BRCA Mutations in Ovarian and Prostate Cancer

Subjects: Oncology

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DNA damage is one of the hallmarks of cancer. Epithelial ovarian cancer (EOC) —especially the high-grade serous subtype—harbors a defect in at least one DNA damage response (DDR) pathway. Defective DDR results from a variety of lesions affecting homologous recombination (HR) and nonhomologous end joining (NHEJ) for double strand breaks, base excision repair (BER), and nucleotide excision repair (NER) for single strand breaks and mismatch repair (MMR). Apart from the EOC, mutations in the DDR genes, such as BRCA1 and BRCA2, are common in prostate cancer as well. Among them, BRCA2 lesions are found in 12% of metastatic castration-resistant prostate cancers, but very rarely in primary prostate cancer. Better understanding of the DDR pathways is essential in order to optimize the therapeutic choices, and has led to the design of biomarker-driven clinical trials. Poly(ADP-ribose) polymerase (PARP) inhibitors are now a standard therapy for EOC patients, and more recently have been approved for the metastatic castration-resistant prostate cancer with alterations in DDR genes. They are particularly effective in tumours with HR deficiency.

DNA damage repair homologous recombination PARP inhibitors ovarian cancer prostate cancer

1. Introduction

Spontaneous DNA damage occurs on the order of 10^4–10^5 events per cell per day, and it is considered to have a causal role in aging. This includes spontaneous/endogenous genotoxic stress, as well as environmental/iatrogenic sources of genotoxic stress [1]. Endogenous sources of DNA damage and chromatin organization contribute to mutational processes that have been recorded in cancer genomes. Moreover, metabolism is a crucial cellular process that can become harmful for cells by leading to DNA damage. This can occur by an increase in oxidative stress or through the generation of toxic byproducts. In contrast, sources for exogenous DNA damage are rare and include ionizing and ultraviolet radiation, as well as various chemicals agents. Different mutational processes generate unique combinations of mutation types, termed “mutational signatures”. In the past few years, large-scale analyses have revealed many mutational signatures across the spectrum of human cancer types [2][3]. Genomic instability can arise from a genetic or epigenetic mutation in a mutator gene such as in a DNA damage repair (DDR) gene [4]. Several mechanisms can be activated to repair damaged DNA, including homologous recombination (HR) repair, nonhomologous end joining (NHEJ), base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR) [5][6]. HR is the main mechanism for high-fidelity repair of double-strand

DNA breaks (DSB) [7]. Mutations in genes related to this pathway may lead to HR deficiency. Among them, *BRCA1/2* mutations are the most frequent and lead to hereditary breast and epithelial ovarian cancer (EOC). Hereditary breast and ovarian cancer due to mutations in these genes is the most common cause of hereditary forms of both breast and ovarian cancer, accounting for 30–70% and approximately 90% of cases, respectively [8]. In individuals harboring mutations in *BRCA1/2* genes, the probability of developing breast cancer over a lifetime is around 85%, and that of EOC is about 20–40% [9]. *BRCA1* and *BRCA2* mutation carriers are mostly single heterozygous with only one mono-allelic deleterious mutation on one of these two genes. Excluding individuals of Ashkenazi descent, it is uncommon to identify carriers of two deleterious mutations either within the same gene (biallelic) or in both genes (trans-heterozygous). Trans-heterozygous mutations in both *BRCA1* and *BRCA2* genes are clinically correlated with an early age of onset and a severe disease compared to single heterozygous *BRCA* mutation carriers. Breast and ovarian cancer risks differ depending on the position and the type of *BRCA1* and *BRCA2* mutations. Importantly, two different mutations on the same allele may be associated with a distinctive phenotype, since each mutation is located in a different domain of the BRCA protein. Consequently, the interaction of BRCA with several other proteins could be disturbed. Therefore, these altered protein-protein interactions may impact on the phenotype. The *BRCA* mutation location also affects the EOC risk. *BRCA1* and *BRCA2* have been identified in the ovarian cancer cluster region in or near exon 11, and in the breast cancer cluster region in multiple regions other than exon 11 so far. In a recently published report, the authors presented the distribution of the age at diagnosis of EOC with *BRCA* mutation in detail, and analyzed the age by each common mutation type in a Japanese population [10]. The most common mutation in *BRCA1* was *L63X*, followed by *Q934 X*, *STOP799*, and *Y1853C*. Among them, *L63X* and *Y1853C* were located in the breast cancer cluster region, whereas *Q934 X* and *STOP799* were in the ovarian cancer cluster region. As far as the *BRCA2* mutations are concerned, the most common was *R2318X*, followed by *STOP1861*, *Q3026X*, *S1882X*, *P3039P*, *STOP613*, *S2835X*, and *STOP2868*. Among them, *R2318X*, *STOP1861*, and *S1882X* were located in the ovarian cancer cluster region, whilst *S2835X* and *STOP2868* were located in the breast cancer cluster region. Finally, *Q3026X*, *P3039P*, and *STOP613* were not located in either the ovarian or breast cancer cluster regions. Moreover, the majority of serous papillary peritoneal carcinoma are high-grade tumours, and thus present *p53* and *BRCA* mutations [11]. A number of additional variants in genes beyond *BRCA1/2* have been identified and are suspected to play a significant role in ovarian carcinogenesis. Approximately 20% of castration-resistant prostate cancer patients harbour germline or somatic mutations in one of the DDR genes, which supports the mechanism of synthetic lethality [12]. The two main composite HR deficiency tests available in clinical practice apply next-generation sequencing (NGS) or microarray assays to simultaneously search for *BRCA* mutations and genomic scars.

2. PARP Inhibitors Development across Tumour Types

There is an urgent need to better understand how the genomic and epigenomic heterogeneity intrinsic to EOC is reflected at the protein level, and how this information could potentially lead to prolonged survival [13]. The PARP inhibitors are a family of enzymes capable of catalyzing the transfer of ADP-ribose to target proteins. Among the 17 identified members of the PARP family, PARP-1 is the best characterized. It is responsible for approximately 90% of PARylation activity, whereas PARP-2 and to a lesser extent PARP-3 function in fewer, but overlapping, DNA

repair processes [14]. With the binding of PARP to damaged sites, its catalytic activity and eventual release from DNA potentiate the response of a cancer cell to DNA breaks induced by chemotherapeutics and radiation [15]. The approved PARP inhibitors inhibit both PARP-1, -2, and -3. AZD5305 is a novel agent, designed as a highly potent and selective inhibitor of PARP-1 with DNA-trapping activity. The phase I/II PETRA trial evaluated AZD5305 as monotherapy in patients with advanced metastatic breast, pancreatic, or prostate cancer with germline *BRCA1*, *BRCA2*, *PALB2*, or *RAD51C* mutations [16]. There was preliminary evidence of early circulating tumour DNA responses. AZD5305 significantly improved pharmacokinetics and exposure to a target compared with the already approved first-generation PARP inhibitors, and thus represents a major advance over them.

Several PARP inhibitors in clinical development have different potencies as PARP-1 catalytic inhibitors and as PARP-'trappers'. PARP inhibitors differ in terms of their metabolism; olaparib and rucaparib are metabolized by cytochrome P450 enzymes, whilst niraparib by carboxylesterase-catalyzed amide hydrolysis [17]. The potent antitumour effects of PARP inhibitors were originally observed in tumours harboring germline *BRCA1/2* mutations, such as familial breast and ovarian cancer. Among evaluated PARP inhibitors, olaparib, niraparib, and rucaparib are approximately 100-fold more potent than veliparib, while talazoparib has the most enhanced trapping potency [18]. The most common adverse events induced by PARP inhibitors are gastro-intestinal manifestations, myelosuppression, and fatigue. Nausea is the most prevalent gastro-intestinal adverse event. Symptoms are mainly mild and daily prokinetic, and antihistamine drugs are therapeutically recommended. Recalcitrant nausea or vomiting can be successfully controlled with a variety of antiemetic drugs, such as metoclopramide, prochlorperazine, phenothiazine, dexamethasone, olanzapine, haloperidol, or lorazepam. Of note, the neurokinin-1 receptor antagonist aprepitant is contraindicated with olaparib, since it is a strong CYP3A4 inhibitor and may derange olaparib's plasma concentrations. Other frequent gastrointestinal symptoms are constipation, vomiting, and diarrhoea, but grade 3 or 4 toxicities occur in less than 4% of patients. The treatment of choice is senna or polyethylene glycol 3350 for constipation, or loperamide for diarrhoea. Haematological toxicities tend to occur early after treatment initiation, with recovery after a few months. Among them, anaemia is the most common, related to PARP2 inhibition and erythrogenesis. In patients treated with niraparib, haematological adverse events represent the majority of grade 3 and 4 events, followed by rucaparib and olaparib. Haematological toxicities are the most common cause of dose modification, interruption, and discontinuation. The indications for transfusions include the symptomatic anaemia and the haemoglobin values of less than 7 g/dL. Thrombocytopenia of any grade is also more pronounced with niraparib. The cause of thrombocytopenia has been shown to be associated with a reversible decrease in megakaryocyte proliferation and maturation. Finally, fatigue is common for all PARP inhibitors and seems to be a class effect. Approximately 60–70% of patients experience fatigue of any grade with the three approved PARP inhibitors. The recommended management includes non-pharmacological approaches, such as exercise, massage therapy, and cognitive behavioural therapy, whilst pharmacological interventions with psychostimulants, such as methylphenidate and ginseng, may be considered in more symptomatic patients. The synthetic lethality may act against severe PARP inhibitor-mediated toxicity.

The successful story of PARP inhibitors in BRCA-deficient advanced breast and ovarian cancer has led to further investigation of their efficacy in prostate cancer, pancreatic and biliary tract malignancies, glioblastoma, and lung cancer. PARP inhibitors may also be effective in malignancies involving somatic mutations in DDR genes beyond

BRCA1/2. They could also potentiate immunotherapeutic activity in many ways. Indeed, they increase neoantigen burden through DNA damage. Presence of HR deficiencies such as *BRCA1/2* mutations cause amplification of tumour mutational burden and contribute to immune checkpoint inhibitor sensitivity. Furthermore, PARP inhibitor-induced DNA damage could promote recruitment of T cells via the stimulator of interferon genes (STING) pathway and type I interferons. Finally, PARP inhibitors can lead to acute inflammation, remodeling of the tumour microenvironment, and thus enhancement of immune response [19].

2.1. Development of PARP Inhibitors in EOC

The standard treatment for ovarian cancer consists of cytoreductive surgery, followed by postoperative platinum-based chemotherapy. Neoadjuvant chemotherapy is an alternative option for selected patients, which offers the opportunity to test upfront chemosensitivity and to identify patients at higher risk of relapse [20]. Nevertheless, disease recurrence is a common phenomenon. Bevacizumab—a humanized monoclonal IgG antibody that targets vascular endothelial growth factor (VEGF) receptor—was the first antiangiogenic agent to show clear therapeutic activity in recurrent disease in combination with chemotherapy, based on the results of two randomized controlled phase III trials [21]. Clinical trials of PARP inhibitors have assessed their efficacy and tolerance in the treatment of EOC. Three PARP inhibitors have been approved for the management of EOC in different settings; olaparib, rucaparib, and niraparib.

Chronologically, in 2014, the EMA approved olaparib in maintenance setting for patients with recurrent high grade serous EOC and *BRCA1/2* mutations. The initial study enrolled 19 patients with platinum-sensitive relapse. This research demonstrated improved PFS vs. placebo (8.4 vs. 4.8 months, hazard ratio (HR) 0.35), which was more pronounced in the subset with germline/somatic *BRCA1/2* mutations (11.2 vs. 4.3 months, HR 0.18) [22]. In the same year, the FDA approved olaparib as the first-in-class PARP inhibitor for germline BRCA-mutated patients, previously treated with at least three lines of chemotherapy [23]. In 2018, the approval was expanded to all platinum-sensitive patients, regardless of *BRCA1/2* status. The confirmatory phase III SOLO-2 trial demonstrated median PFS of 19.1 vs. 5.5 months for olaparib and placebo, respectively, in germline BRCA1/2 mutants [24].

Rucaparib was approved by FDA and EMA in December 2016 and May 2018, respectively, for those previously treated with two or more lines of platinum-based chemotherapy, who cannot tolerate further platinum. The phase II ARIEL2 study confirmed that rucaparib prolonged PFS in patients with platinum-sensitive recurrence [25]. BRCA1/2-mutant cancers had improved response (80% vs. 10%) and prolonged PFS compared to the LOH low subgroup (HR 0.27, $p < 0.0001$). A subsequent post hoc analysis concluded that a cut off of 16% compared to 14% for the LOH assay may represent a better predictor of PFS [26].

Finally, the FDA and EMA approved niraparib in maintenance setting in March and November 2017, respectively, based on the phase III NOVA trial [27]. Patients with platinum-sensitive disease were enrolled, regardless of either germline BRCA1/2 or HR deficiency status, while results were stratified to investigate the potential predictive role of HR deficiency biomarkers. Definition of HR deficiency was determined by the myChoice HRD test, which incorporates LOH, telomeric allelic imbalance (TAI), and large-scale state transitions (LST). Median PFS for the

non-germline BRCA carriers but signature-positive patients favoured niraparib (12.9 vs. 3.8 months, $p < 0.001$). Even patients without the HR-related signature achieved longer median PFS (6.9 vs. 3.8, $p = 0.02$). These data support that overall platinum-sensitivity status is correlated with PARP inhibitor sensitivity, although more benefit is seen in patients with canonical HR defects. A recently published meta-analysis explored the diversity of efficacy and safety of different PARP inhibitors in patients with EOC [28]. The results showed that either olaparib, niraparib, or rucaparib could prolong PFS over a placebo, whereas their long-term benefit was not limited to *BRCA* mutation status. Nevertheless, the analysis indicated that there was no difference in OS between olaparib and niraparib vs. the placebo. Finally, olaparib had the fewest grade 3 or higher adverse events, whereas no difference was identified between niraparib and rucaparib. However, researchers must be careful when considering those interpretations due to the methodological heterogeneity of the analysis.

Registration studies that led to approvals of PARP inhibitors for treatment of EOC are resumed in **Table 1**.

Table 1. Clinical trials of PARP inhibitors in ovarian cancer.

Study	Phase	Population	Treatment Arms	Outcome	P	Ref
STUDY 19	II	(1) Platinum-sensitive, advanced HGSOC (2) At least two prior lines of platinum-based CTH (3) Unselected for BRCA status	(A) Olaparib 400 mg BID (B) Placebo	(A): Median PFS 1. Overall population: 8.4 vs. 4.8 m 2. BRCA mutants: 11.2 vs. 4.3 m 3. BRCA wild type: 7.4 vs. 5.5 m (B): OS 1. Overall population: 29.8 vs. 27.8 m 2. BRCA mutants: 34.9 vs. 31.9 m 3. BRCA wild type: 24.5 vs. 26.2 m (C): ORR 12% vs. 4%	(A1): <0.001 (A2): <0.0001 (A3): 0.0075 (B1): 0.44 (B2): 0.19 (B3): 0.96 (C): 0.12	[22]
STUDY 42	II	(1) Platinum-resistant, advanced HGSOC (2) BRCA mutations	Olaparib 400 mg BID	(1) ORR: 34% (2) MDR: 7.9 m (3) PFS: 7 m (4) OS: 16.6 m		[23]
SOLO 2	III	(1) Platinum-sensitive, advanced HGSOC or HGEOC (2) At least two prior lines of	(A) Olaparib 300 mg BID (B) Placebo	Median PFS: 19.1 vs. 5.5 m	<0.0001	[24]

Study	Phase	Population	Treatment Arms	Outcome	P	Ref
		platinum-based CTH (3) BRCA mutations				
ARIEL2	II	Platinum-sensitive, advanced HGSOC or HGEOC	Rucaparib 600 mg BID	(A): Median PFS 1. BRCA mutants: 12.8 m 2. BRCA wild type LOH high: 5.7 m 3. BRCA wild type LOH low: 5.2 m (B): ORR 1. BRCA mutants: 80% 2. BRCA wild type LOH high: 39% 3. BRCA wild type LOH low: 13%	(A1): <0.0001 (A2): 0.011 (A3): 0.011	[25]
NOVA	III	(1) Platinum-sensitive, advanced HGSOC (2) At least two prior lines of platinum-based CTH (3) Stratification by gBRCAmut	(A) Niraparib 300 mg BID (B) Placebo	Median PFS (1) gBRCA mutants: 21 vs. 5.5 m (2) BRCA wild type HRD (+): 12.9 vs. 3.8 m (3) Overall non-gBRCA mutants: 9.3 vs. 3.9 m	(1): <0.0001 (2): <0.00001 (3): <0.0001	[27]
STUDY 10	I/II	(1) Platinum-sensitive, advanced HGSOC or HGEOC; (2) gBRCAmut (phase II PART 2A)	Rucaparib 600 mg BID	(1) ORR: 59.5% (2) MDR: 7.8 m		[29]
SOLO 1	III	(1) Platinum-sensitive, advanced HGSOC (2) BRCA mutations	(A) Olaparib 300 mg BID (B) Placebo	Median PFS: NR vs. 13.8 m 3-year PFS: 69% vs. 35%	<0.001 <0.001	[30]
SOLO 3	III	Recurrent gBRCAm EOC	(A) Olaparib (B) CTH	Median PFS: 13.4 vs. 9.2 m	0.013	[31]
PRIMA	III	Newly diagnosed advanced EOC with response to platinum-based CTH	(A) Niraparib 300 mg BID (B) Placebo	Median PFS (1) HRD (+): 21.9 vs. 10.4 m	(1): <0.001	[32]

Study	Phase	Population	Treatment Arms	Outcome	P	Ref
				(2) Overall population: 13.8 vs. 8.2 m	(2): <0.001	
QUADRA	II	(1) Platinum-sensitive, advanced HGSOC (2) HRD (+)	Niraparib 300 mg BID	(1) ORR 27.5% (2) DCR 68.6%		[33]
ARIEL3	III	Recurrent EOC after response to platinum-based CTH	(A) Rucaparib 600 mg BID (B) Placebo	Median PFS (1) BRCA mutants: 16.6 vs. 5.4 m (2) HRD (+): 13.6 vs. 5.4 m (3) ITT population: 10.8 vs. 5.4 m	(1): <0.0001 (2): <0.0001 (3): <0.001	[34]
PAOLA-1	III	Newly diagnosed, advanced, high-grade ovarian cancer with response after first-line platinum-taxane CTH plus bevacizumab	(A) Bevacizumab + olaparib maintenance (B) Bevacizumab + placebo	Median PFS (1) Overall population: 22.1 vs. 16.6 m (2) HRD (+): 37.2 vs. 17.7 m (3) HRD without BRCA mutations: 28.1 vs. 16.6 m	(1): <0.001	[35]

Abbreviations: PARP: poly(ADP-ribose) polymerase, Ref: reference, HGSOC: high-grade serous ovarian cancer, HGEOC: high-grade endometrioid cancer, gBRCAmut: germline BRCA mutation, BID: twice a day (bis in die), ORR: overall response rate, MDR: median duration of response, m: months, CTH: chemotherapy, PFS: progression-free survival, OS: overall survival, NR: not reached, EOC: epithelial ovarian cancer, HRD: homologous recombination deficiency, DCR: disease control rate, LOH: loss of heterozygosis, ITT: intent-to-treat.

otherapy, prostate eath [36]. AR splice Within this atment of metastatic castration-resistant prostate cancer [37]. AR is a critical regulator of DDR in prostate cancer, through regulation of the expression and activity of DNAPK. This is an enzyme that is key for the process of repairing DSB through NHEJ and also serves as a transcriptional modulator. AR-induced DNAPK activation promotes transcriptional networks that lead to cell migration and metastasis, thus linking the AR-DNA repair axis to tumour progression [38]. The combination of PARP inhibition and AR signaling inhibitors could represent an example of synthetic lethality. AR is a ligand-inducible transcription factor, whereas AR signaling inhibitors cause HR deficit. ADT results in the state of BRCAness, leading to sensitivity of prostate cancer to PARP inhibition in combination with AR signaling inhibitors [39]. Multiple clinical trials are studying PARP inhibitors as either monotherapy or combined therapy for prostate cancer. Among them, olaparib was the first PARP inhibitor showing efficacy in metastatic castration-resistant prostate cancer patients with prior progression to standard treatment. The combination of rucaparib with AR has been approved to guide therapy based on paclitaxel harmful *BRCA* mutations in patients with metastatic castration-resistant prostate cancer. This is the rationale behind the clinical trials of veliparib and talazoparib as well. Key clinical trial data for these four PARP inhibitors in prostate are depicted in **Table 2**.

Table 2. Clinical trials of PARP inhibitors in prostate cancer.

Clinical Trial ID	Phase	PARP Inhibitor	Population	PSA Response Rate	Primary Endpoint	Ref
NCT01682772	II	Olaparib	mCRPC patients previously treated with abiraterone or enzalutamide, and cabazitaxel	33% of patients (95%, 20–48)	RR, PSA, CTC	[40]
NCT01682772	II	Olaparib	mCRPC patients: (1) previously treated with one or two taxanes (2) DDR gene mutations	PSA levels decrease by ≥ 50%: 100% of BRCA2 and FANCA mutated mCRPC patients	RR, PSA, CTC	[41]
NCT02987543	III	Olaparib	mCRPC patients: (1) disease progression whilst on enzalutamide or abiraterone (2) ≥1 HRR gene mutation	Olaparib group: 30% of patients Control group: 10% of patients	rPFS	[42]
NCT02952534	II	Rucaparib	mCRPC patients: germline or somatic alteration in ≥1 prespecified HRR gene	47.8% of BRCA-mutated patients (95%, 26.8–69.4)	ORR	[43]
NCT04455750	III	Rucaparib	mCRPC patients, resistant to testosterone-deprivation therapy	Not completed	rPFS, OS	[44]
NCT02854436	II	Niraparib	mCRPC patients: (1) DDR gene mutations (2) disease progression on taxane and AR-targeted therapy	57% of patients (95% CI, 34–77)	ORR	[45]
NCT03148795	II	Talazoparib	mCRPC patients: (1) DDR-mutated (2) disease progression on taxane or AR-targeted therapy	Not completed	ORR	[46]
NCT04821622	III	Talazoparib	mCSPC patients with DDR gene mutations	Not completed	rPFS	[47]

The United Kingdom (UK)-based TOPARP (Trial of PARP inhibition in prostate cancer) phase II trial was conducted in two stages. TOPARP-A assessed anti-tumour activity of olaparib in a sporadic metastatic castration-resistant prostate cancer population, whilst TOPARP-B was conducted in a subset with known genomic background, specifically *BRCA2* or *ATM* mutations [40][41]. In the TOPARP-A study, olaparib led to a response rate of 33% (95% CI 20–48), reduction in CTC of 29%, and 50% decrease in PSA levels of 22% over the whole cohort [40]. However, when TOPARP-B patients were stratified based on NGS results, 88% responded to olaparib, namely, 80% of those with *ATM* mutations and all BRCA2 mutants. On the other hand, only 2 of 33 biomarker-negative patients (6%) had

Abbreviations: PARP: poly(ADP-ribose) polymerase; Ref: reference; mCRPC: metastatic castration-resistant prostate cancer; RR: response rate; PSA: prostate specific antigen; CTC: circulating tumour cells; DDR: DNA damage repair; HRR: homologous recombination repair; rPFS: radiographic progression-free survival; ORR: objective response rate; OS: overall survival; AR: androgen receptor; mCSPC: metastatic castration-sensitive prostate cancer.

a response to olaparib (sensitivity of 88% and specificity of 94%) [41]. These studies concluded that olaparib is primarily effective in metastatic castration-resistant prostate cancer patients with HR deficiency. Tumours with *BRCA1* or *BRCA2* alterations were more sensitive to olaparib as compared to those with alterations in any other DDR gene.

In the phase III biomarker-driven PROfound trial, the patients were divided into two cohorts. Cohort A assigned patients with *BRCA1*, *BRCA2*, and *ATM* mutations, and cohort B comprised those with mutations in one of the remaining 12 DDR genes [42]. The patients were given olaparib 300 mg twice daily and second line AR signaling inhibitors in a 2:1 ratio. In cohort A, the median radiographic PFS was 7.4 and 3.5 months in favour of olaparib, whilst the median OS was 18.5 and 15.1 months, respectively (HR 0.64, p = 0.02). The study met the primary endpoint for radiographic PFS. Based on the positive results of the PROfound trial, the FDA approved olaparib in January 2020 for the treatment of metastatic castration-resistant prostate cancer in patients with deleterious DDR gene mutations, followed by new hormone therapy. Even though it is an approved modality in the United States of America and Europe, this is not the case in the UK.

The TRITON2 and GALAHAD phase II trials investigated the potential therapeutic benefit of rucaparib and niraparib, respectively, in metastatic castration-resistant prostate cancer patients with DDR mutations and disease progression after AR signalling inhibitor or chemotherapy [43][45]. The TRITON2 trial enrolled 190 metastatic castration-resistant prostate cancer patients to be treated with rupacarib 600 mg twice daily. Among them, 52% had a *BRCA1/2* mutation, and the remaining had *ATM* (30%), *CDK12* (7%), *CHEK2* (4%), and other mutated genes (7%). The ORR was 44% for patients with *BRCA* mutations, but only 9.5% for *ATM,* and 0% for the remaining DDR genes [43]. These positive preliminary findings led to the FDA approval of rucaparib in May 2020 for *BRCA1/2* mutated metastatic castration-resistant prostate cancer patients who progressed after one to two lines of AR-directed therapy and one taxane-based chemotherapy. However, the TRITON2 study has not detected accurate biomarkers in non-*BRCA*-mutated tumours.

The GALAHAD trial enrolled 165 metastatic castration-resistant prostate cancer patients with germline pathogenic or somatic biallelic pathogenic alterations in *BRCA1* or *BRCA2* (BRCA cohort), or in other prespecified DDR genes (non-BRCA cohort), who were treated with niraparib 300 mg twice daily. The composite response rate—defined as ORR, conversion of CTC to <5/7.5 mL blood or ≥50% decline in PSA—was 63% in the BRCA and 17% in the non-BRCA cohort, respectively [45]. Similar to olaparib, rucaparib was approved by the FDA—but not by the EMA—for the treatment of metastatic castration-resistant prostate cancer patients with germline and/or somatic *BRCA1/2* mutations, who progressed on AR signaling inhibitor or taxane. Of note, the GALAHAD study stratified patients with biallelic mutations, whilst the TRITON2 and PROfound trials evaluated mono- and biallelic mutations in tumour tissue or plasma and tumour tissue, respectively. Whether the origin and type of *BRCA1/2* mutation (monoallelic vs. biallelic, somatic vs. germline) may potentially affect therapeutic response to PARP inhibitors requires further investigation.

3. Developing Predictive Biomarkers for PARP Inhibitors

The first clinical biomarker for the evaluation of response to PARP inhibitors was platinum sensitivity. The platinum-free interval is correlated with the clinical benefit rate of olaparib in *BRCA1/2* mutated EOC patients. The reported —in a phase I study—clinical benefit rate for the olaparib were 69.2% and 45.8% for the platinum-sensitive and platinum-resistant groups, respectively [48]. The subset of patients with germline *BRCA1/2*-mutated, platinum-sensitive disease achieved the best response to olaparib. On the other hand, the response to platinum-based chemotherapy is not always compatible with the response to PARP inhibitors. This is based on the fact that platinum sensitivity may result from defects in other DDR mechanisms, including NER [49]. Moreover, the secondary restoration of the function of *BRCA1/2* or other HR genes may lead to resistance to PARP inhibition, rather than to platinum resistance [50].

Multiplexed NGS panels investigate the mutation status of multiple genomic regions of interest, either through amplification or capture-based technologies. Multiplexed panels are successfully implemented in clinical practice, based on their lower cost and burden of bioinformatics requirements for the analysis of the data.

Molecular signatures, such as the HR deficiency scores, are crucial for therapeutic decisions. Most of the evidence on the predictive value of such signatures was obtained from the randomized trials of PARP inhibitors rucaparib and niraparib in EOC. HR deficiency is involved in the tumourigenesis of approximately 50% of high-grade serous ovarian carcinoma, whilst about 20% are caused by mutations in HR genes beyond *BRCA1/2* [51].

Several FDA-approved companion diagnostic tests for PARP inhibitors are currently available. BRACAnalysis CDx consists of two in vitro assays for germline *BRCA1/2* mutational identification; the BRACAnalysis CDx Sanger sequencing and the BRACAnalysis CDx Large Rearrangement Test (BART®). They are used for sequence variants and large rearrangements, respectively. Potential limitations of BRACAnalysis CDx are the detection of deletions > 5 bp, insertions > 2 bp, RNA transcript processing errors, and differentiation between gene duplication and triplication [52]. An additional critical limitation of these signatures is that the mutational/LOH patterns do not revert when a tumour has recovered HR function. As such, they may not be able to accurately predict PARP inhibitors' sensitivity in the subset of patients who have been previously treated and progressed on DNA damaging chemotherapy. Myriad's myChoice HR deficiency is an enhancement of BRACAnalysis CDx that identifies both germline and somatic *BRCA1/2* mutations, along with HR deficiency [53]. The created genomic scarring composite score represents a sum of LOH, TAI, and LST.

The RAD51 assay is also a promising candidate for predicting responses to PARP inhibition. RAD51 is an important protein in the HR repair pathway that can be easily detected with an immunofluorescence assay [54]. The induction of RAD51 foci formation after DNA damage has been associated with HR repair proficiency [49]. RAD51 can accurately identify all *PALB2*-mutated tumours as HR-deficient in clinical breast samples [55]. The RAD51 foci assay has also successfully been used as an in vitro predictive biomarker for PARP inhibition in cultures from the ascitic fluid of patients with EOC [56].

As far as prostate cancer is concerned, it has been reported that 30% of patients with metastatic castration-resistant prostate cancer respond to treatment with PARP inhibitors [41]. The first successful prostate cancer

biomarker study was the previously mentioned PROfound study, which demonstrated that patients with *BRCA1*, *BRCA2*, and *ATM* alterations responded better to PARP inhibitors and achieved a longer radiographic PFS and OS. In contrast, patients with long-tail DDR alterations did not experience clinical benefit [57]. Moreover, prostate cancer with *BRCA2* had better outcome as compared to those with *BRCA1* mutations, after treatment with PARP inhibitors [58]. Furthermore, Lotan et al., reported that in a three-cohort study, patients with primary prostate cancer and germline *BRCA2* mutations had the highest genomic scarring composite score, followed by the *ATM* and *CHEK2* alterations [59]. Apparently, those with *BRCA2* mutations respond better to PARP inhibitors as compared to the prostate cancer patients with *ATM* and *CHEK2* alterations [42]; nevertheless, the same correlation with higher genomic scarring composite scores has been revealed in the respective DDR gene mutations [59]. The implication of PARP inhibitors beyond *BRCA1/2* mutation—in cases of the 'BRCAness' phenotype—highlights the importance of future trials investigating predictive biomarkers beyond BRCA [60].

The activity of PARP1 is believed to be a new biomarker for sensitivity to PARP inhibitor, as it has been reported that increased PARP1 activity correlates positively with disease progression in prostate cancer. PARP1 enhances E2F1-related mechanisms of HR [61]. E2F1 is a transcription factor that regulates the cell cycle and activates cell proliferation. Therefore, the inhibition of PARP1 results in BRCAness, due to decreased expression of DDR genes.

Finally, a recent study used CRISPR-Cas9 screens for the potential identification of PARP inhibitors' sensitivity marker. Interestingly, it has been revealed that alterations in the genes encoding the RNase H2 enzyme complex (RNASEH2A, RNASEH2B, and RNASEH2C) may cause PARP inhibitor sensitivity through impaired ribonucleotide excision repair [62].

4. BRCA Mutations and Radiation Response

Mutations in genes implied in response to DNA damage were shown to impact on radiation response in various preclinical models. Indeed, the NHEJ and HR are two major mechanisms required for repair of radiation-induced DSBs [63]. In vitro and in vivo experiments demonstrated increased sensitivity to ionizing radiation in ovarian cancer cells carrying defective BRCA1, with data suggesting a role of BRCA1 in Foxp3 mediated radiation resistance [63]. There are therefore theoretical concerns on potential increased radiation sensitivity of normal tissue among *BRCA1* mutation carriers, but also potential increased effectiveness against tumours. Despite this preclinical background, clinical data, mainly obtained in breast cancer patients, did not provide a clear signal that there would be differences in prognosis after adjuvant radiotherapy in patients with BRCA-associated breast cancer or sporadic breast cancer [64]. The place of radiotherapy for ovarian cancers is now quite limited, though the survival benefit afforded by molecular targeted agents leads to long-term survivors, with new indications for stereotactic body radiotherapy in oligoprogressive or oligopersistent disease. For prostate cancer, radiation therapy has a more substantial role, especially in curative strategies. There is a strong rationale to associate radiotherapy with PARP inhibitors, and preclinical data confirmed the potential of such association, leading to more frequent DNA damages, but also to immunogenic effects (e.g., enhanced infiltration of cytotoxic T lymphocytes into the tumour bed, increased expression of PD-1/PDL-1) [65]. To date, only few early phase clinical trials tested PARP inhibitors with radiotherapy, showing the feasibility of such association [66]. Howeve, it remains uncertain whether such an

association would lead to different efficacy or safety profiles among patients with *BRCA1/2* mutations. The possibility to reverse systemic resistance to immunotherapy or to PARP inhibitors through irradiation of selected metastatic sites is another area of research [67].

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