Review Article

Current evidence of *BRCA* mutations in genitourinary and gynecologic tumors: a scoping review

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Background and Objective: Breast cancer genes *BRCA1* and *BRCA2* are tumor suppressor genes associated with an increased risk for developing particular types of tumors. Besides breast cancer, they are involved in the occurrence of a number of genitourinary and gynecologic cancers, such as ovarian, prostate and endometrial cancers. This article provides a comprehensive review of the literature on *BRCA*-mutated ovarian, prostate and endometrial cancers with a focus on the therapeutic implication of *BRCA* mutations.

Methods: Full-length manuscripts published in English until 2021 gathered from PubMed were used to inform this review.

Key Content and Findings: Regimens containing PARP inhibitors are effective for cancer patients having a *BRCA* gene mutation. While three PARP inhibitors are FDA-approved for the treatment or maintenance of ovarian cancer (olaparib, rucaparib and niraparib); several ongoing clinical trials are assessing the efficacy of these drugs in endometrial and prostate cancers. Several therapeutic agents have been studied in combination with PARP inhibitors enabling further antitumor responses.

Conclusions: The advances in the molecular testing field as well as the ongoing preclinical and clinical studies will undoubtedly pave the way for the discovery and implementation of new robust approaches in the era of precision medicine.

Keywords: *BRCA*; ovarian cancer; endometrial cancer (EC); prostate cancer (PC); PARP inhibitors; precision medicine

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Introduction

Mutations in the tumor suppressor genes breast cancer genes 1 (*BRCA1*, 17q21, 113705 OMIM) and 2 (*BRCA2*, 13q12.3, 600185 OMIM) (*Figure 1A*) are associated with a significant increased risk of particular types of epithelial malignancies (1). Both genes are inherited in an autosomal dominant fashion, they encode proteins that are part of the homologous recombination (HR) repair pathway (*Figure 1B*), and that are actively involved in the DNA damage repair (DDR) process (2-4). Therefore, functional BRCA1 and BRCA2 proteins have a crucial role in the repair of double-stranded DNA breaks (5). Hereditary components, such as mutations in *BRCA1* and *BRCA2*, have been found to account for around 5% to 10% of all breast

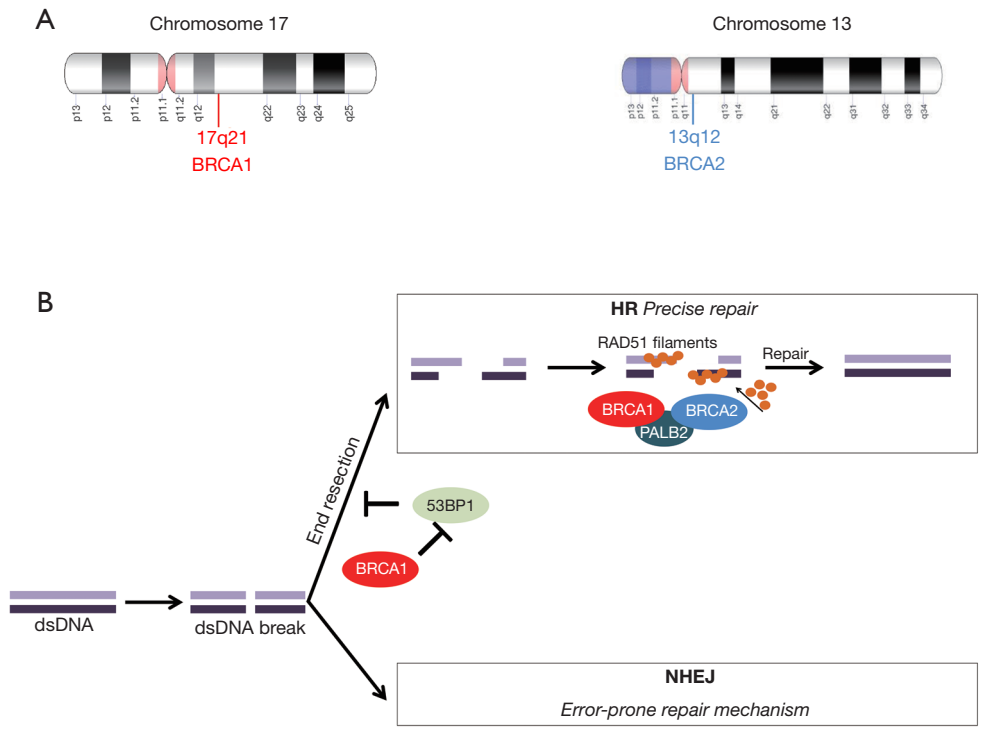

Figure 1 Overview of the roles of BRCA1 and BRCA2 in the DNA repair mechanism. (A) *BRCA1* and *BRCA2* loci on chromosomes 17 and 13, respectively. (B) The initiation of the double-stranded DNA (dsDNA) break correction starts with BRCA1 binding to the site of damage, thus initiating the precise repair via homologous repair (HR) and preventing non-homologous end joining (NHEJ).

cancers (6). Among hereditary breast cancers, germline mutations in *BRCA1* and *BRCA2* account for around 30% of all cases; they are mainly associated with early-onset breast cancer, bilateral breast cancer, triple negative (ER, PR and HER2 negative) breast cancer, with the major feature being strong familial history of breast cancer (7,8). Apart from breast and ovarian cancers, mutations in *BRCA1* and *BRCA2* are associated with an increased risk for cancers of the uterine tubes and peritoneum cancers, while *BRCA2* mutations are linked to an increased risk for male breast cancer as well as pancreatic cancer, PC and melanoma (9). All cancers, correlated with a confirmed germline *BRCA* mutation, are part of the "hereditary breast and ovarian cancer" (HBOC) syndrome (9,10). It has been reported that HBOC patients are also at an increased risk for developing other types of neoplasms such as PC, gastric cancer, pancreatic cancer and melanoma (11).

In this review, we attempt to provide a comprehensive review of the literature on *BRCA*-mutated ovarian, prostate and endometrial cancers (EC), while highlighting the prevalence and prognostic role of *BRCA* mutations in genitourinary and gynecologic cancers. We also outline the therapeutic implications and the potent role of PARP inhibitors in the aforementioned genitourinary and gynecologic cancers. The authors present the following article in accordance with the Narrative Review reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-47/rc).

Methods

Systematic literature search was conducted in PubMed using the terms: BRCA, BRCA1 and BRCA2, ovarian cancer, endometrial cancer, prostate cancer, PARP inhibitors. Only English language articles were included (*Table 1*).

Ovarian cancer and *BRCA*

Ovarian cancer (OC) is the eighth most common cancer in women worldwide, and to date the majority (75–80%) of patients are diagnosed at an advanced stage of the disease (12,13). It represents the second most common gynecological malignancy with a worldwide incidence of around 225,000 women per year (14).

Table 1 Summary of the search strategy

Items	Specification
Date of search (specified to date, month and year)	August to November 2021
Databases and other sources searched	PubMed
Search terms used (including MeSH and free text search terms and filters)	BRCA, BRCA1, BRCA2, ovarian cancer, endometrial cancer, prostate cancer and PARP inhibitors
Timeframe	From inception until November 2021
Inclusion and exclusion criteria (study type, language restrictions, etc.)	Inclusion criteria: studies published in English and including the search terms used
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	AC, ER and SB conducted the data selection

Over the last two decades, the standard of care for women with advanced OC has been a combination of cytoreductive surgery and systemic platinum-based chemotherapy. However, most of the patients with advanced disease have unfortunately, a high risk of relapse within 3 years into the treatment (15). Most OC are part of the autosomal dominantly-inherited cancer-predisposition syndrome HBOC that predisposes to breast and ovarian cancers. HBOC syndrome stems from germline mutations mainly in *BRCA1* or *BRCA2* (11). Heterozygous carriers of *BRCA1* or *BRCA2* mutations have an increased lifetime risk of developing OC, with an estimated likelihood of 40–60% for *BRCA1* and 11–30% for *BRCA2* (16,17). Germline mutations in *BRCA* genes have been reported in several histological subtypes of OC (Endometrioid, clear cell) with the highest rates of mutations reported in high-grade serous OC (18-21). The prevalence of *BRCA1/2* mutations in OC vary between 10 and 25% depending on the OC subtype (22-25). The presence of a germline *BRCA* mutation in high-grade serous OC patients confers a survival benefit when compared to patients with no germline mutation (26). *BRCA2* mutation carriers, in particular, have a higher survival rate probably due to the role of BRCA2 protein in regulating the process by which the crosslink damage repair occurs (27).

The histologic, molecular, and genetic evidences unveiled over the last decade show that the majority of the fallopian tube cancers and primary peritoneal carcinoma should be considered collectively a single entity and treated similarly to OC (28). In 2014, the FIGO's Committee for Gynecologic Oncology revision of the staging of ovarian cancer incorporated ovarian, fallopian tube, and peritoneal cancer into the same system (29). These three entities were traditionally included in the same pivotal trials of PARP inhibitors however, a recent SEER analysis showed a differential effect of the treatment eras across the different tumors (30). The findings of this study cannot be over-interpreted because of its retrospective methodology and the inherent limitations to registry analysis. Subgroup analyses of the phase III randomized controlled trials, by tumor subset, would shed more light on the differential effects of PARP inhibitors.

It is currently well established that *BRCA*-associated OC display distinct clinical characteristics with a relatively earlier age at diagnosis, improved survival, visceral disease, and higher response rates to specific chemotherapies and other types of treatments (discussed in the section "Targeting BRCA-mutated cancers" of this review) (13,31).

EC and *BRCA*

EC is the fifth most common female cancer in developed countries (32). EC can be divided into two histological categories, with different incidence and prognosis: type I (80% of cases) including low grade tumors with a relatively good prognosis and type II (20% of cases) including high grade endometroid tumors with a relatively poor prognosis (32,33). Numerous risk factors are reported to be linked to EC including non-genetic (i.e., exposure to estrogens, menarche at early age, late onset menopause, obesity etc.); and genetic factors reported in several familial cases (34,35).

Hereditary EC is part of 3 different syndromes: Lynch syndrome, Cowden syndrome and HBOC syndrome (35-37). Lynch syndrome is caused by dominant mutations

in DNA mismatch repair (MMR) genes such as MutL Homolog 1 (*MLH1*), MutS Homolog 2 (*MSH2*), MutS Homolog 6 (*MSH6*) and PMS1 Homolog 2 (*PMS2*); patients who carry a germline mutation in one of these MMR genes have a 20–70% cumulative lifetime risk to develop EC, particularly women with mutations in *MSH2* or *MLH1* (36-38). Cowden syndrome is a rare condition stemming from a mutation in the tumor suppressor gene Phosphatase and Tensin Homolog (*PTEN*), it is characterized by the development of tumors in multiple organs and includes an increased risk for EC (35). While HBOC patients have an increased likelihood to develop EC, the classification of EC as part of HBOC is still debatable, although, new evidence favoring EC as part of the *BRCA*-associated HBOC syndrome with unfavorable clinical outcome, has been reported (39), which might have important implications on the treatment strategies and clinical management of EC patients.

In most data reported on EC with germline *BRCA* mutations, the incidence of developing EC was assessed by age group, ethnicity or EC subtypes showing a slightly increased risk of EC in mutated-*BRCA* carriers, mainly *BRCA1*. In 2019, a multinational cohort study involving more than 11,000 *BRCA1* mutation carriers, clearly outlined the association between *BRCA1* mutations and the risk for EC (40). This was the earliest report linking *BRCA* mutations to the risk of developing EC. Further studies also reported high rates of *BRCA1* and *BRCA2* mutation carriers, in Jewish women with papillary serous uterine cancer (41-43). Another study, reported that the main contributor to the increased risk of EC among *BRCA* mutation carriers is tamoxifen exposure (44). The data was further corroborated to a lesser extent in another prospective study (45). On the other hand, studies disputing any association between *BRCA* mutations and the risk of developing EC were reported (46,47), namely a large cohort study of 1,170 cases of EC showing low incidence of germline *BRCA1/2* mutations in EC type I, type II and uterine serous cancers (48). A recent meta-analysis evaluating the risk of EC in *BRCA1* or *BRCA2* germline mutation carriers, reported that the prevalence rate of EC in *BRCA1/2* mutations carriers was 0.59% (49). In these studies, EC prevalence was 0.62% among *BRCA1* mutation carriers and 0.47% among *BRCA2* mutation carriers (49).

PC and *BRCA*

PC is the second most common neoplasm in men worldwide (50). In spite of all the advances achieved in PC care, the clinical outcome of patients with metastatic castration-resistant prostate cancers (mCRPC) is poor and the median overall survival (OS) still unsatisfactory (51). PC is ranked among the most heritable human cancers, a large proportion of mCRPC patients carry potentially actionable germline and somatic genetic variants, with *BRCA2* mutations representing the most common alteration (52-55).

Molecular studies have shown that genomic landscapes and patterns are different between mCRPC and localized PC (53,56,57). For instance, the incidence of germline mutations in DDR genes among men with metastatic PC reportedly ranges between ~11% and ~33%, which is significantly higher than in men with localized PC (56,57). Among the DDR defected genes, *BRCA2* is the most frequently mutated, followed by genes with lower mutation frequency such as *ATM*, *TP53*, *CDL12*, *CHEK2*, *BRCA1*, *FANCA*, *RAD51*, *MLH1* and other genes (56-58). A large study investigating 692 patients with metastatic PC, the prevalence of *BRCA2* mutations was 5.3% and *BRCA1* mutations was 0.9% (57). Several retrospective studies suggested a strong association between *BRCA2* mutations and PC risk with a 2 to 6 folds elevated risk compared to men in the general population; while BRCA1 mutations are mianly associated with a moderate risk of PC at younger ages (59-64). *BRCA2* mutations are considered as strong independent negative prognostic factors in patients with mCRPC, and are associated with short metastasis-free survival and cancer-specific survival (65,66). Furthermore, *BRCA* mutations are frequently diagnosed at an advanced stage (T3/T4), associated with nodal involvement and metastatic disease (65).

Conflicting results reported in several retrospective studies, made it unclear whether *BRCA2* mutations could affect the outcome of mCRPC patients treated according to standard recommendations (67-69). Reports have suggested that the choice of first-line therapy is the main factor that may affect the outcome for germline mutated *BRCA2* patients (70). PC is a clinically-heterogeneous disease, with patients responding variably to treatments leading to different outcomes; probably because of the molecular heterogeneity of PC cells. Therefore, molecular profiling could be of a great benefit, allowing the detection of *BRCA* mutations that can predict response to treatments such as the Poly-ADP ribose polymerase (PARP) inhibitors and the platinum agents. The therapeutic implication of *BRCA* mutations in PC will be detailed in the following section.

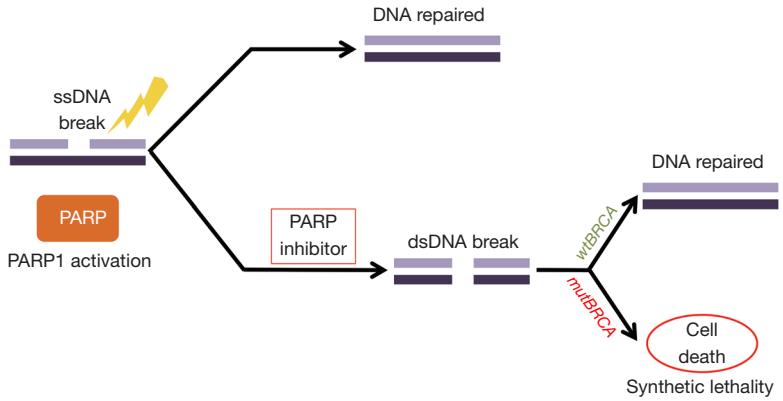

Figure 2 The concept of synthetic lethality. Poly-ADP ribose polymerase (PARP) inhibitors drugs inhibit PARP1 leading to cell death in mutant *BRCA1* or *BRCA2* (mutBRCA) cancer cells. While in wild-type BRCA (wtBRCA) cells, even in the presence of PARP inhibitors, the DNA damage will be repaired. ssDNA, single-stranded DNA; dsDNA, double-stranded DNA.

Targeting *BRCA*-mutated cancers

BRCA1/2 mutations are biomarkers that have an important role in the selection of treatment for breast and other cancers. Tumors that arise in individuals with a *BRCA* mutation have a homologous repair deficiency (HRD) (*Figure 1B*) (5), which may cause the cells to be sensitive to platinum-based chemotherapies and PARP inhibitors. In 2005, it was reported by two independent research groups that *BRCA*-deficient cancers are sensitive to PARP inhibition, uncovering the synthetic lethal interaction process that takes place between PARP inhibition and *BRCA* mutations (71,72).

Platinum-based chemotherapy

Platinum-based chemotherapy activity relies on its ability to interfere with DNA repair mechanisms leading to DNA damage and apoptosis in different cancer types. Whenever the tumor cells DNA repair mechanism is altered, the responses to platinum chemotherapy are enhanced (73). These cytotoxic drugs kill cancer cells through DNA damaging, DNA synthesis and mitosis inhibition; they also induce apoptosis (73).

Platinum-based anticancer agents have been extensively explored in numerous clinical trials, and have currently a wide spectrum of clinical application either as monotherapy or in combination with other chemotherapeutic agents, mainly in mCRPC but also in hormone-sensitive diseases (74,75). OC with a germline mutant *BRCA1* or *BRCA2* has a greater sensitivity to platinum-based treatment, as well as an improved OS compared to non-*BRCA*-related OC. However, despite initial high response rates to platinum and taxane-based first line chemotherapy, most OC patients would relapse, with a median progression-free survival (PFS) of 18 months (76).

Furthermore, relapses are followed by a substantial decrease in sensitivity to platinum-based chemotherapy resulting in the development of a resistance to platinum agents and the subsequent platinum-refractory disease, which is characterized by a progression of the disease within 6 months of platinum treatment initiation, and which usually has a very poor prognosis (77).

PARP inhibitors

PARP inhibitors rely on the concept of synthetic lethality in *BRCA*-deficient tumors through their inability to repair double-stranded DNA breaks, which leads to cell death (*Figure 2*) (78). In normal cells, PARP family of enzymes repair DNA damage at the site of single strand breaks through HR, base excision repair (BER) or nucleotide excision repair (NER) mechanisms (79). The concept of synthetic lethality describes a situation where a mutation in either of two genes individually has no serious effect, but where the combination of mutations leads to cell death; this was demonstrated in cell lines with *BRCA1* or *BRCA2* mutations (71,72). The mechanism behind the synthetic lethal interaction between PARP inhibition and loss of BRCA function is thought to be related to the accumulation of single-stranded breaks, that would block the replication fork and lead to double strand breaks (5,78). Normal cells have the potential to repair double strand breaks and stay

viable however, cancer cells with HRD are unable to do so. In the context of cancer cells with non-functional *BRCA*, it is thought that double strand breaks accumulate leading to highly toxic genomic lesions and instability, and finally cell death (5,78,80).

Therapeutic inhibitors of this pathway were first explored and the results published in 2009, in a phase I study (NCT00516373) on olaparib. The study demonstrated the anti-tumor activity of olaparib in cancers harboring *BRCA* mutations, with fewer adverse effects compared to conventional chemotherapy (31). In 2014, the European medicines agency (EMA) granted approval to olaparib in a maintenance setting for patients carrying *BRCA* mutations with recurrent high-grade serous epithelial OC, fallopian tube or primary peritoneal carcinoma (81). Few months later, the US food and drug administration (FDA), approved olaparib for the same aforementioned cancers, in patients with germline *BRCA* mutations previously treated with three lines or more of chemotherapy (82). Recently, a 5-year follow up phase III (NCT01844986) trial reported that the benefit derived from 2 years maintenance therapy with olaparib was sustained beyond the end of treatment, with an extended median PFS (56 months) (83).

Following olaparib's approval (NCT01874353), a remarkable improvement in PFS was reported in two randomized phase III clinical trials between 2016 and 2017, which led to the approval of rucaparib and niraparib (NCT01847274 and NCT01968213) as maintenance therapy for complete or partial platinum-sensitive recurrent *BRCA*-mutated ovarian cancers (84-86). The FDA and EMA approved the use of rucaparib in 2016 and 2018, respectively, for the treatment of high-grade serous epithelial OC, fallopian tube or primary peritoneal carcinoma with germline or somatic *BRCA* mutations, after two or more lines of chemotherapies (87-89). In 2017, the FDA and EMA approved niraparib as a maintenance treatment in patients achieving complete or partial remission after platinum-based therapy in patients with recurrent epithelial OC, fallopian tube or primary peritoneal carcinoma. In newly diagnosed patients with advanced OC who had a favorable response to platinum-based chemotherapy, niraparib treatment showed a longer PFS, regardless of the presence or absence of HRD (90). It was therefore suggested that resistance to platinum-therapy decreases sensitivity to PARP inhibition; however, another study, showed significant antitumor effect in patients classified with platinum-resistant disease (31,91).

Further testing and data analyses were conducted, upon which, PARP inhibitors were approved not only as maintenance but also as induction therapy, for pretreated recurrent ovarian cancer (82,88,92). Clinical trials further demonstrated notable clinical activity of PARP inhibitors in OC even in the absence of germline *BRCA* mutations (81,93). This was first reported in a phase II clinical study (NCT00679783) including patients with OC and unknown *BRCA* status, *BRCA*-negative or *BRCA*-positive, treated with olaparib (93). Subsequently, both FDA and EMA approved the use of olaparib as a maintenance therapy of platinum-sensitive recurrent OC regardless of *BRCA* mutational status (81,86).

Currently, clinical trials on olaparib, niraparib, rucaparib and talazoparib are being conducted in different settings and disease stage as monotherapy or in novel and standard of care combinations. For example, olaparib as maintenance monotherapy in platinum-sensitive relapsed germline-unmutated-*BRCA* OC (NCT03402841); niraparib as maintenance therapy in newly-diagnosed OC patients (NCT04986371); rucaparib as maintenance therapy after bevacizumab maintenance following carboplatin-based first-line chemotherapy in OC patients (NCT04227522); talazoparib and radiation therapy in treating patients with locally recurrent gynecologic cancers (NCT03968406), and many other clinical trials.

In PC, several PARP inhibitors are still under investigation especially in mCRPC patients. Research conducted in human PC cell line (DU145), confirmed what is known about olaparib this time in PC cells, confirming the trapping of PARP1 and PARP2 and providing a rationale for further researches (94). Olaparib was the first PARP inhibitor exhibiting significant activity in mCRPC patients. In a phase II clinical trial, among patients with DDR, 88% showed favorable response to olaparib and an improved radiologic PFS and OS (56). Olaparib, niraparib, rucaparib as well as talazoparib are currently being tested in many ongoing clinical trials (phase I, II or III) in order to assess the role and efficacy of PARP inhibitors in mCRPC (70) (i.e., NCT03874884, NCT02861573, NCT03787680, NCT03732820, NCT03834519, NCT03431350, NCT03748641, NCT03840200, NCT02975934, NCT04019327, NCT03395197, and other trials).

In EC, it is true that preclinical evidence reported sensitivity of PTEN-deficient cells to PARPi; however, to date there is no clinical evidence of activity in PTEN-altered tumors. Data from *in vitro* studies showed that *PTEN*-deficiency provides a significantly greater sensitivity to PARP inhibitors (KU0058948 or olaparib) (95,96). Indeed, *PTEN*-deficient EC cells were reported to be more sensitive to olaparib and talazoparib than wild-type *PTEN*

cell lines *in vitro*. Furthermore, since the PI3K/mTOR pathway is overactivated in *PTEN*-mutated cells, the use of PI3K inhibitors reportedly enhanced the sensitivity of these cells to PARP inhibitors (97). Moreover, *in vivo* studies conducted in mice, showed that PARP inhibitors in combination with hormonal therapy may increase the antitumor efficacy in *PTEN*-deficient EC (98). In two distinct case reports describing the use of olaparib with EC, the first patient had recurrent EC (*PTEN*-deficient, somatic *BRCA1/2* negative) with brain metastasis, and responded well to olaparib; she, however had progression of the disease 8 months upon the initiation of the treatment (99). The second case had a low-grade EC that relapsed (germline *BRCA2*-mutated), she received olaparib as a maintenance therapy, and showed a durable response and a stable disease documented for over 15 months (100). Currently, the role and efficacy of olaparib, niparaparib, rucaparib and talazoparib in recurrent, advanced and metastatic EC, as monotherapies or in combination with other therapies (i.e., NCT03745950, NCT03951415, NCT02755844, NCT04065269, NCT03617679, NCT03694262, NCT03552471, NCT04080284, NCT03016338, NCT02127151, NCT03968406, and others) are under evaluation in numerous phase I and II clinical trials.

Additionally, several clinical trials demonstrated significant benefit and improvement of PARP inhibitors, when used in other cancers such as HER2-negative *BRCA*-mutated breast cancers, and pancreatic cancers (82,101,102). Indeed, in 2018 olaparib and talazoparib were FDA-approved for patients with HER2-negative *BRCA*-mutated metastatic breast cancer with disease recurrence following chemotherapy (101,102). To date, there is insufficient data on the use of talazoparib for the treatment of OC. Few phase I clinical trials have been carried out on this matter (NCT01286987) (103,104), while other studies are still underway (NCT02316834, NCT02326844). Further studies and clinical trials are still needed, in order to compare the effect of talazoparib in OC with approved PARP inhibitors and to evaluate the benefits of this drug in OC.

Combining PARP inhibitors with other therapies

Combining PARP inhibitors with other therapies was explored in several studies that reported potential augmentation of DNA damages, enabling further antitumor responses. Several therapeutic agents have been studied in combination with PARP inhibitors, including inhibitors of vascular endothelial growth factor (VEGF), and PD-1/PD-L1, anti-CTLA4 monoclonal antibodies, mTOR inhibitor, AKT inhibitor, and PI3K inhibitor, as well as MEK 1/2, and WEE1 inhibitors (105). Current ongoing clinical trials are evaluating the combining effect of PARP inhibitors to other therapeutic agents. For instance, combined PARP inhibitors and immune checkpoint strategy was reported to induce important and efficient toxicity levels. On the other hand, combining olaparib with durvalumab (anti PD-L1) or niraparib with pembrolizumab (anti PD-1) demonstrated promising anti-tumour activity and safety similar to monotherapy strategy (106-108). Furthermore, combining PARP inhibitors with antiangiogenic agents such as olaparib and cediranib, a potent inhibitor of VEGF, showed promising results and a significant longer PFS compared to olaparib alone (109).

To sum up, among the four FDA-approved PARP inhibitors as monotherapy (*Figure 3*), to date, only three have been approved for the treatment or maintenance of OC: olaparib, rucaparib and niraparib. Several clinical trials evaluating the use of the FDA-approved PARP inhibitors as well as new molecules, as monotherapy or in combination, for the treatment of genitourinary and gynecologic tumors, are ongoing.

BRCAness, beyond BRCA1 and BRCA2 mutations

Over the last decade, it became clear that a proportion of sporadic cancers, especially HBOC (i.e., ovarian cancer), do not harbor *BRCA* mutations; although, they share similar pathological and clinical features as *BRCA*-mutated cancers. This concept was named "BRCAness" and it reflects the presence of a common phenotype between sporadic cancers and familial cancers harboring *BRCA* mutations (110). BRCAness describes the situation where a homologous recombination DNA repair defect is present with no germline *BRCA* mutation detected (111). The defective HR observed may be caused by several mechanisms, such as: hypermethylation of *BRCA1* promoter, somatic *BRCA* mutations, or defects in individual genes that can modulate HR repair (*ATM*, *ATR*, *CHEK1*, *CHEK2*, *DSS1*, *RAD51*, *NBS1*, *FANC* family of genes) (112). Also, *EMSY* amplification and *PTEN* mutation/deletion were reportedly associated with HRD (112); however, other studies reported that the link between *EMSY* or *PTEN* genes and HRD phenotype is not established (113,114).

Nowadays, the activity of PARP inhibitors is beyond the presence of germline *BRCA* mutations and more commonly applicable to HRD OC (90,115). This concept

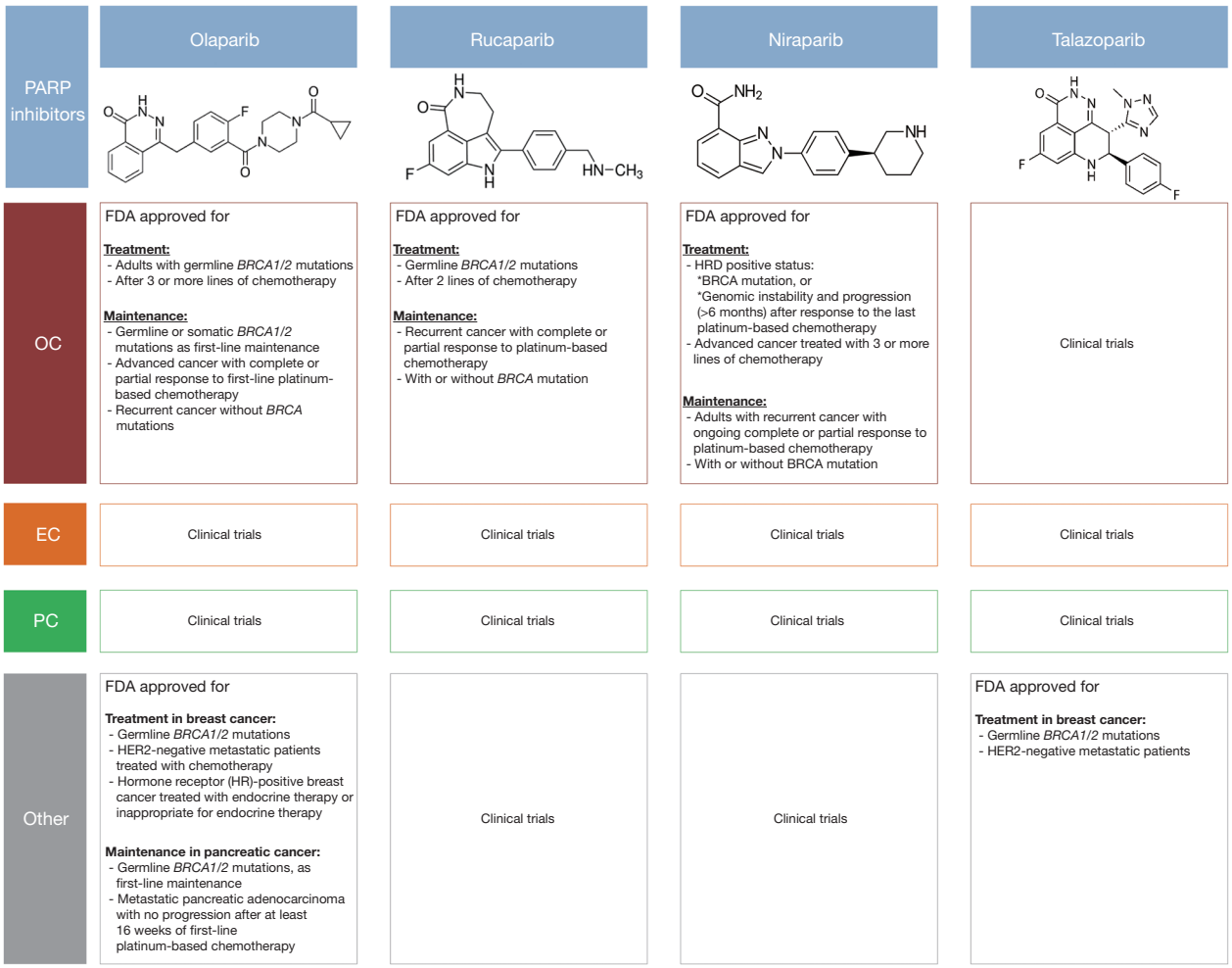

Figure 3 FDA-approved PARP inhibitors as monotherapy. Current status of FDA-approved PARP inhibitors (olaparib, rucaparib, niraparib and talazoparib) in ovarian cancer (OC), endometrial cancer (EC) and prostate cancer (PC).

is therapeutically and clinically important. Indeed, in several clinical trials on OC, it was reported that PARP inhibitors show activity despite the absence of *BRCA* mutations (81,93).

The ability to determine BRCAness has been improved by the recent advances accomplished in the field of molecular profiling of tumors. However, there is still limited activity detected beyond BRCA mutations. Identification of further functional biomarkers of HR repair (HRR) and responses to PARPi (56,116), would potentially expand our knowledge of cancer cells, and validate the utility of innovative targeted therapies such as PARP inhibitors.

Conclusions and perspectives

The booming of research investigating the interactions between cancer genes and potential therapeutic targets, reflects the success behind the discovery and development of the synthetic lethal therapies with PARP inhibitors for patients with *BRCA*-mutated cancer. To date, PARP inhibitors remain the only FDA-approved therapy using the synthetic lethality approach. Nevertheless, large-scale studies already uncovered additional synthetic lethal interactions that might be of use in targeting cancer cells (117), while other studies are underway for potential discovery of new therapeutic targets along the same concept. The advent of new scientific technologies, such as CRISPR interference (CRISPRi) method or its variant technique "Perturb-Seq" that allows the identification of gene signatures, new components to pathways and gene targets, may be a valuable additional tool that can be used to delineate large-scale

genetic interactions (118,119). Altogether, the advances in the molecular and genomic fields as well as the ongoing preclinical and clinical studies will undoubtedly pave the way for the discovery and implementation of new robust approaches in the era of precision medicine.

Identification of a *BRCA* mutation may not only help the afflicted patient, but it would as well allow genetic counseling and testing to be performed in relatives. Available data from preclinical, clinical and translational studies, enabled ongoing research for the evaluation of different therapeutic strategies such as combinations of PARP inhibitors and immune checkpoint inhibitors: PD-1/PD-L1 inhibitors in OC (NCT04191135, NCT03911453), and PI3K inhibitors in OC, PC and EC (NCT04586335); or association of PARP inhibitors and anti-angiogenic agents (i.e., NCT04566952). Outcoming results from several ongoing clinical trials would provide more comprehensive data on the clinical benefit of new drugs and new combinations (120).

An important non negligible factor however, is the resistance to PARP inhibitors. Previous studies reported that resistance may occur through different cellular mechanisms such as the restoration of homology-directed DNA repair as a result of *BRCA* reversions, or through the loss of 53BP1 (an important preclinical finding) by mutation/downregulation (121,122). Detection of these biomarkers and further identification of new ones would enable patient selection for PARP inhibitors. Another approach would be to overcome the acquired resistance to PARP inhibitors, for example by inhibiting CDK12, WEE1 or ATR (123-125). Along with the success accomplished with the development of PARP inhibitors, further studies exploring alternative approaches to overcome drug resistance are still needed in the purpose of widening the scope of clinical trials and shedding light on potential new therapeutical targets.

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