We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 5

Individualized Novel Therapies for Patients with Tumor Suppressor Genes *BRCA1* and *BRCA2* Mutated Epithelial Ovarian Cancer

Sandra García-Nieto, Carmen Guillén-Ponce, Carmen Alonso, María-Carmen Rodríguez-Soriano, María-Luz Pombo, Earl Julie and Samir A. Farghaly

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/61938

Abstract

Ovarian cancer is the leading cause of death in women with gynecological cancer, since a large proportion of patients are diagnosed at later stages of the disease. The incidence of ovarian cancer in the general population is 2%, but patients with germline mutations in the *BRCA* genes have a risk of developing ovarian cancer of up to 2050% with a cumulative risk of ovarian cancer at 70 years of age of 40% in *BRCA1* and 18% in *BRCA2* mutation carriers. Although it is a chemosensitive tumor, most of the patients after surgery and chemotherapy based on taxanes and platinum will relapse later in life. Due to the high risk of developing ovarian cancer in patients with *BRCA* germline mutations, new treatments rely increasingly on histological and molecular characteristics of the primary tumor, achieving greater selectivity and lower toxicity compared with standard cytotoxic agents. Poly (ADP-ribose) polymerase (PARPS) inhibitors are the first biologically active agents for patients with ovarian cancer with alterations in the DNA repair pathway, particularly in the high-grade serous subtype of ovarian cancer.

The results of clinical trials published so far mean that olaparib has been approved, pending the results of the Phase III trials. The European Medicines Agency (EMA) adopted olaparib (lynparza ®) on the December 18, 2014, as a maintenance therapy after response to platinum-based chemotherapy in relapsed platinum-sensitive ovarian cancer patients with a *BRCA* mutation. By contrast, the Food and Drug Administration (FDA) approved olaparib on December 19, 2014, in patients with high-grade ovarian epithelial serous tumors and a *BRCA* mutation who have progressed during three or more lines of chemotherapy. Olaparib is also used in primary fallopian tube and peritoneal cancers with *BRCA* mutations.

Keywords: PARP inhibitors, Olaparib, Mutant epithelial ovarian cancer, Tumor suppressor Genes *BRCA1* and *BRCA2*, Novel therapies for ovarian cancer

1. Introduction

The usual treatment of advanced disease of ovarian cancer is surgery [1] followed by taxane and platinum-based chemotherapy, although a large proportion of patients will relapse throughout their lives. Therefore, current clinical trials focus on the detection of molecular targets that can act more selectively and efficiently on ovarian cancer [2].

It is known that chemotherapy treatments damage the DNA and there are molecules that are responsible for repair and proper maintenance of the genome such as poly (adenosine diphosphate-ribose) polymerase (PARP), which plays a key role in the repair of DNA single-strand breaks; so, researchers have focused on the mechanism for the development of new therapies, including the PARP inhibitors.

Olaparib is the first PARP-inhibitor class recently approved for the treatment of ovarian cancer with mutations in *BRCA* (breast cancer), delivered orally and with good tolerance, with myelosuppression and gastrointestinal toxicity as the most frequent adverse effects. Throughout the chapter, we describe the features of hereditary ovarian cancer with *BRCA* mutation, and the steps to follow once the mutation is detected in patients at risk of ovarian cancer. The characteristics of PARP inhibitors are discussed, focusing on olaparib, and their use and dosage recommendations after reviewing the main Phase II trials for which it has been approved; also, we comment on Phase III olaparib trials that are currently underway.

2. *BRCA1* and *BRCA2* genes

Most breast cancers and hereditary ovarian cancers are associated with mutations in two genes, breast cancer type 1 and 2 susceptibility genes (*BRCA1* and *BRCA2*), whose prevalence varies among different geographical areas and ethnic groups, being known as the founder effect among Ashkenazi Jews, whose descendants have an increased risk with any of the three founder mutations (two *BRCA1* mutations, 187delAG and 5385insC, and one *BRCA2* mutation, 6174delT). Founder mutations come from a single carrier ancestor initially extending from a small town with some degree of inbreeding, highly recurrent alterations, or even characteristics of an ethnic group [3].

BRCA1 and *BRCA2* are tumor suppressor genes and are involved in the repair of double-strand breaks of DNA, maintaining genome integrity. Germline mutations in the *BRCA1* and *BRCA2* genes are caused by the loss of one of their wild type alleles, and therefore have a single functioning allele, promoting genomic instability and tumorigenesis [4].

Studies suggest that mutation in p53 favor loss of functionality of the *BRCA 1/2* genes inducing tumorigenesis [5,6]. The function of p53 is to detect DNA damage during the cell cycle, allowing repair; so if p53 is altered, DNA repair is incomplete or inadequate, causing cell death in normal cells [7]. The p53 mutation was detected in almost 90% of patients with high-grade serous carcinoma (HGSC) in patients with *BRCA 1/2* mutation.

http://dx.doi.org/10.5772/61938

The *BRCA1* is located on the long arm of chromosome 17 (17q21) gene. It has a sequence of 5,592 nucleotides, divided into 24 exons. The *BRCA1* protein is localized with *BRCA2*, PALPB2, and RAD51 (essential proteins in homologous recombination) in areas of repair of double-strand breaks of DNA. *BRCA1* is part of BASC (*BRCA1* Associated genome surveillance) complex multiprotein complex responsible for the detection, removal, and repair of DNA breaks. In conclusion, *BRCA1* interacts with other oncogenes, repressors, and activators of transcription, cell cycle regulators, etc., involved in genomic stability. It has also been linked to the development of other cancers, particularly pancreas, uterus, and prostate cancers [8].

The *BRCA2* gene is located on chromosome 13q (13q12), and has a sequence of 11,385 nucleotides in 27 exones. *BRCA2* plays a key role in the cell cycle, especially in cytokinesis and meiosis, as well as in homologous recombination DNA repair [9]. Mutations in this gene have been linked to other cancers such as cancer of the gallbladder, pancreas, stomach, and malignant melanoma.

Hereditary breast and ovarian cancer (HBOC) syndrome is characterized by an autosomal dominant inheritance with high penetrance, presenting increased susceptibility to breast and ovarian cancer, although it has been shown that *BRCA1* and *BRCA2* genes are expressed in most tissues and cells analyzed, suggesting that the pathological impact of a mutation is tissue-specific and that there must be alternative pathways that compensate for their loss of function in other tissue types [10].

Women with hereditary ovarian cancer may have higher rates of response to chemotherapy and improved survival rates in cases of sporadic cancer.

In 2012, the results of an analysis were published [11] in which data from 26 observational studies on the survival of women with ovarian cancer with germline mutations in *BRCA1* and *BRCA2* mutations.

Data from 1,213 cases with a germline mutation in *BRCA1* (n = 909) and *BRCA2* (n = 303) and 2,666 no mutation carriers were included. The observed overall survival (OS) for 5 years was 36% in non-carriers of mutation patients versus 44% for patients with a *BRCA1* mutation and 52% for patients with a mutation in *BRCA2*. There was an increased survival in *BRCA* mutation carriers versus non-carriers. *BRCA2* carriers had a better prognosis. There were several significant differences in the clinical characteristics of *BRCA1* and *BRCA2* compared with non-carriers. The *BRCA1* and *BRCA2* tumors were more likely to be serous histology and less likely to be mucinous histology. Patients with *BRCA1* and *BRCA2* mutation were more likely to have a tumor stage III/IV and present greater degree of differentiation compared to non-carriers. *BRCA1* carriers were also younger at diagnosis.

Detection of *BRCA1* and *BRCA2* genes is accomplished by DNA extraction from peripheral blood lymphocytes. Detection techniques must be able to identify everything from small changes to large duplications or deletions of exons.

There are over one thousand different mutations to *BRCA1* and *BRCA2*, most of them being small insertions or deletions causing a change in the reading frame (frameshift) and producing a stop codon. However, amino acid substitutions producing a stop codon (nonsense) or

mutations located at sites of exon splicing that alter the splicing of the genes and producing full or partial loss of exons [12] can also be found to occur.

It is known that the mutation in the *BRCA1* gene presents a risk of ovarian cancer throughout life of up to 40%, while the *BRCA2* gene has a 20% risk. Although penetrance may vary in the same family carrying a mutation, suggesting that the risk can be influenced by allelic heterozygosity, modifier genes, and environmental and hormonal cofactors [13,14].

After the diagnosis of breast cancer in a patient with a *BRCA* mutation, there is a subsequent risk of developing ovarian cancer of up to 12.7% in women for *BRCA1* and 6.8% for *BRCA2* [15].

Diagnosis in elderly or the absence of family history does not exclude the presence of a germline mutation as approximately 35% of the *BRCA* mutation carriers have no family history. Genetic tests are expensive, so you should select the most appropriate individuals for genetic testing, varying recommendations between populations and countries.

The presence of *BRCA* somatic and germline mutations are predictors of response to different chemotherapy treatments because they exhibit greater sensitivity and response to platinum-type drugs or PARP inhibitors, which are involved in the repair of DNA single-strand breaks [16].

It is important that families carrying this mutation are informed about the risks of developing various types of cancer, including education about prenatal diagnosis and assisted reproduction. Another option is IVF with previously selected embryos. Although, the decision should finally be made on an individual basis and will depend on the preference of each patient.

3. Patients with ovarian cancer *BRCA* genes mutations syndrome

Ovarian cancer is the principal cause of death in women with gynecological cancer, due to the late onset of symptoms and the absence of a method for early detection. Nulliparity, early menarche, and late menopause are associated with an increased risk of occurrence; however, the strongest risk factor is the history of ovarian cancer in a first-degree relative [17].

Malignant primary ovarian tumors fall into three main groups: epithelial, sex cord / stromal, and germ cell tumors. Epithelial tumors being ovarian carcinomas (CBs), which are the most common group, represent up to 90% of ovarian cancers. Low-grade and high-grade serous carcinoma (LGSC and HGSC), mucinous carcinoma (MC), endometrioid carcinoma (EC), and clear cell carcinoma (CCC) are the five histological subtypes of OCs that are known. It is important to make a proper histological typing to determine the prognosis and response to different treatments, including cisplatin [18].

A large proportion of ovarian tumors are sporadic, and only a minority is due to an inherited cause. *BRCA1* and *BRCA2* mutations have been identified in approximately 15% of all epithelial ovarian cancers and up to 22.6% in HGSC. Somatic mutations in *BRCA1* and *BRCA2* have also been identified in as much as 7% of all ovarian cancers [19,20]. Although up to 50%

http://dx.doi.org/10.5772/61938

of patients with HGSC harbor homologous recombination defects including the homologous recombination pathway independent of *BRCA 1/2*, this is known as *BRCA*-like behavior.

BRCA-like behavior is similar to when there is a loss of function or mutation of the *BRCA* genes with the same clinical and molecular characteristics. Examples include promoter methylation *BRCA1* (observed up to 35% of patients with epithelial ovarian cancer) and p53 mutation,

c-myc amplification or other proteins are needed for proper homologous recombination [21–24]. The loss of function of suppressor gene *PTEN* has also been shown to produce *BRCA*-like behavior [25], more common in breast and prostate cancers [26,27].

The HGSC subtype has a greater sensitivity to PARP inhibitors without a *BRCA* mutation, probably due to changes in DNA repair that occur up to 50% of cases as we have mentioned previously [28,18,29].

Studies describe that *BRCA* mutation carriers diagnosed with ovarian cancer have higher survival rates compared with sporadic cases [30–32]. This could be due to increased sensitivity to cisplatin.

In HBOC syndrome, mutations in the *BRCA-1* and *BRCA-2* genes associated with the development of ovarian cancer [29] occur. Other inherited syndromes have also been associated with an increased occurrence of ovarian cancer such as Lynch syndrome (hereditary nonpolyposis colorectal cancer syndrome), characterized by mutations in the DNA repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes [33].

3.1. Prevention of ovarian cancer in women who have mutations in *BRCA1* and *BRCA2* genes

Primary prevention strategies consist of primarily risk-reducing surgeries, the procedure of choice being prophylactic salpingo-oophorectomy bilateral from 35 to 40 years, or after childbearing. Some experts also recommend prophylactic hysterectomy to dry the small portion of remaining fallopian knotweed, although 92% of fallopian tube neoplasms originate in the middle or distal portion of the tube [34]. Although the final decision will be made by the patient.

Patients with *BRCA1* mutation are at increased risk of developing ovarian cancer from the age of 40; the recommendations as explained above are made from that age. This is not so with patients carrying the *BRCA2* mutation; the increased risk of ovarian cancer starts after age 50, so surgery can be postponed for a few years and secondary effects of surgery reduced [35].

After prophylactic surgery, one of the most important side effects which can deteriorate the quality of life of patients is premature menopause, with increased risk of osteoporosis and cardiovascular diseases such as hypertension, diabetes, and hypercholesterolemia. So that closer monitoring is recommended for cardiovascular risk [36].

Secondary prevention is early detection strategies in women carrying mutations in the *BRCA1* and *BRCA2* genes. Current recommendations include performing transvaginal ultrasound twice a year (preferably day 1–10 of the menstrual cycle), together with detection of serum CA-125 levels (after day 5 of the menstrual cycle for), from age 30 or five to ten years earlier

than the earliest age of first diagnosis of ovarian cancer in the family. But these methods have limited sensitivity and specificity, with no observed benefit in women carrying mutation since no mortality was reduced. All women who refuse to perform prophylactic surgeries should undergo screening every six months [37].

Despite the greatly reduced risk of developing ovarian cancer after prophylactic surgery, patients should know that a minority (from 3.9% to 4.3%) of them will develop primary peritoneal carcinoma 20 years after the last oophorectomy in patients with *BRCA*-1 mutations. So before you perform these procedures, patients should be informed of the risks and morbidities associated with these interventions [38,39].

4. Inhibitors of poly (ADP -ribose) polymerase

The preservation of the genetic code by DNA repair is essential for proper cell function. Currently, there is a better understanding of the DNA repair pathways, so it has been studied more carefully for potential drug targets [40].

There are at least five ways engaged in DNA repair, two of them involved in the repair of double-strand breaks (error-prone, non–homologous, end–joining, predominantly active in G1 cells, and error-free HRR, which predominates in dividing cells) [41].

The major DNA repair pathways are direct repair, mismatch repair (MMR), the base excision repair (BER), nucleotide excision repair (NER), and double-strand break repair recombination, which includes both non-homologous, end-joining and homologous recombination repair (HRR) [41,42].

There are certain external agents such as ionizing radiation producing damaging DNA strand breaks. Normal cells have the ability to repair this damage by a protection mechanism maintaining its normal function, but the tumor cells' ability to repair DNA is a radio-resistance mechanism. In recent years, studies have identified a number of agents in these pathways such as PARP inhibitors [43].

Poly (ADP-ribose) polymerase (PARP) inhibitors are a new class of targeted agents against ovarian cancer [44–46]. PARP is a nuclear enzyme whose function is to repair single-stranded DNA.

There are three generations of PARP inhibitor. The first generation of inhibitors included nicotinamide analogs. 3-Aminobenzamide was the first PARP inhibitor but was not considered powerful enough compared to the second generation [47]. Currently, clinical trials are aimed at third-generation inhibitors with greater potency and specificity, decreasing side effects, this includes olaparib.

DNA repair is essential for proper cell function. Each cell sustains many thousands of episodes of DNA damage every day, which will be repaired by a wide variety of repair mechanisms [48,49].

http://dx.doi.org/10.5772/61938

The *BRCA 1/2* genes are responsible for DNA repair known as homologous recombination (HR) repair. HR is a form of double-strand break repair that occurs in the G2 phase of the cell cycle where the second double-stranded copy of the DNA is used as a template to form an error-free repair [49].

Other DNA repair pathway, such as the non-homologous, end-joining (NHEJ) pathway, also plays a role in the anti-cancer mechanism of action of PARP inhibitors [50].

PARP inhibitors act by trapping PARP-1 and PARP-2 on the double-strand break and blocks DNA replication, which is more toxic to cells than the accumulation of DNA breaks [51]. Overall, in tumors in where there is an apparent defect in homologous DNA repair (and thus a defect in the repair of double-stranded breaks), they seem to be susceptible to PARP-inhibitor therapy. These include tumors associated with germline or somatic mutations in *BRCA 1/2* [52].

There are at least 17 PARP counterparts, with only three PARP-1, PARP-2, and PARP-3s that play a critical role in DNA repair [53,54]. The best known are PARP-1 and PARP-2 [55, 56], and the most studied PARP-1.

PARP-1 was the first to be reported in 1963 [57]. Durkacz [58] stated that modulating PARP1 could enhance the effect of chemotherapy.

PARP-1 contains three functional domains: the N-terminal DNA-binding domain (DBD), the center self-modification domain (DMA), and the C-terminal catalytic domain (CD). The DBD is involved in recognition of DNA-strand breakage and in the binding of PARP-1 to DNA. AMD can interact with many DNA damage response proteins and the CD includes a PARP signature motif and catalyzes the formation of PAR [59]. PARP-1 is essential for base excision repair (BER).

PARP-1 also contributes to other cellular processes such as gene transcription, and the regulation of the chromatin structure, to restart stalled replication forks due to nucleotide depletion or collisions with bulky lesions [52].

PARP-1 has been used in in vitro studies in combination with chemotherapy, to demonstrate its ability to inhibit the classical mechanisms of DNA repair, showing also increased distribution of cytotoxicity to the tumor, increasing their exposure by improving vascular perfusion. This resulted in further studies with PARP-1.

The DNA repair biology has allowed us to identify patients most likely to respond to treatment with PARP inhibitors [60].

PARP inhibitors act by synthetic lethality, which occurs when two independent conditions alone do not cause cell death but in combination are lethal. It occurs when a patient has an alteration in the homologous recombination (HR) such as in carriers of a mutation in *BRCA1* and *BRCA2* genes and the application of PARP inhibitors, causing cell death [61,62]. Up to 5% of cutaneous melanomas and gastric cancers, 1% of prostate cancers, and even 19% of familial pancreatic cancers will carry a germline mutation in *BRCA 1/2*, thus they have an altered HR and therefore they may also respond to PARP inhibitors [63].

PARP-2 cooperates with PARP-1 to synthesize poly (ADP-ribose) [pADPr] after damage in the DNA chain [41]. PARP-3 suppresses error-prone NHEJ [52, 64,65] while associated with

PARP-1 for DNA repair. The clinical development of PARP-inhibitors has lead to its use as monotherapy or in combination with chemotherapy agents. Olaparib has been recently approved for the treatment of hereditary breast ovarian cancer syndrome, and other PARP-inhibitors such as veliparib, rucaparib, or niraparib are being studied [66].

4.1. Combination therapy of PARP inhibitors and radiotherapy

The efficacy of radiotherapy in the treatment of cancer have been known for several years either concomitantly with chemotherapy or as adjuvant use in therapy.

New clinical trials not only focus on researching new systemic treatments alone or in combination with other chemotherapy agents but also study their association with radiotherapy. These new therapies are the PARP inhibitors that have shown activity in conjunction with radiation therapy in several cancer cell lines. Data suggest that PARP inhibitors may enhance the effects of radiation in various types of tumors, such as lung cancer, colorectal, and cervical among others [67]. However, the mechanism of action is still unknown, one hypothesis is that it is due to mutual damage (of PARP-inhibitors and radiotherapy) of DNA or whether tumor re-oxygenation contributes to this radio sensitization via the vasoactive effects of the PARP inhibitors remains to be fully determined [43].

A recently published Phase I clinical trial [68] combined low-dose abdominal level fractionated radiotherapy with increasing doses of the PARP-inhibitor veliparib in patients with peritoneal carcinomatosis secondary to advanced malignant solid tumors. Patients were treated with veliparib (80–320 mg daily) for a total of 3 cycles.

The dose of radiotherapy consisted of 21.6 Gy in 36 fractions, 0.6 Gy twice daily on days 1 and 5 for weeks 1–3 of each cycle. Twenty-two patients were included. Disease stabilization (≥24 weeks) was observed in 7 patients (33%). Median progression-free survival (MPFS) was 4.47 months and median overall survival (MOS) was 13.04 months. In the trial, there were 8 patients with ovarian and fallopian cancers with an observed MPFS of 6.77 months and an MOS of 17.54 months, combined with a higher quality of life. The toxicity grade 3 and 4 lymphopenia were more frequent (68%), anemia (9%), and thrombocytopenia (14%). With these results, the authors concluded that the combination of radiotherapy and veliparib resulted in a stabilization of the response in patients with solid tumors and peritoneal carcinomatosis, especially in the subgroup of patients with ovarian cancer, besides being a well-tolerated regimen.

5. OLAPARIB

Because many cytotoxic agents work by damaging the DNA, there has been a great deal of interest in the use of inhibitors of DNA repair such as new treatments against cancer, especially in patients with mutations in the *BRCA* genes with altered function, and will be more likely to develop different types of neoplasms due to increased tumorigenesis [69].

Olaparib is a member of the class of N-acylpiperazines formally obtained by condensation of the carboxyl group of 2-fluoro-5 - [(4-oxo-3,4-dihydrophthalazin-1-yl) methyl] benzoic acid with the free amino group of N- (cyclpropylcarbonyl) piperazine.

http://dx.doi.org/10.5772/61938

5.1. Initial clinical trials with OLAPARIB

In 2008, Rottenberg et al. [70] postulated the hypothesis of the use of olaparib (then called AZD2281, KU-0059436) in cancer triple negative breast, because these tumors harbor defects in DNA repair and mutations in *BRCA1*. To do this, they used PARP inhibitors (AZD2281) in genetically engineered mouse models of breast cancer *BRCA1*, resulting in an inhibition of tumor growth and increased overall survival with no signs of toxicity. Drug resistance developed after long-term treatment due to upregulation of efflux pumps; however, this was overcome by co-administration of the P-glycoprotein inhibitor tariquidar. They observed that the combination of AZD2281 with cisplatin or carboplatin increased progression-free survival, suggesting the effectiveness of AZD2281 as DNA-damaging agents.

Evers et al. [71] studied sensitivity to conventional cytotoxic drugs AZD2281 in cell lines with *BRCA2* mutations. AZD2281 was observed to be the drug that caused greater tumor reduction in the presence of *BRCA2* mutations, alone or in combination with cisplatin.

Fong et al. [60] conducted a Phase I clinical trial with escalating doses of mg to 600mg olaparib, in a population of 60 patients, including 22 mutation carriers in the *BRCA1* and *BRCA2* gene. Dose-limiting toxicity was observed in one of eight patients receiving 400 mg twice daily (grade 3 fatigue and mood alteration) and two of five patients who received 600 mg twice daily (grade 4 thrombocytopenia and drowsiness grade 3). In 63% of patients with cancer and carriers of *BRCA* mutations, a clinical benefit for a period of 4 months or more was observed and 8 patients had ovarian cancer.

In this study, patients resistance to platinum response was observed.

A year later, the same team of Fong et al. confirmed previous results by expanding a cohort of patients with mutations in *BRCA1* and *BRCA2*, including primary peritoneal cancer with ovary, and fallopian tube cancers (13 platinum-sensitive, 24 platinum-resistant, and 13 platinum-refractory) observing a clinical benefit response of up to 46%. The overall clinical benefit rate decreased due to insensitivity to platinum (platinum-sensitive patients: 69%, platinum-resistant: 46% refractory to platinum: 23%). The median response duration was 28 weeks, concluding that patients who were platinum-sensitive present a greater response to olaparib, in addition to showing a benefit in resistant and refractory patients [72].

Seventy five percent of *BRCA1*-mutated breast cancers are classified as triple-negative breast and *BRCA1* or *BRCA2* mutation carriers and have the tendency to develop ovarian cancer. In a Phase II clinical trial [63], the investigators administered 400 mg of olaparib twice daily in patients with ovarian cancer HGSC and triple-negative breast cancer. Patients were stratified according to whether they were carriers of *BRCA1*, *BRCA2*, and *BRCA* wild-type gene. The primary endpoint was objective response rate by Response Evaluation Criteria In Solid Tumors (RECIST). It was observed that 41% of patients with *BRCA* mutation carrier ovarian cancer and 24% of patients with wild-type *BRCA* showed no response to olaparib RECIST criteria. No confirmed objective responses were reported in patients with breast cancer and they concluded that olaparib is an efficient drug for treatment of *BRCA* mutant ovarian cancer.

Kaye et al. published the results of a Phase II trial in 2012. The study included 97 patients with ovarian cancer and *BRCA1* or *BRCA2* germline mutations that had recurred within 12 months

of prior platinum therapy. They randomized in a 1:1:1 ratio to receive olaparib 200 mg or 400 mg bd or pegylated liposomal doxorubicin (PLD) 50 mg / m2 intravenously. The median PFS was 6.5 months, 8.8 months, and 7.1 months for the olaparib 200 mg, 400 mg olaparib, and PLD groups, respectively. Objective response rates were 25, 31, and 18% for olaparib 200 mg, 400 mg olaparib, and PLD, respectively. Proving that olaparib 400 mg twice daily is an appropriate dose. A surprising finding was the effectiveness of PLD [74]. These results affirm the data published by Adams et al. [75] which show increased PLD activity in patients carrying a *BRCA* mutation.

Lederman et al. [76] reported on a Phase II trial; they administered olaparib as a maintenance therapy in patients with recurrent ovarian cancer or fallopian tube or primary peritoneal cancer of high-grade, which was platinum-sensitive. Patients were randomized to receive olaparib 400 mg twice daily or placebo within 8 weeks after the last dose of platinum-based chemotherapy. The primary endpoint was progression-free survival (PFS). A first analysis performed after progression in 57.7% of patients showed that PFS was significantly longer in the olaparib group than in the placebo group. Median PFS was 8.4 months in the olaparib group versus 4.8 months in the placebo group ($P < 0.001$). Subgroup analysis of progression-free survival showed that, in the olaparib group, patients had a lower risk of progression than those in the placebo group. Having had a complete response to the treatment of platinum-based chemotherapy before entering the study was a significant prognostic factor for longer progression-free survival (hazard ratio, 0.46; $P < 0.001$). Time to progression according to the RECIST guidelines or CA-125 level was significantly longer in the olaparib group than in the placebo group (median, 8.3 months vs. 3.7 months ($P < 0.001$). The response rate was 12% (7 of 57 with measurable disease patients at study entry) in the olaparib group, as compared with 4% ($P = 0.12$).

In the interim analysis of overall survival (OS), 101 patients (38%) had died: 52 in the olaparib group and 49 in the placebo group. No significant difference in overall survival was observed ($P = 0.75$). The median overall survival was similar in the two study groups (29.7 months in the olaparib group and 29.9 months in the placebo group). Although *BRCA* mutation status was known for 37% of all patients who entered the study, a subgroup analysis suggested that olaparib could increase PFS in patients with a *BRCA* mutation.

The incidence of adverse events grade 3 or 4 was higher in the olaparib group (35.3%) compared to the placebo group (20.3%). The most common adverse events leading to discontinuation or dose reduction of olaparib were vomiting, nausea, and fatigue. There were no statistically significant differences in quality of life test performed patients.

In another study, Lederman et al. [77] presented test data 19, a second retrospective analysis of OS, and *BRCA* mutation status of the Phase II trial published by them in 2012. The primary endpoint was PFS, analyzed for the overall population and by *BRCA* status. *BRCA* mutation status was known in 96% of patients in the group of olaparib compared to 95% in the placebo group, of whom 56% versus 50% had a deleterious or suspected tumor or deleterious *BRCA* germline mutation. The median PFS was significantly longer in the olaparib group compared to the placebo group, 11.2 months vs. 4.3 months; in the wild-type *BRCA* patients the findings were similar, 7.4 months vs. 5.5 months. In a second interim analysis (58% maturity), the OS was similar in patients with mutated *BRCA* and wild-type *BRCA*, this may be secondary to the

http://dx.doi.org/10.5772/61938

fact that 23% of patients receiving placebo could subsequently receive an inhibitor of PARP. In the results, they observed that some patients responded to olaparib in the absence of a *BRCA* mutation, this could be due to epigenetic silencing of *BRCA* or homologous recombination genes such as RAD51D.

There were more treatment interruptions and dose reductions in the olaparib group compared to placebo. Adverse effects grade 3 or 4 in the olaparib group were fatigue in 7% vs. 3% in the placebo group, and anemia 5% vs. <1%, respectively. Serious adverse effects were reported in 18% of patients receiving olaparib compared to 9% on placebo. Tolerability was similar regardless of the mutational status.

Although the number of patients treated with somatic *BRCA* mutations was lower, responses were also seen during maintenance therapy.

The test of olaparib superiority over the placebo in platinum-sensitive patients demonstrated that patients relapsed after treatment. In addition, it was shown that *BRCA* mutations, whether somatic or germ line, are the main determinants of response to olaparib.

After the results of test data19 were published, olaparib was approved by EMA as a maintenance therapy after response to platinum-based chemotherapy in relapsed platinum-sensitive ovarian cancer, fallopian tube, and primary peritoneal cancers patients with a *BRCA* mutation. In contrast, the FDA-approved olaparib in patients with high-grade serous ovarian epithelial tumors, primary fallopian tube and peritoneal cancers with a *BRCA* mutation who had progressed during three or more lines of chemotherapy.

Before starting treatment with olaparib, they confirmed the presence of a *BRCA* germline or somatic mutation, using a valid method of analysis in a specialized laboratory.

It also assessed the efficacy and tolerability of olaparib in combination with chemotherapy followed by maintenance olaparib versus chemotherapy alone in patients with high-grade serous ovarian cancer, including primary peritoneal and fallopian tubes, platinum-sensitive who had received three or more lines of platinum-based chemotherapy. AM Oza et al. [78] published data based on chemotherapy combination of carboplatin (area under the curve [AUC] 4 mg / mL per min) plus paclitaxel (175 mg / m2) every 21 days with olaparib 200 mg twice daily (during days 1–-10 of each cycle of 21 days), 6 total cycles followed olaparib maintenance monotherapy (400 mg twice daily) until disease progression or unacceptable toxicity, compared to chemotherapy alone (carboplatin AUC 6 mg / mL paclitaxel 175 mg / m2) without maintenance. The primary endpoint was PFS, the secondary efficacy endpoints were overall survival; percentage change in tumor size; the proportion of patients with an objective response according to RECIST; cancer antigen 125 (CA-125) response.

The results concluded that the PFS was higher in the olaparib plus chemotherapy group (median 12.2 months) compared with chemotherapy alone (median of 9.6 months). *BRCA* mutation status was known in 107 patients. *BRCA* mutations were observed in 41 (38%) of 107 patients (20 in the chemotherapy group and 21 in more olaparib chemotherapy alone); of the 41 patients with *BRCA* mutation, the PFS at 12 months was 70% for patients in the combination arm vs. 12.5% in the chemotherapy alone arm. There were no statistically significant differences

in OS or percentage change in tumor size. The proportion of patients with an objective response by the central review was similar between treatment groups. The two treatment groups had a similar proportion of patients with a CA-125 response and ovarian cancer response. The most frequent grade 3 or 4 adverse effects in the combination arm were neutropenia (43%) vs. (35%) in patients with chemotherapy alone and anemia ([9%] vs. [5%]). The most frequent adverse effects of mild or moderate intensity were alopecia, nausea, diarrhea, headache, and peripheral neuropathy among others, they were all more common in the combination group.

Not only olaparib has been studied in combination with chemotherapy, but their association was also analyzed with cediranib, an anti-angiogenic agent with activity against the VEGF receptor (VEGFR) 1, VEGFR2, and VEGFR3. In Phase I clinical trials, combination responses and manageable toxicities were observed, so that a Phase II clinical trial was developed aimed at demonstrating whether their combination would result in increased PFS versus olaparib monotherapy in women with recurrent platinum-sensitive ovarian cancer. The trial was conducted by Liu [79].

They recruited women with ovarian (HGSC and EC), fallopian tube or primary peritoneal cancer, or patients with a *BRCA* germ line mutation. Patients were randomized to receive olaoparib in 400 mg capsules twice daily or the combination of cediranib 30 mg daily and olaparib 200 mg capsules twice daily. The primary endpoint was PFS. 46 women received 44 olaparib monotherapy and combination therapy women. Median PFS was 17.7 months for the women treated with cediranib plus olaparib compared with 9 months in patients receiving olaparib monotherapy. Grade 3 and 4 adverse events were more common with the combination therapy, including fatigue, diarrhea, and hypertension. Thus, the authors concluded that PFS increases considerably with the combination therapy, so Phase III clinical trials are necessary to confirm these results, including assessments of quality of life.

Because of the mechanism of action of olaparib, the use of PARP inhibitor in other tumors with mutations in the *BRCA 1/2* gene could be effective, a Phase II clinical trial with different tumors was performed, all patients had *BRCA 1/2* mutations and recurrent cancer. The study was conducted by Kaufman et al. [52]. It was a prospective, multi-center, randomized trial, and patients were recruited in several centers in Israel, Australia, Germany, Spain, Sweden, and the United States between February 21, 2010, and July 31, 2012. It included patients with ovarian cancer resistant to prior platinum; with three breast cancer chemotherapy regimens for metastatic disease; pancreatic cancer progression during treatment with gemcitabine; with prostate cancer progression or on hormonal and one systemic therapy. Olaparib was administered 400 mg twice per day. The primary efficacy end point was tumor response rate according to RECIST. Secondary end points included: objective response rate (in those with measurable disease at baseline), PFS, duration of response, safety, and tolerability.

And 298 patients were evaluated, of whom 193 had ovarian cancer, 62 had breast cancer, 23 had advanced pancreatic cancer, and 8 patients with advanced prostate cancer. The remaining 12 patients had a range of cancers, including cancers of the biliary tract, bladder, colorectum, lung, esophagus, and uterus.

The tumor response rate was 26.2% (78 of 298; 95% CI, 21.3 to 31.6) overall and 31.1% (60 of 193; 95% CI, 24.6 to 38.1) in patients with ovarian cancer, 12.9% (eight of 62; 95% CI, 5.7 to 23.9)

http://dx.doi.org/10.5772/61938

in breast, 21.7% (five of 23; 95% CI, 7.5 to 43.7) in pancreatic, and 50.0% (four of eight; 95% CI, 15.7 to 84.3) in prostate cancers. In 42% of all patients, stable disease was observed after 8 weeks of treatment, up to 46.8% having achieved stabilization in cases of breast cancer. Overall median duration of the response was 208 days (ovarian cancer, 225 days; breast cancer, 204 days; pancreatic cancer, 134 days; prostate cancer, 327 days). Median time to onset of response was 56.0 days (ovarian cancer, 56.5 days; breast cancer, 54.5 days; pancreatic cancer, 113.0 days; prostate cancer, 54.5 days). The objective response rate (restricted to those with measurable disease at baseline) was 29.3% (95% CI, 23.9 to 35.2).

A similar response rate for patients with a *BRCA1* mutation (26.3 % ; 95 % CI, 20.3 to 33.0) and those with a *BRCA2* mutation was also noted.

The most common side effects were fatigue, nausea, and vomiting. About 54% of patients experienced grade 3 toxicity, most frequently fatigue and anemia, 40.3 % of patients had to modify (interruption and / or reduction) olparib dose due to adverse effects. Nine patients died as a result of severe adverse effects.

After these results, they concluded that the response to olaparib is independent of the anatomical organ of origin, provided that there is a mutation in *BRCA 1/2*.

Despite the demonstrated efficacy of PARP inhibitors in patients with *BRCA 1/2* mutation, there has been less activity in patients with breast cancer, perhaps due to the biologic heterogeneity and low *BRCA 1/2* mutation rate in somatic triple negative breast cancer [80–83].

5.2. Phase III clinical trials

Currently, there are two Phase III trials underway with olaparib, both sponsored by Astra Zeneca: SOLO 1 (NCT01844986) and SOLO2 (NCT01874353). Both are multi-center, double-blind, in which randomly assigned patients (2: 1) receive 300 mg of olaparib daily maintenance in patients diagnosed with high-grade serous or endometrioid ovarian cancer, primary peritoneal including and / or fallopian tube cancer with a *BRCA* mutation, and having partial or complete response after completion of platinum-based chemotherapy. To be included in SOLO1 trial, patients must have been newly diagnosed, with advanced (FIGO stage III-IV) disease, and responding to first-line treatment with platinum. To be included in SOLO2, patients must have completed ≥2 lines of platinum therapy. The main objective for both clinical trials is progression-free survival [84].

Not only they are testing olaparib, but there are also other Phase III trials with PARP inhibitors, such as veliparib, rucaparib, and niraparib, trying to improve the identification of patients who might best respond to PARP inhibitors [80] and reducing associated toxicities.

5.3. Combination therapy of OLAPARIB with other therapeutic agents

Olaparib has been tested in several clinical trials in combination with other chemotherapy because it was thought that it could increase sensitivity to chemotherapy by inhibiting DNA repair which could be responsible for drug resistance. This has been associated with topotecan [85], dacarbazine [86], paclitaxel [87], and cisplatin and gemcitabine [88]. In several Phase I

clinical trials, myelosuppression increased in the combination therapy versus monotherapy, especially with topotecan and cisplatin.

Olaparib has also been studied in combination with bevacizumab. Dean et al. [89] designed a Phase I clinical trial, as they hypothesized that bevacizumab antiangiogenic activity and hypoxia inducing DNA damage may enhance olaparib therapeutic activities. They showed that a dose of olaparib 400 mg twice daily in combination with Avastin 10mg / kg every two weeks was tolerated well. They are considering the combination for future clinical trials.

5.4. Dosage

The recommended lynparza® (olaparib) dose is 400 mg (eight capsules) twice a day, i.e., a total daily dosage of 800 mg. Treatment should begin before eight weeks of completion of the last cycle of chemotherapy with a regimen containing platinum. Continual treatment is recommended until disease progression. The recommended dose is reduced to 200 mg orally twice daily (total daily dose 400 mg). Elderly patients require a dose reduction initially, and it can be administered in patients with mild renal impairment (creatinine clearance> 50 mL / min).

5.5. Adverse reactions

Among the most frequent toxicities in clinical trials are hematologic toxicity with mild to moderate anemia, lymphopenia, neutropenia, and thrombocytopenia at manageable levels. Other frequently observed side effects are headache, fatigue, decreased appetite, abdominal discomfort, nausea, vomiting, diarrhea, and dyspepsia.

Another event that was observed was the development of myelodysplastic / AML syndrome, in only a small number of patients receiving olaparib alone or in combination with other antineoplastic during clinical trials. All had previously received platinum-based chemotherapy regimens, radiation, and other DNA-damaging agents.

There have been cases of pneumonitis, some of them being fatal. If patients are treated with Lynparza, respiratory symptoms such as cough, dyspnea, and fever should be closely monitored. If there is any alteration in the chest radiography, treatment must be stopped and the patient is treated appropriately. Paralyzer can cause birth defects if given to pregnant women. A reliable contraception should be recommended during treatment and one month after the last dose [90,63].

6. Mechanisms of resistance to PARP inhibitors

Targeted therapy based on the patient's mutation status is the future of the treatment of ovarian cancer. *BRCA* deficiency may be reversed by mutational changes in the reading frame, resulting in wild-type *BRCA* protein production. A second mutation (compensatory mutations or crossovers) can cause changes in the reading frame *BRCA* mutation, HR rebuilding, and restoring its functionality, explaining why not all tumors with *BRCA* mutation respond to PARP inhibitors [91]. Some *BRCA1* mutant alleles encode functional proteins but are degraded,

http://dx.doi.org/10.5772/61938

stabilizing the activity of the mutated protein and can reset the HR [92]. Another mechanism could be the upregulation of the pump glycoprotein efflux reducing concentrations of the intracellular PARP inhibitor [93,94] or loss of 53BP1, a key protein in the NHEJ pathway.

7. Conclusions

The context of the *BRCA 1/2*-mutant genotype has a significant impact on disease behavior and outcome. An encouraging data on responses to PARP inhibitors in *BRCA 1/2*-mutant carriers with prostate, pancreatic, and breast cancer have been reported and are likely to be associated with platinum sensitivity. It is apparent that establishing the germ-line and/or tumor *BRCA 1/2* mutation status in patients with cancers known to be associated with *BRCA 1/2* mutations is of notable importance due to the potential therapeutic options. Chemotherapy recommendation for patients with *BRCA 1/2* mutant epithelial ovarian cancer ought to be based on rechallenging these patients with platinum-based treatment, and prolonging the platinum-free interval in the event of early relapse following platinum-based treatment. The timing and sequence of therapy, and the indications for rechallenging patients with platinum-based chemotherapy, including routes and schedules of administration (IV vs. IP, weekly vs. thrice weekly), olaparib plus paclitaxel and carboplatin followed by laparib maintenance monotherapy, significantly improved progression-free survival versus paclitaxel plus carboplatin alone, in patients with *BRCA*-mutated recurrent platinum-sensitive ovarian cancer, with acceptable tolerability profile. It differs as more data emerges from analyses of the mutation status of *BRCA 1/2* genes and other HR-related genes in tumor samples from previously completed studies. In addition, stratification based on HR-deficiency phenotype/genotype may become the standard in future clinical trials involving patients with *BRCA 1/2* mutant epithelial ovarian cancer. It has been established that olaparib plus paclitaxel and carboplatin followed by olaparib maintenance monotherapy significantly improved progression-free survival versus paclitaxel plus carboplatin alone, in patients with *BRCA*-mutated recurrent platinum-sensitive ovarian cancer, with acceptable tolerability profile.

8. Future directions

Tumors with alterations in DNA repair lead to a defective HR, based on synthetic lethality and being very sensitive to PARP inhibitors. This happens with HGSC *BRCA* mutation carriers demonstrating its response to olaparib. We still need to better identify patients who will respond to PARP inhibitors because a proportion of patients developed resistance to these treatments, so research is needed to understand the mechanisms of action of PARP inhibitors and mechanisms of resistance. The only biomarkers that have been shown to be predictive of response while using PARP inhibitors are the *BRCA 1/2* mutations both somatic and germ line, in the absence of other biomarkers, we are limited to using the PARP inhibitors only in patients with *BRCA* mutation 1/2, although it may be effective in other tumors despite the absence of *BRCA* mutation.

We have studied the operation of Rad5 using antibody detection of Rad5 as new response PARP-inhibitors biomarkers, although initial results suggest that is not sufficient, specific and sensitive for use in clinical application, so we need to keep looking for new biomarkers or methods that help us to identify the appropriate patients for treatment with PARP inhibitors [52]. As not all genes responsible for DNA repair are known, another option that has not yet been implemented is to apply functional tests of DNA-repair capability, this would help us identify the abnormalities and tumors suitable for treatment with PARP inhibitors [95], the molecules involved in *BRCA*-like tumors whose information is essential to broaden the scope of action of PARP-inhibitors, without limiting its use for patients with *BRCA* 1/2 mutations. A current research topic is whether these new drugs work better alone or in combination with standard cytotoxic agents, avoiding toxicities and resistance mechanisms [96]. They have been shown to be well tolerated with manageable toxicity, but the long-term action is unknown. Some experts question whether inhibiting DNA repair can lead to deleterious effects such as an increased risk of developing other types of cancer in the future. Another topic of interest is its effect in combination with radiotherapy or as maintenance therapy. As of now, we do not know what effect PARP inhibitors may have in patients with low tumor burden, and what would be the benefit when these agents are used as maintenance therapy or chemoprevention.

Author details

Sandra García-Nieto[1], Carmen Guillén-Ponce[3*], Carmen Alonso[1],
María-Carmen Rodríguez-Soriano[2], María-Luz Pombo[1], Earl Julie[3] and Samir A. Farghaly[4]

*Address all correspondence to: carmenguillenponce@gmail.com

1 Oncology Department. Hospital General Universitario de Albacete. Albacete, Spain

2 Oncology Department. Hospital Virgen de la Luz. Cuenca, Spain

3 Oncology Departmen. Hospital Universitario Ramón y Cajal. Madrid, Spain

4 Joan and Sanford I. Weill Medical College/ The Graduate School of Medical Sciences, and The New York Presbyterian Hospital-Weill Cornell Medical Center, Cornell University, New York, NY, USA

References

[1] Chi DS, Eisenhauer EL, Zivanovic O, etal. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecol Oncol 2009;114:26–31.

[2] Jemal A, Bray F, Center MM, et al. Global cancer statistics.CA Cancer J Clin 2001;61:69–90.

[3] Diez O, Osorio A, Duran M, et al. Analysis of *BRCA1* and *BRCA2* genes in Spanish breast/ovarian cancer patients: a high proportion of mutations unique to Spain and evidence of founder effects. Hum Mutat 2003;22:301–12.

[4] Vicus D, Finch A, Cass I, et al. Prevalence of *BRCA1* and *BRCA2* germline mutations among women with carcinoma of the fallopian tube. Gynecol Oncol 2010.

[5] Jonkers J, Meuwissen R, van der Gulden H, et al. Synergistic tumor suppressor activity of *BRCA2* and p53 in a conditional mouse model for breast cancer. Nat Genet 2001;29:418–25.

[6] Liu X, Holstege H, van der Gulden H, et al. Somatic loss of *BRCA1* and p53 in mice induces mammary tumors with features of human *BRCA1*-mutated basal-like breast cancer. Proc Natl Acad Sci USA 2007;104:12111–6.

[7] Meek DW. Tumour suppression by p53: a role for the DNA damage response? Nat Rev Cancer 2009;9:714–23.

[8] Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene *BRCA1*. Science 1994;266:66–71.

[9] Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene *BRCA2*. Nature 1995;378:789–92.

[10] Elledge SJ, Amon A. The *BRCA1* suppressor hipothesis: an explanation for the tissue-specific tumor development in *BRCA1* patients. Cancer Cell 2002;1:129–32.

[11] Kelly L. Bolton; Georgia Chenevix- Trench; Cindy Goh, BA, et al. Association Between *BRCA1* and *BRCA2* Mutatiions and Survival in Women with invasive Epithelial Ovarian Cancer. J Am Med Assoc January 25, 2012;307:4.

[12] Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature 2001;411:366–74.

[13] Narod SA, Foulkes WD. *BRCA1* and *BRCA*-2:1994 and beyond. Nat Rev Cancer 2004;665–76.

[14] King MC, Marks JH, Mandello JB. Breast and ovarian cancer risks to due to inherited mutationes in *BRCA1* and *BRCA2*. Science 2003;302:643–46.

[15] Metkalfe KA, Lynch HT, Ghadirian P, et al. The risk of ovarian cancer after breast cancer in *BRCA1* and *BRCA2* carriers. Gynecol Oncol 2005;96:222–6.

[16] Burk RD. *BRCA1* mutations and survival in women with ovarian cancer 6. N Engl J Med 1997;336:1255–7.

[17] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;6:69–90.

[18] Pennington KP, Walsh T, Harrell MI, Lee MK, Pennil CC, Rendi MH, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res 2014;20:764–75.

[19] Alsop K, Fereday S, Meldrum C, DeFazio A, Emmanuel C, George J, et al. *BRCA* mutation frequency and patterns of treatment response in *BRCA* mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012;30:2654–63.

[20] Hennessy BT, Timms KM, Carey MS, Gutin A, Meyer LA, Flake DD, et al. Somatic mutations in *BRCA1* and *BRCA2* could expand the number of patients that benefit from poly (ADP ribose).

[21] Press JZ, De Luca A, Boyd N, et al. Ovarian carcinomas with genetic and epigenetic *BRCA1* loss have distinct molecular abnormalities. BMC Cancer 2008;8:17.

[22] Turner N, Tutt A, Ashworth A. Hallmarks of '*BRCA*ness' in sporadic cancers. Nat Rev Cancer 2004;4:814–9.

[23] Long KC, Kauff ND. Hereditary ovarian cancer: recent molecular insights and their impact on screening strategies. Curr Opin Oncol 2011;23:526–30.

[24] Walsh T, Casadei S, Lee MK et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci USA 2011;108:18032–7.

[25] Malkin D, Li FP, Strong LC et al. Germline p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233–8.

[26] Saal LH, Gruvberger-Saal SK, Persson C, et al. Recurrent gross mutations of the *PTEN* tumor suppressor gene in breast cancers with deficient DSB repair. Nat Genet 2008;40:102–7.

[27] Fraser M, Zhao H, Luoto KR, et al. *PTEN* deletion in prostate cancer cells does not associate with loss of RAD51 function: implications for radiotherapy and chemotherapy. Clin Cancer Res 2012;18:1015–27.

[28] Gelmon KA, Tischkowitz M, Mackay H, Swenerton K, Robidoux A, Tonkin K, et al. Olaparib in patients with high grade serous or poorly differentiated ovarian carcinoma or triple negative breast cancer: a phase 2, multicenter, open-label, nonrandomized study. Lancet Oncol 2011;12:852–61.

[29] Pennington KP, Swisher EM. Hereditary ovarian cancer: beyond the usual suspects. Gynecol Oncol 2012;124:347–53.

[30] Ben DY, Chetrit A, Hirsh-yechezkel G, et al. Effect of *BRCA* mutations on the length of survival in epithelial ovarian tumors. J Clin Oncol 2002;20:463–6.

[31] Majadak EJ, Debniak J, Milczek T, et al. Pronostic impact of *BRCA1* pathogenic and *BRCA1*/*BRCA2* unclassified variant mutations in patients with ovarian carcinoma. Cancer 2005;104:1004–12.

[32] Pharoah PD, Easton DF, Stockton DL, Gaytner S, Ponder BA. Survival in familial, *BRCA*-ASSOCIATED, and *BRCA2*-associated epithelial ovarian cancer. Unite Kingdom Coordinating Committee for Cancer Research (UKCCCR) Familial Ovarian Cancer Study Group. Cancer Res 1999;59:868–71.

[33] Lynch HT, Smyrk T, Lynch J. An update of HNPCC (Lynch syndrome). Cancer Genet Cytogenet 1997;93:84–99.

[34] Varado-Cabrero I, Young RH, Vamvakas EC, Scully RE. Carcinoma of the fallopian tube: a clinicopathological study of 105 cases with observations on staging and prognostic factors. Gynecol Oncol 1999;72:367–79.

[35] Rebbeck TR, Levin AM, Eisen A, et al. Breast cancer risk after bilateral prophylactic oophorectomy in *BRCA1* mutation carriers. J Natl Cancer Inst 1999:91:1475–9.

[36] Madalinska JB, Hollenstein J, Bleiker E, et al. Quality-of-life effects of propuhylactic salpingo-oophorectomy versus gynecologic screening among women at an increased risk of hereditary ovarian cancer. J Clin Oncol 2005;23:6890–8.

[37] Casey MJ, Synder C, Bewtra C, Narod SA, Watson P, Lynch HT. Intra-abdominal carcinmatosis after prophylactic oophorectomy in women of hereditary breast ovarian cancer syndrome kindreds associated with *BRCA1* and *BRCA2* mutations. Gynecol Oncol 2005;97:457–67.

[38] Finch A, Shaw P, Rosen B, Murphy J, Narod SA, Colgan TJ. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 *BRCA1* and *BRCA2* carriers. Gynecol Oncol 2006;100:58–64.

[39] Powell CB, Kenley E, Chen LM, et al. Risk-reducing Salpingo-oophorectomiy in *BRCA*mMutation carriers: role of serial sectioning in the detection of occult malignancy. J Clin Oncol 2005;23:127–32.

[40] Hansen K, Kelly M. Review of mammalian DNA repair and translational implications. J Pharmacol Exp Ther 2000;295:1e9.

[41] Plummer R. Poly (ADP- ribose) polymerase (PARP) inhibitors: from bench to bedside. Clin Oncol 2014;26:250–6.

[42] Christmann M, Tomicic MT, Roos WP, Kaina B. Mechanisms of human DNA repair: an update. Toxicology 2003;19:3e34.

[43] Pernin V, Mégnin-Chanet F, Pennaneach V, et al. Inhibiteurs de PARP et radiothérapie: rationnel et perspectives pour une utilisation en clinique. Cancer/Radiothérapie 2014 Dec;18:790–8.

[44] Do K, Chen AP. Molecular pathways: targeting PARP in cancer treatment. Clin Cancer Res 2012;19:977–84.

[45] Lord CJ, Ashworth A. The DNA damage response and cancer therapy. Nature 2012;481:287–94.

[46] Liu JF, Konstantinopoulos PA, Matulonis UA. PARP inhibitors in ovarian cancer: Current status and future promise. Gynecol Oncol 2014;133:362–9.

[47] Bauer PI, Buki KG, Hakam A, Kun E. Macromolecular association of ADP-ribose osyltransferase and its correlation with enzymic activity [J]. Biochem J 1990;270:17–26.

[48] Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature 2001;411:366–74.

[49] Calvert H, Azzariti A. The clinical development of inhibitors of poly(ADPribose) polymerase. Ann Oncol 2011;22(1):53–9.

[50] LoRusso P, Ji J, Li J, et al. Phase I study of the safety, pharmacokinetics and pharmacodynamics of the poly(ADP-ribose)polymerase (PARP) inhibitor veliparib (ABT-888) in combination with irinotecan (CPT- 111) in patients with advanced solid tumors. J Clin Oncol 2011;29 [Suppl.: abstract 3000].

[51] Tan AR, Toppmeyer D, Stein MN, Moss RA, Gounder M, Lindquist DC, et al. Phase I. trial of veliparib (ABT-888), a poly(ADP-ribose)polymerase (PARP) inhibitor in combination with doxorubicin and cyclophosphamide in breast cancer and other solid tumors. J Clin Oncol 2011;29 [Suppl.: abstract 3041].

[52] 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: Official J Am Soc Clin Oncol 2015;33:244–50.

[53] Sousa FG, Matuo R, Soares DG, et al. PARPs and the DNA damage response. Carcinogenesis 2012;33:1433–40.

[54] De Vos M, Schreiber V, Dantzer F. The diverse roles and clinical relevance of PARPs in DNA damage repair: Current state of the art. Biochem Pharmacol 2012;84:137–46.

[55] Lord CJ, Ashworth A. The DNA damage response and cancer therapy. Nature 2012;481:287–94.

[56] Rouleau M, Patel A, Hendzel MJ, Kaufmann SH, Poirier GG. PARP inhibition: PARP1 and beyond. Nat Rev Cancer 2010;10:293–301.

[57] Chambon P, Weill JD, Mandel P. Nicotinamide mononucleotide activation of new DNA-dependent polyadenylic acid synthesizing nuclear enzyme [J]. Biochem Biophys Res Commun 1963;11:39–43.

[58] Durkacz BW, Omidiji O, Gray DA, et al. (ADP- ribose)n participates in DNA excision repair [J]. Nature 1980;283(5747):593–6.

[59] Hassa PO, Haenni SS, Elser M, Hottiger MO. Nuclear ADP-ribosylation reactions in mammalian cells: where are we today and where are we going? Microbiol Mol Biol Rev 2006;70:789–829.

[60] Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. N Engl J Med 2009;361:123–34.

[61] Bryant HE, Schultz N, Thomas HD, et al. Specific killing of*BRCA2*-deficient tumors with inhibitors of poly (ADP-ribose) polymerase [J]. Nature 2005;434:913–7.

[62] Bryant HE, Petermann E, Schultz N, et al. PARP is activated at stalled forks to mediate Mre11-dependent replication restart and recombination [J]. EMBO J 2009;28:2601–15.

[63] Gelmon KA, Tischkowitz M, Mackay H, Swenerton K, Robidoux A, Tonkin K, et al. Olaparib in patients with recurrent highgrade serous or poorly differentiated ovarian carcinoma or triplenegative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 2011;12:852–61.

[64] Rulten SL, Fisher AE, Robert I, et al. PARP-3 and APLF function together to accelerate nonhomologous end-joining. Mol Cell 2011;41:33–45.

[65] Boehler C, Gauthier LR, Mortusewicz O, et al. Poly(ADP-ribose) polymerase 3 (PARP3), a new comer in cellular response to DNA damage and mitotic progression. Proc Natl Acad Sci USA 2011;108:2783–8.

[66] Lee J-M, Ledermann JA, Kohn EC. PARP-inhibitors for *BRCA* 1 / 2 mutation-associated and *BRCA*-like malignancies. Ann Oncol 2014;25:32–40.

[67] Powell C, Mikropoulos C, Kaye SB, et al. Pre-clinical and clinical evaluation of PARP inhibitors as tumour-specific radiosensitisers. Cancer Treat Rev 2010;36:566–75.

[68] Kim A. Reiss, Joseph M. Herman, Marianna Zahurak et al. A phase I study of veliparib (ABT-888) in combination with low-dose fractionated whole abdominal radiation therapy in patients with advanced solid malignancies and peritoneal carcinomatosis. Clin Cancer Res 2015;January 1(21):68.

[69] Simon R, Zhang X. On the dynamics of breast tumor development in women carrying germline *BRCA1* and *BRCA2* mutations. Int J Cancer 2008;122:1916–7. Ali M, Telfer BA, McCrudden C, et al. Vasoactivity of AG014699, a clinically active small molecule inhibitor of poly(ADP-ribose) polymerase: a contributory factor to chemopotentiation in vivo? Clin Cancer Res 2009;15:6106–12.

[70] 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 drugs. Proc Natl Acad Sci USA 2008;105:17079–84.

[71] Evers B, Drost R, Schut E, et al. Selective inhibition of *BRCA2*-deficient mammary tumor cell growth by AZD2281 and cisplatin. Clin Cancer Res 2008;14:3916–25.

[72] Fong PC, Yap TA, Boss DS, et al. Poly (ADP)-ribose polymerase inhibition: frequent durable responses in *BRCA* carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol 2010;28:2512–9.

[73] Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 2010;376:245–251.

[74] Kaye SB, Lubinski J, Matulonis U, et al. Phase II, openlabel, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer. J Clin Oncol 2012;30(4):372–9.

[75] Adams SF, Marsh EB, Elmasri W, et al. A high response rate to liposomal doxorubicin is seen among women with *BRCA* mutations treated for recurrent epithelial ovarian cancer. Gynecol Oncol 2011;123(3):486–91.

[76] Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366:1382–92.

[77] Ledermann J, Harter P, Gourley C. Olaparib maintenance therapy in patients with platinumsensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by *BRCA* status in a randomised phase 2 trial. Lancet Oncol 2014;15:852–61.

[78] Oza AM, Cibula D, Benzaquen AO, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Th lancet Oncology 2015;16:87–97.

[79] Joyce F Liu, William T Barry, Michael Birrer, et al. Combination cedirani and olaparib versus olaparib alone for women with recurrent platinum- sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol 2014;15:1207–14.

[80] Scott CL, Elizabeth M, Scott HK. Poly (ADP-ribose) Polymerase inhibitors: recent advances and future development. J Clin Oncol 33.

[81] Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 2011;121:2750–67.

[82] Balko JM, Giltnane JM, Wang K, et al. Molecular profiling of the residual disease of triple-negative breast cancers after neoadjuvant chemotherapy identifies actionable therapeutic targets. Cancer Discov 2014;4:232–45.

[83] Gonzalez-Angulo AM, Timms KM, Liu S, et al. Incidence and outcome of *BRCA* mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res 2011;17:1082–9.

[84] Kathleen NM, DiSilvestro P, Elizabeth S, Sally G, Pujade-Lauraine E. SOLO1 and SOLO2: Randomized phase III trials of olaparib in patients (pts) with ovarian cancer and a *BRCA1/2* mutation (*BRCA*m). J Clin Oncol 2014;32:5s(suppl; abstr TPS5616).

[85] Samol J, Ranson M, Scott E, et al. Safety and tolerability of the poly(ADP-ribose) polymerase (PARP) inhibitor, Olaparib (AZD2281) in combination with topotecan for the treatment of patients with advanced solid tumours: a phase I study. Invest New Drugs 2011;30(4):1493–500.

[86] Khan OA, Gore M, Lorigan P, et al. A phase I study of the safety and tolerability of olaparib (AZD2281, KU0059436) and dacarbazine in patients with advanced solid tumours. Br J Cancer 2011;104:750–5.

[87] Dent RA, Lindeman GJ, Clemons M, et al. Safety and efficacy of the oral PARP inhibitor Olaparib (AZD2281) in combination with paclitaxel for the first or second-line treatment of patients with metastatic triple-negative breast cancer: results from the safety cohort of a phase I/II multicenter trial. J Clin Oncol 2011;28(15S):1018 (abstract).

[88] Rajan A, Carter CA, Kelly RJ, et al. A phase I combination study of olaparib with cisplatin and gemcitabine in adults with solid tumours. Clin Cancer Res 2012;18(8): 2344–51.

[89] Dean E, Middleton MR, Pwint T, et al. Phase I study to assess the safety and tolerability of Olaparib in combination with Bevacizumab in patients with advanced solid tumours. Br J Cancer 2012;106(3):468–74.

[90] Chen Y, Zhang L, Hao Q. Olaparib: a promising PARP inhibitor in ovarian cancer therapy. Arch Gynecol Obstet 2013;288:367–74.

[91] Norquist B, Wurz KA, Pennil CC, Garcia R, Gross J, Sakai W, et al. Secondary somatic mutations restoring *BRCA1*/2 predict chemotherapy resistance in hereditary ovarian carcinomas. J Clin Oncol 2011;29:3008–15.

[92] Johnson N, Johnson SF, Yao W, et al. Stabilization of mutant *BRCA1* protein confers PARP inhibitor and platinum resistance. Proc Natl Acad Sci U S A 2013;110:17041–6.

[93] Sakai W, Swisher EM, Karlan BY, et al. Secondary mutations as a mechanism of cisplatin resistance in *BRCA2*-mutated cancers [J]. Nature 2008;451:1116–20.

[94] 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. PROC Natl Acad Sci USA 2008;105:17079–84.

[95] Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res 2014;20:764–75.

[96] Liu JF, Konstantinopoulos PA, Matulonis UA. PARP inhibitors in ovarian cancer: Current status and future promise. Gynecol Oncol 2014;133:362–9.