* mutations, HR involves many gene products that have an active role in the process of DNA repair. This multifactorial pathway and all its components can be suggestive of the chance of finding a sensitivity biomarker [75].

Olaparib therapy in *BRCA* mutant breast and ovarian tumors has been discussed in the literature since its approval in 2014, and it has proven to be highly effective in halting disease progression. In a study by Moore and colleagues, olaparib maintenance therapy provides substantial benefits in PFS for women with newly diagnosed advanced ovarian carcinoma, with a 70% lower chance of progression than the placebo [54]. The determination of the *BRCA* mutation variants is currently being conducted, and they are categorized according to their pathogenicity [76]. Nonetheless, the relationship between *BRCA* variants and the response to PARPi is yet to be explored. In a study by Pan and Xie (2017), it was concluded that the variation of response to PARPi and other agents that work on DNA damage response pathways should be explored to reach a better quality of care and decrease the morbidity of ovarian cancer [77].

A study by Eriksson, Wettermark, and Bergfeldt (2018) concluded that olaparib treatment is well tolerated in *BRCA* mutated breast cancer. Zimmer *et al.* (2018) have also given recommendations to explore which phenotypes would benefit best from PARPi therapy and investigate other biomarkers that may have a positive impact on the

treatment of breast cancer [78]. Ashworth and Lord (2018) have discussed the fact that PARPi resistance might be due to variants of the *BRCA* mutations and other DNA damage response enzymes [79].

Olaparib has been the first PARPi to investigate its pharmacodynamics and pharmacokinetics among patients with ovarian and breast cancers. Across the enrolled 60 patients, 22 had germline *BRCA1/BRCA2* mutation. The results demonstrated the dose of 400mg twice per day as a tolerated maximum dose of olaparib. The reported side effects were mainly in grades 1 and 2, which involved anorexia, fatigue, nausea, vomiting, and altered taste [80].

Succeeding clinical phase II trials among patients having *BRCA* mutations demonstrated a 41% response rate among patients having advanced breast malignancies, as well as a 33% response rate among patients having epithelial recurrent ovarian cancer, which indicated a response rate of the tumor among patients with metastatic breast cancers with three regimens of chemotherapy at 12.9% [81]. For epithelial relapsed ovarian cancer resistant to platinum-based chemotherapy, the overall response rate was 31.1%, as shown in **Figure 6**. Based on these findings, a clinical subsequent phase II experiment was initiated by Ledermann *et al.* [82], which shows an overall outcome that indicates the olaparib enhanced median PFS compared to the placebo.

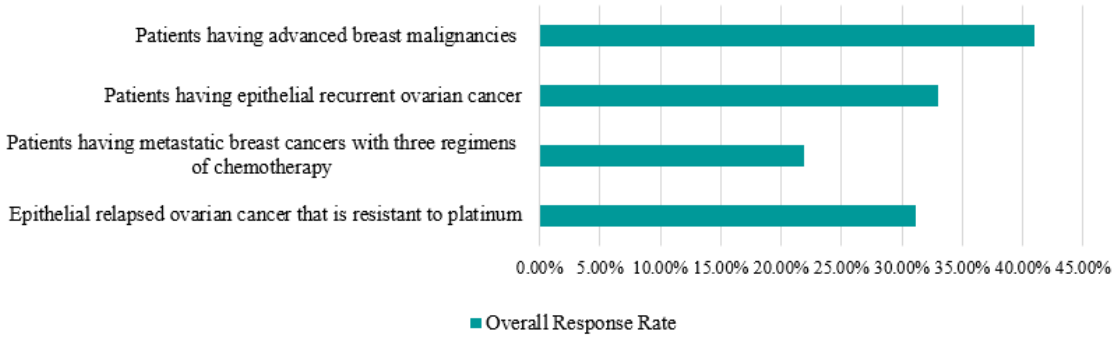

Figure 6. The overall response rate among patients with *BRCA* mutations

The subgroup analysis through the overall status of somatic and germline *BRCA* mutations indicated a significant benefit within median PFS among the olaparib arm compared to the placebo arm. Ledermann and Pujade-Lauraine's study (2019) resulted in the MEA and FDA registration of olaparib for treating epithelial ovarian cancers [83].

The solo phase III trial (the POLO trial), which included metastatic pancreatic cancer patients and those with germline *BRCA*1/*BRCA*2 mutations whose cancer had not advanced since receiving platinum-based first-line chemotherapy, resulted in a statistically significant improvement in PFS from using olaparib only, compared with the placebo. The olaparib group had a substantially longer median PFS, and a higher objective response rate and median response duration.

Based on the placebo-controlled, randomized POLO trial, an approach driven by biomarkers to the treatment of prostate cancer could be achieved within the practice; in 2019, the FDA approved olaparib for usage as a maintenance therapy for patients having suspected deleterious or *BRCA*-mutated germline pancreatic metastatic cancer, as observed through a test approved by the FDA, and whose illness had not worsened at 16 weeks, at least, with a first-line regimen of chemotherapy based on platinum [84].

For achieving a synergistic effect and further enhancing of clinical efficacy, PARPi has been suggested when combined with chemotherapy. However, this combination is defective due to its overlapping toxicity of the bone marrow [85]. A phase I clinical trial was operated to examine and determine the efficacy of olaparib in conjunction with cisplatin in patients with advanced breast carcinoma, epithelial ovarian cancer, and solid tumors. The tolerated maximum dose could not be stated as any of the cohort studies said the dose-limiting levels of toxicity. So, it was concluded that the cisplatin scheme 60mg/m2/day combined with a treatment of 50mg intermittent olaparib tablets was a tolerated dose.

As a result, Oza *et al.* [46] conducted a randomized clinical phase II trial to investigate the use of olaparib in combination with paclitaxel and carboplatin, followed by maintenance therapy with olaparib. This is compared to the paclitaxel and carboplatin standard therapy among patients with high-grade, recurrent, epithelial serous ovarian cancer, which is sensitive to platinum. The PFS rate was stated to be 12.2 months versus 9.6 months for the olaparib group. Among patients with *BRCA* mutations, the difference was stated to be even more. It was deducted that the combined cohort sample had a manageable and sufficient tolerability profile but that the chemotherapy dose would need to be reduced upfront.

Dent *et al.* (2013) studied the toxicity and tolerability of olaparib plus paclitaxel once a week in 19 triple-negative metastatic breast carcinoma patients. Initial research did not reveal a maximum dosage that could be tolerated [86]. It is worth stating that a previous randomized trial compared doses of olaparib and demonstrated that 400mg was better than a dose of 200mg for median PFS times. Hence, a dose of 400mg is the suggested dose. The findings indicated that using olaparib for a maintenance treatment resulted in a significantly longer PFS and a slightly better OS among patients with ovarian cancer. There were no major variations in rates of degradation or growth between the olaparib arm and the interventional group using FACT-O questionnaires for health-related life quality [82, 87].

Compared with using a placebo, olaparib leads to more general side effects, including fatigue, nausea, diarrhea, vomiting, and anemia, at doses of 300mg or 400mg twice daily. However, olaparib did not increase the frequency of most side effects compared to other chemotherapeutic medications. Olaparib maintenance therapy was generally well-tolerated and efficacious among patients with advanced *BRCA*-mutated ovarian cancers [88].

CONCLUSION

BRCA-Mutations are considered a strong risk factor for breast and ovarian cancers. The status of *BRCA* mutations can offer significant insight regarding treatment and prevention options. With proper surveillance and management, carriers of *BRCA* mutations have certain options for preventing or detecting cancer at the initial stages. There is also an increased chance of successful recovery. Maintenance treatment has a significant role in the usage of PARPi, as a first- and second-line in responding to chemotherapy based on platinum and as third-line maintenance therapy. However, the relationship between *BRCA* variants and the response to PARPi is yet to be explored. A better understanding of the genetics of breast cancer may aid in treatment approach personalization, based on molecular and clinical patient characteristics. More studies are needed to assess the BRCA variants and the response rate to PARP inhibitors.

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