Poly(ADP-Ribose) Polymerase Inhibitors in Prostate Cancer: Molecular Mechanisms, and Preclinical and Clinical Data

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Abstract
Genomic instability is one of the hallmarks of cancer. The incidence of genetic alterations in homologous recombination repair genes increases during cancer progression, and 20% of prostate cancers (PCas) have defects in DNA repair genes. Several somatic and germline gene alterations drive prostate cancer tumorigenesis, and the most important of these are BRCA2, BRCA1, ATM and CHEK2. There is a group of BRCAness tumours that share phenotypic and genotypic properties with classical BRCA-mutated tumours. Poly(ADP-ribose) polymerase inhibitors (PARPis) show synthetic lethality in cancer cells with impaired homologous recombination genes, and patients with these alterations are candidates for PARPi therapy. Androgen deprivation therapy is the mainstay of PCa therapy. PARPis decrease androgen signalling by interaction with molecular mechanisms of the androgen nuclear complex. The PROFOUND phase III trial, comparing olaparib with enzalutamide/abiraterone therapy, revealed increased radiological progression-free survival (rPFS) and overall survival (OS) among patients with metastatic castration-resistant prostate cancer (mCRPC) with BRCA1, BRCA2 or ATM mutations. The clinical efficacy of PARPis has been confirmed in ovarian, breast, pancreatic and recently also in a subset of PCa. There is growing evidence that molecular tumour boards are the future of the oncological therapeutic approach in prostate cancer. In this review, we summarise the data concerning the molecular mechanisms and preclinical and clinical data of PARPis in PCa.

Key Points
Molecular tumour profiling is a new approach for personalised targeted therapy in cancer patients.
PARP inhibitors are a new promising class of drugs that show clinical efficacy in genomically defined, heavily pre-treated prostate cancer patients.
Olaparib and rucaparib were recently approved by the US Food and Drug Administration (FDA) for prostate cancer.
Many clinical trials are ongoing to determine the efficacy of PARP inhibitors in different prostate cancer stages, different prostate cancer hormonal statuses, and in various drug combinations. The major challenges remain the proper indication of genomic alterations with regard to the effectiveness of the treatment.

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1 Introduction

Several germline and somatic genetic alterations are associated with prostate cancer (PCa) initiation, promotion and progression [1, 2]. Hereditary PCa accounts for around 9% of PCa patients and includes germline mutations in homologous repair deficiency (HRD) and mismatch repair (MMR) deficiency genes [3, 4]. The most clinically relevant of these are mutations in the \(\text{BRCA2}\) and \(\text{BRCA1}\) genes (breast-cancer susceptibility gene, \(\text{BRCA2/1mut}\)), because genomic instability increases the risk of PCa development [5, 6]. \(\text{BRCA1}\) and \(\text{BRCA2}\) are proteins involved in homologous recombination repair (HRR), a process that repairs DNA damage [7, 8]. In vitro studies show that PCa cells with \(\text{BRCA1mut}\) and \(\text{BRCA2mut}\) are up to 1000 times more sensitive to Poly(ADP-ribose) inhibitors (PARPis) [9]. In the era of molecular biology, one new option for cancer treatment is targeting mechanisms that affect genome instability, one of the hallmarks of cancer [10, 11]. PARPis are breakthrough molecules that target DNA repair, increase therapeutic options for PCa patients (Table 1) [9, 12–15].

In May 2020, olaparib and rucaparib were approved by the US Food and Drug Administration (FDA) for PCa. Olaparib was approved for adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone. Rucaparib was approved for patients with deleterious germline or somatic \(\text{BRCA}-\text{mutated mCRPC}\) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

2 The Role of Poly(ADP-Ribose) (PARP) in DNA Damage

The presence of endogenous and exogenous base DNA damage increases the risk of cancer due to genomic instability. Several mechanisms are responsible for DNA damage response (DDR), depending on the type of damage. DNA repair pathways maintain the integrity of the genome by base excision repair, nucleotide excision repair, HRR, non-homologous end joining (NHEJ), translesion synthesis and MMR [7, 16]. The most common DNA damage is single-strand breaks, which are repaired with the involvement of PARP enzymes in base-excision mechanisms. Importantly, PARPis also are activated in double-strand break repair in HRR. PARP enzymes are DNA damage sensors and catalyse the transfer of ADP-ribose to target proteins via cleavage of NAD+ (nicotinamide adenine dinucleotide) in the poly ADP-ribosylation reaction that activates the DNA repair machinery. Moreover, PARP modulates chromatin structure, and replication and transcription of DNA [17].

3 The Concept of Synthetic Lethality

DDR is the method by which cancer cells monitor and repair damaged genetic material. In cancer cells, DDR is characterised by an increased level of replication stress and a high level of DNA damage. The loss of at least one DDR pathway in cancer cells provided the background and rationale for a new drug target via the concept of synthetic lethality (conditional genetics) [18]. Inactivation of one gene allele by mutation and inhibition is not toxic for cells, but when the second pair of the gene is affected this leads to cancer cell death. Inhibition of PARP leads to DNA-repair disruption and the accumulation of single-strand breaks. This results in the creation of double-strand breaks, which, physiologically, are repaired with BRCA and PARP involvement during HRR. \(\text{BRCA1}\) and \(\text{2}\) are tumour suppressors that regulate several cellular processes. \(\text{BRCA1}\) is involved in DNA repair and checkpoint activation, whereas \(\text{BRCA2}\) is a mediator of the core mechanism [6, 8]. If \(\text{BRCA}\) is mutated, PARP inhibition prevents DNA repair. Alternative, ineffective repair pathways are activated that lead to genome instability, cell-cycle arrest and cell death [6, 19–22]. In 2005, Farmer et al. confirmed the hypothesis that targeting PARP may be an effective treatment strategy in \(\text{BRCA}\) mutant cells [9]. Moreover, in vitro and in vivo studies show synthetic lethality phenomena between antiandrogen therapy and PARPi. Research on ovarian carcinoma has shown that high PARP activity significantly improves progression-free survival (PFS) [23]. Gui et al. suggested that PAPR2 inhibition may be a better option in PARP targeting, in the context of HRD, clinical tolerance, and the basic biology of cancer progression [24]. All available PARPi (olaparib, rucaparib, talazoparib and niraparib) inhibit PARP1 and 2. Additionally, olaparib and rucaparib inhibit PARP 3 [25].

4 Role of PARP in Prostate Cancer (PCa) Biology

4.1 Role of PARP in Androgen Signalling

Androgen receptors (AR) in the cell nucleus modulate the expression of several genes, for example \(\text{PSA}\) and \(\text{TMPRSS2}\), which are crucial for prostate biology [26]. Inhibition of androgen signalling is the mainstay of PCa therapy. ARs regulate transcription and translation via cooperation with over 150
Table 1 PARPis in prostate cancer therapy

|                  | PROFOUND                                      | TRITON2                                        | GALAHAD                                        | TALAPRO-1                                      |
|------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Experimental arm** | Olaparib                                      | Rucaparib                                      | Niraparib                                      | Talazoparib                                   |
| **Control arm**   | Enzalutamide                                   | –                                             | –                                             | –                                             |
| **Phase**         | III                                           | II                                            | II                                            | II                                            |
| **Biomarkers**    | Yes (BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD51L) | Yes (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51, RAD51, RAD51, CRAD51, DRAD51L) | Yes (BRCA1/2, ATM, FANCA, PALB2, CHEK2, BRIP1, HDAC2) | Yes (ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C) |
| **Primary outcome measures** | rPFS                                          | ORR, PSA response                            | ORR                                           | ORR                                           |
| **Assessment of DRD status** | Tissue-based test (somatic mutation)           | Plasma- or tissue-based test (somatic and germline mutation) | Plasma- or tissue-based test (somatic and germline mutation) | Tissue-based test (somatic mutation) |
| **Median of rPFS** | BRCA1/2, ATM 7.4 vs. 3.6 mo (HR 0.34; 95% CI 0.25–0.47; P<0.0001) | ND                                            | BRCA1/2-8.2 mo (95% CI 5.2–11.1) Non BRCA-5.3 mo (95% CI 1.9–5.7) | ND                                            |
| **ORR**           | 22% (experimental arm) vs. 4% (control arm)    | BRCA1/2-25%, ATM-2%, CDK12-0%, CHEK2-0%, Other-5% | BRCA1/2-41%                                      | BRCA1/2-43.9%                                 |
| **Median of OS**  | BRCA1/2, ATM- 18.5 mo vs. 15.1 mo (HR 0.64; 95% CI 0.43–0.97; P=0.0173) | ND                                            | BRCA1/2-12.6 mo (95% CI 9.2–15.7) Non BRCA-14 mo (95% CI 12.6–14.0) | ND                                            |
| **SE Grade 3/4**  | Anaemia (21.1% vs. 5%), fatigue and asthenia (3% vs. 5%) | Anaemia (17.9%), asthenia (10.5%), thrombocytopenia (6.3%) | Anaemia (29%), thrombocytopenia (15%), neutropenia (7%) | Anaemia (42.5%), nausea (32.7%) |

*mo months, ND no data, ORR objective response rate, OS overall survival, PSA prostate specific antigen, rPFS radiographic progression-free survival, SE serious event*
co-repressors and co-stimulators, including GATA2, HOXB13 and NKX3, and some of these drive prostate carcinogenesis. FOXA1 is a protein that binds to chromatin and physically interacts with ARs and modulates AR transactivation. Overexpression of FOXA1 is associated with a poorer prognosis in patients with PCa [27]. PARP2, through interaction with FOXA1, enhances AR activity. The clinically relevant aspect of tumour PARP1 loss is a downregulation of nuclear androgen receptors. PARPs are one of the transcription regulators of AR and their inhibition decreases the expression of AR genes [28]. Genetic or pharmacological depletion of PARP2-FOXA1 interactions inhibits AR-mediated activity and tumour growth [28, 29]. In addition ARs promote the DNA damage response and regulate genes responsible for DDR, including for HR, NHEJ and MMR [20, 30, 31]. Antiandrogen therapy decreases expression of HR genes and ATM signalling.

### 4.2 Relationship Between PARP and the Tumour Microenvironment

Recently, the relationship between cancer and the tumour microenvironment has become a new issue in prostate pathology [32]. PARP affects reciprocal interactions between cells in the tumour microenvironment, affecting prostate tumorigenesis and its aggressiveness [17, 28, 33–36]. Immunohistochemical studies have shown that expression of PARP1 and PARP2 is higher in PCa than in benign tissue. Although PARP1 contributes to 90% of cellular activity, the expression of PARP2 correlates with biochemical recurrence in PCa [37]. PARP1 deficiency in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model led to the development of less differentiated tumours with a higher proliferative index compared to wild-type rodents. The driving mechanism involved TGF-β (transforming growth factor β)-dependent and Smad-regulated epithelial-mesenchymal transition [35, 38]. PARP modulates the development and growth of cancer by altering cancer-initiating cells, the immune response, angiogenesis, autophagy and the tumour hypoxic response. Preclinical studies on the tumour microenvironment show that, under hypoxia, expression of HRR genes is lower due to the activity of E2F transcription factors and histone methylation, which increases the sensitivity of tumour cells to PARPi [19, 21, 22, 39]. The hypoxic microenvironment increases the transcriptional activity of the AR and facilitates the development of castration-resistant prostate cancer (CRPC), which correlates with HRR gene alterations [40, 41].

### 4.3 Relationship Between the PARP and E26 Transformation-Specific (ETS) System

The ETS (E26 transformation-specific family) is a family of transcription factors that regulate key cellular functions, like migration or proliferation of cells [42]. Gene rearrangements lead to increased activity of the ETS system, which enhances cancer growth and development. In turn, fusion between TMPRSS2 and ERG, which show functional similarity to ETS gene fusions, is present in around 50% of PCa cases and regulates key PCa biological functions [43–45].

Overexpression of ETS genes leads to DNA double-strand breaks. PARP and DNA-dependent protein kinase modulates transcriptional activity of the ETS system. PARP1 also interacts with the androgen-receptor regulated TMPRSS2:ERG gene fusion protein. Olaparib has been shown to reduce the potential of invasion in ERG-positive PCa cell lines through inhibition of invasion-associated genes, for example, EZH2, which may provide new molecular therapeutic targets [43]. Despite promising results from preclinical studies, ETS stratification in clinical trials with abiraterone and veliparib did not confirm the clinical utility of ETS as a predictive factor [46]. Molecular stratification based on ETS status and PTEN expression in PCa may better predict clinical outcomes in localised and metastatic stages of disease [47, 48]. TMPRSS2-ERG-positive and PTEN-negative tumours are more sensitive to PARPi and radiation therapy [49].

### 5 Genetic Testing in PCa

#### 5.1 The incidence of Genetic Alterations

The incidence of pathogenic somatic and germline mutations differs between localised and metastatic PCAs (Table 2). In patients with primary PCAs, the incidence of *BRCA2* mutations in those under 65 years of age is low (1.2%), but at the CRPC stage this increases to 12% [50]. The incidence of germline *BRCA1/2* or *ATM* mutations is higher in metastatic PCAs than localised PCAs [51]. An analysis of 3607 PCa patients revealed that 620 patients (17.2%) had pathogenic germline mutations. Importantly, the authors of the study highlighted that 37% of the tested patients did not meet the NCCN criteria for genetic consulting. The most common pathogenic mutations among entire cohorts were *BRCA2* (4.74%), *CHEK2* (2.88%) and *ATM* (2.03%). The prevalence of specific mutations among all patients with germline

| Gene | Localized PCa | Metastatic PCa |
|------|---------------|----------------|
| *BRCA2* | 0.2 | 3.53 | 13.3 |
| *ATM* | 1.0 | 4.0 | 1.59 | 7.0 |
| *BRCA1* | 0.6 | 0.87 | 0.7 |
| *CHEK2* | 0.4 | 0.0 | 1.87 | 3.0 |
mutations was 24.3%, 14.1% and 9.6%, respectively, for BRCA2, CHEK2 and ATM [52]. The results are, in general, in accordance with the study by Pritchard et al., where germline mutations were identified in 11.8% of the cohort. The most common HRR gene alterations were BRCA2 (44%), ATM (13%), CHEK2 (12%), BRCA1 (7%), PALB2 (4%), RAD51D (4%), ATR (2%), NBN (2%), PMS2 (2%), GEN1 (2%) and MSH2, MSH6, RAD51C, MRE11A, BRIP1 and FAM175A (1% each) [50]. The non-BRCA proteins included DNA damage sensors (ATM, CHEK), DNA regulators (CDK12) or proteins that co-operate with the BRCA gene in the DNA repair process (FANCA, PALB2). Other components of the DDR system (e.g. ATR, CHEK1) are also being investigated as new therapeutic targets [53, 54].

Table 2 gives the incidence of germline and somatic mutations in localised and metastatic prostate cancer [13, 50, 55, 56].

5.2 Significance of BRCA Mutation in PCa

BRCA genes are considered the most clinically relevant genes of the tumour-predisposing genes in PCa. The standardised incidence for BRCA1 mutations is 2.35 (95% confidence interval (CI) 1.43–3.88), compared to 4.45 for BRCA2 (95% CI 2.99–6.61) [57, 58]. A recently published meta-analysis clearly showed that PCa incidence is greater among BRCA mutation carriers, especially those with BRCA2 [5]. BRCA2 germline mutations increase the risk of PCa 8.6-fold by age 65 years [59]. The other germline mutations, like HOXB13 or ATM, are considered to be high-penetration genes that increase the risk of PCa, but therapeutic and diagnostic values remain unclear [60]. The first analysis of the IMPACT trial suggested that patients aged 40–69 years with BRCA2 mutations may benefit from annual PSA testing [61]. PCa that develops in BRCAmut carriers displays different clinicopathological properties, occurring earlier and often with an intraductal or ductal histology with lymphovascular invasion. Moreover, the PCa in these patients often has a higher Gleason score or tumour stage. However, the results of this research are contraindicatory [62]. Due to the more aggressive course of disease, patients have a greater risk of progression after local treatment and a shorter cancer-specific survival, metastasis-free survival, and overall survival (OS). The significance and relevance of germline and somatic mutations other than in classical HR genes remains to be sufficiently elucidated. BRCA2 K3326* is a nonsense variant of the gene without a significant impact on DDR function [31]. Moreover, there are some doubts concerning the assessment of HRD status. Up to 8% of non-metastatic PCa patients may have HRD that is not derived from classical HRD (BRCA) and is associated with a PARPi response. This may be the result of CDH1 gene loss (encodes cadherin 1) or inactivation of the SPOP gene (encodes Speckle-type POZ protein), which are early events in cancer development [44, 63].

5.3 BRCAness

Some tumours, known as ‘BRCAness’, share phenotypic (phenocopies) and genetic properties with BRCA–mutated tumours, which partly depend on DNA repair of genetic defects. In other words, BRCAness can be defined as an error in DNA repair that is controlled by HRR. The BRCAness phenotype may be induced pharmacologically or due to genetic alterations in genes that modulate HRR, including ATM, ATR, CHEK1, RAD51, the Fanconi anaemia complementation group family of genes and others. New ideas for targeting BRCAness are the result of a better understanding of the function of BRCA proteins as replication fork protectors. BRCA1 and BRCA2 stabilise the RAD51 filament on the reversed replication forks, thereby protecting the open double-stranded end of the regressed arm. Meiotic recombination 11-Like (MRE11) is a nuclease that leads to the degradation of replication fork protection in the absence of BRCA proteins. In HRR, MRE11 forms a complex with RAD50 and NBS1 (Nijmegen breakage syndrome 1), which leads to ATM recruitment. In addition, checkpoint kinases, which regulate BRCA functions (ATR/CHK1, WEE1) and promote cycle progression (AURORA1 and its TPX2 cofactor, Polo-Like Kinase 1), contribute to BRCAness status and may be investigated in the future [64]. BRCAness induced by non-BRCA mutations is one of the most investigated issues associated with PARPi. Non-BRCA alterations were investigated in the TRITON2 study, and PSA and radio- logical responses in the non-BRCA group (ATM, CDK12, CHEK2) were limited, in contrast to patients with FANCA, PALB2, BRIP1 and RAD51B mutations [65]. However, there are doubts concerning BRCAness. Possible experimental biomarkers for BRCAness include the HRR gene alteration, functional assays of HRR capacity, and transcriptomic and mutational signatures [66].

5.4 Significance of Germline Testing in PCa

According to oncological guidelines, some patients with PCa should receive consultations with genetic specialists to diagnose families at higher risk of cancer development and choose appropriate therapeutic management. NCCN guidelines recommend germline testing for patients with high-risk or very high-risk PCa in all tumour stages, some families with a history of cancer, and specific populations of PCa patients who have an increased likelihood of PCa development, such as Ashkenazi Jews [67]. According to NCCN recommendations, germline panel testing using NGS should include BRCA2, BRCA1, ATM, CHEK2, PALB2, MLH1,
obtained from lymphocytes or buccal cells [67].

5.5 Significance of Somatic Testing in PCa

Since registration of new targeted therapies that broaden the therapeutic landscape for PCa patients, a somatic (acquired) mutation test is recommended for every patient with metastatic PCa. In addition, positive results of genetic testing should lead to the referral of patients for genetic consulting. There are some doubts as to which material is the best for genetic testing. Metastatic sites may be better sources for detecting genetic alterations than tissue from the primary tumour due to their higher degree of genetic alterations as a result of heterogeneity and instability of the tumour genome. The highest frequency of mutations among HRD genes is present in brain and visceral metastases. It is recommended to repeat somatic mutation tests in cases of cancer progression [68]. Horak et al. described an interesting case of a 43-year-old patient with PCa with a PALB2 somatic mutation who was treated with cisplatin and PARPi. Upon liver progression, secondary genetic tests revealed possible mechanisms of drug resistance [69]. An alternative for new, repeated biopsies is the assessment of cell-free or circulating tumour cell DNA (ctDNA).

6 Clinical Aspects of PARP Inhibitors (PARPi)

6.1 Basics of PCa Treatment and PARPi

Since its discovery by Hoggins and Hodge, antiandrogen therapy has been the mainstay of metastatic prostate cancer therapy. Antiandrogens mediate multistep inhibition of signalling pathways in tumour cells and lead to an increased OS among PCa patients. Despite the initial effectiveness of this treatment, PCa transforms into an incurable, castration-resistant stage of disease due to ligand dependent and independent mechanisms that restore AR activity [70]. Currently available options for PCa patients consist of chemotherapy (docetaxel, cabazitaxel), molecularly directed, second-generation anti-androgens (abiraterone acetate, enzalutamide, apalutamide, darolutamide), radiopharmaceutical therapy (Radium-223), immunotherapy (sipuleucel-T, pembrolizumab) and PARPi (olaparib, rucaparib). A deeper understanding of the molecular and genetic landscape of PCa allows better stratification to old therapies, in addition to the design of new complex therapies [12, 67]. The OlympiAD, POLO and SOLO1 clinical trials determined PARPi efficacy in breast, pancreatic and ovarian cancer [71–73]. PARPi have opened up an era of genetically based targeted therapies in PCa and are a promising option. Many clinical trials are underway investigating different stages of PCa. The efficacy of PARPi is being evaluated in the localised, non-metastatic or disseminated stages of disease, independent of castration status. PARPi are being tested in monotherapy, polytherapy, with or without chemotherapy, targeted therapies, immunotherapy, radiation or prostatectomy (Table 3).

6.2 PARPi monotherapy

The first data about PARPi in patients with PCa came from a phase I study of 60 BRCAm patients treated with olaparib, among which 5% had CRPC, and one patient achieved > 50% PSA and radiological bone response [74]. The aim of the TOPARP studies was to evaluate PARPi effectiveness, identify the molecular pattern of PCa cells and look for predictive biomarkers. The first clinical data came from the open-label, single-arm TOPARP-A phase II study (Trial of Olaparib in Patients with Advanced Castrate Resistant Prostate Cancer). In the first part of the study, the activity of olaparib 400 mg twice daily was evaluated in genetically unselected patients with mCRPC. Initially, 50 patients were enrolled onto the study, but only 49 could be evaluated. All of the evaluated patients received docetaxel, 98% enzalutamide or abiraterone, and 58% cabazitaxel. The enrolled patients did not receive platinum-based regimens. The primary end-points were radiological response rate, a greater than 50% reduction in PSA, and a reduction in circulating tumour cells (CTC) from > 5 to < 5 cells per 7.5 mL of blood. Whole-exome sequencing and transcriptome studies were performed on fresh-frozen cores in tumour-biopsy samples obtained before treatment during screening. Germline targeted sequencing was performed on DNA from saliva samples. The copy number of the genes was validated with droplet digital polymerase-chain-reaction testing. In addition, tumour samples from biopsies performed before and during treatment were analysed. Biomarker-positive patients had a homozygous deletion or deleterious mutation in a gene involved in DNA repair or in sensitivity to PARP inhibition. Sixteen of the 49 patients (33%) had a response. In the second part of the study, a pre-planned biomarker analysis was performed in the sensitive group. Seven patients had BRCA2 loss (four with biallelic somatic loss and three with germline mutations), and five patients had an alteration in the ATM gene. Every patient with the BRCA2 mutation responded. Moreover, responses were observed in patients with somatic homozygous deletions of BRCA1 and FANCA, somatic frameshift mutations in PALB2, heterozygous PALB2 deletions, biallelic aberrations in HDAC2, and homozygous somatic deletions of BRCA1 or CHEK2 with FANCA deletion. The group of patients with BRCA1/2 and
ATM mutations had an 88% response rate but there was no radiological response among ATM patients. Interestingly, patients with biallelic PALB2 mutation achieved a durable response and only two patients without DNA-repair gene alterations had a response (6%). Radiological progression-free survival (rPFS) and OS were longer.
in the biomarker-positive group than in those who were negative (rPFS: 9.8 vs. 2.7 months, \(P < 0.001\); OS: 13.8 vs. 7.5 months, \(P = 0.05\)) [12].

The second open-label randomised TOPARP-B phase II trial was designed to confirm the previous results from the TOPARP-A study. Patients with metastatic PCa, pre-treated with one to two lines of chemotherapy, were randomised to 400 mg or 300 mg olaparib twice daily. The patients were stratified according to DDR gene aberrations. The primary end-points were the same as in part A. Among patients who were assigned to 400 mg twice daily of olaparib, the composite response was achieved in 54.3% of patients (95% CI 39.0–69.1), the radiological response was achieved in 24.2% (95% CI 11.1–42.3), the PSA response in 37% (95% CI 23.2–52.5), and CTC conversion in 53.6% (95% CI 33.9–72.5). Patients who had \(BRCA1/2\) mutations achieved the greatest composite overall response (83.3%; 95% CI 65.3–94.4) in comparison to \(PALB2\) (57.1%; 95% CI 37.7–74.9), and other mutations (20%; 95% CI 18.4–90.1), \(CDK12\) (25%, 95 CI 8.7–49.1), and ATM loss sensitised cells to ATR inhibition. The results of the study led to FDA approval for rucaparib. The efficacy of rucaparib is currently being evaluated in the TRITON 3 (NCT02975934) phase III trial. Eligible mCRPC patients with ATM mutations presented a response contrary to patients with germline or biallelic loss of \(ATM\) in contrast to patients with \(BRCA\) mutated tumours, the ORR and PSA response rates were observed in patients with \(BRCA1\) alterations (59.8%; 95% CI 49.6–69.4 vs. 15.4%; 95% CI 1.9–45.4). Non-\(BRCA\) gene alterations were seen in 78 patients (\(ATM = 49, CDK12 = 15, CHEK2 = 12, other DDR = 14\)). ORR and PSA responses were reported in patients with non-\(BRCA\) gene alterations, as follows: \(ATM\) (10.5% vs. 4.1%), \(CDK12\) (0% vs. 6.7%), \(CHEK2\) (11.1% vs. 16.7%). Importantly, patients with \(PALB2, FANCA, BRIP1\) and \(RAD51B\) mutations presented a response contrary to patients with germline or biallelic loss of \(ATM\). In contrast to \(BRCA\) mutated tumours, the ORR and PSA responses in patients with \(ATM, CHEK2\) and \(CDK12\) mutations were low. The TRITON2 study, on the one hand, confirmed safety and efficacy in \(BRCA\)-mutated tumours, but on the other hand showed that there are no accurate biomarkers in non-\(BRCA\)-mutated tumours, which needs further investigation [65]. The results of the study led to FDA approval for rucaparib. The efficacy of rucaparib is currently being evaluated in the TRITON 3 (NCT02975934) phase III trial. Eligible mCRPC patients who experienced disease progression after one prior line of next generation AR-targeted therapy with \(BRCA1,2\) or \(ATM\) deleterious mutations will be randomised to rucaparib or one of the standard therapies (abiraterone acetate, enzalutamide or docetaxel). Rucaparib is also being evaluated...
in non-metastatic hormone-naïve PCa with BRCAness (ROAR trial, NCT03533946) after prostatectomy and/or radiation therapy, with or without systemic therapy. The primary outcome measure is 50% reduction in PSA levels. BRCAness is defined as an alteration in any of the following genes: ATM, ATR, BARD1, BRCA1, BRCA2, BRIPl, CDK12, CHEK1, CHEK2, ERCC3, FAM175A, FANCA, FANCL, GEN1, HDAC2, MLH1, MRE11, NBN, PALB2, PP2R2A, RAD51 or RAD54L. Mutations are tested by soft-tissue based genomic testing or liquid biopsy-based genomic or genetic testing.

In contrast to the previously described studies, the DDR status among patients for the ongoing phase II, single-arm GALAHAD study is being evaluated with a plasma or tissue gene panel (BRCA1/2, ATM, FANCA, PALB2, CHEK2, BRIP1, HDAC2). The study was designed to determine the safety and efficacy of niraparib among mCRPC patients who progressed on taxane-based chemotherapy and AR-targeted therapy. The primary end-point was ORR by RECIST 1.1/PCWG3 criteria and composite response rate (cRR) conversion of circulating tumour cells to <5/7.5 mL blood, or ≥50% decline in PSA. The preliminary results of the study presented during ESMO 2019 showed that biallelic DDR defects in BRCA (46 patients) were associated with a higher ORR 41% (95% CI 23.5–61.1) than non-BRCA (35 patients) 9% (95% CI 1.1–29.2). In addition, patients with BRCA1/2 biallelic DRD in comparison to non-BRCA gene alterations achieved a greater PSA response (50%; 95% CI 34.9–65.1 vs. 3%; 95% CI 0.1–14.9), CTC conversion (47%; 95% CI 31.0–64.2 vs. 21%; 95% CI 7.1–42.2), CRR (63%; 95% CI 47.6–76.8 vs. 17%; 95% CI 6.6–33.7), median rPFS (8.2; 95% CI 5.2–11.1 vs. 5.3 months; 95% CI 1.9–5.7) and median OS (12.6; 95% CI 9.2–15.7 vs. 14.0 months; 95% CI 5.3–20.1) [79]. The results will be confirmed in the MAGNITUDE (NCT03748641) phase III randomised, placebo-controlled study. The comparator for niraparib is abiraterone with prednisone.

TALAPRO-1 is a phase II study in men with mCRPC and DDR mutation (ATM, ATR, BRCA1/2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2 or RAD51C). Enrolled patients received one to two chemotherapy regimens (one or more taxane based) and novel hormone therapy (enzalutamide or abiraterone). The primary end-point is ORR. The secondary end-points are time to response and its duration, PSA decrease ≥50%, time to PSA progression, CTC count conversion, rPFS, OS, and safety. The initial results of the interim analysis were presented during the American Society of Clinical Oncology (ASCO) meeting in 2020. The results of the study show that talazoparib presented the strongest activity measured as a composite response (OR and/or PSA response ≥50% and/or CTC conversion) in BRCA1/2 tumours (76.1%); however, the response in ATM (50%) and PALB2 (27.8%) patients was also promising [80].

In preclinical tumour models, veliparib potentiated the activity of DNA-damaging agents like temozolomide, cisplatin, carboplatin and also radiation [81]. It was suggested that veliparib can overcome temozolomide resistance in PCa cell lines and that this combination increased the survival of mice in comparison to temozolomide monotherapy [82]. Veliparib maintenance after carboplatin-based chemotherapy regimens in metastatic BRCA2 mutated ERG positive CRPC led to a durable complete response with a good toxicity profile [83]. The clinical utility of veliparib was evaluated in a phase II study. Patients were stratified according to ETS status and randomised to the following arms: abiraterone, with or without veliparib. ETS fusion failed to be a predictive factor [84]. The results of this study were negative; however, a subgroup of patients with DDR achieved a higher PSA rate, PSA decline ≥90% and a median PFS that was 6.4 months longer. There have been no phase III clinical trials with veliparib to date.

PARPi in monotherapy is currently being evaluated in the neoadjuvant setting and in non-metastatic CSPC. Patients with high-risk, localised PCa with DNA alterations in the repair pathway will receive three cycles of niraparib (NCT04030559) or olaparib (BrUOG 337B, NCT 03,432,897) before prostatectomy. In the NCT0347135 trial, olaparib is being tested in high-risk, non-metastatic, biochemically recurrent PCa after prostatectomy. An analysis of biomarkers will be performed. In addition to the known drugs, newly designed PARPi are being investigated as a treatment option in phase I trials in advanced and metastatic solid tumours (NCT04182516, NMS-03305293; NCT03508011, IMP 4297-Senaparib). Pamiparib is a selective PARPi/2 inhibitor with a capability to penetrate the brain. Presently, it is being tested in a phase II trial in mCRPC positive for CTC with HRD (NCT03712930).

6.3 PARPi in Combination Therapy

After the promising results of PARPi in monotherapy, they are now being tested with drugs which, in recent years, have significantly broadened the treatment options for PCa patients, like novel antiandrogens, chemotherapy, radiopharmaceuticals and immunotherapy. The aim of combination therapy is to extend the population of patients who will benefit, especially in the group without DDR alteration.

Abiraterone and enzalutamide are second-generation AR axis-targeted therapies that decrease AR signalling, and increase OS in hormone-sensitive and -resistant PCa. The reciprocal relationship between AR signalling and PARPi supports the development of combinational strategies. PARPi may enhance the potency of AR-targeted therapies, because PARPi modulates interactions between chromatin and AR [28, 85]. The efficacy of both drugs was evaluated in combination with PARPi in a phase II, randomised,
placebo-controlled trial that compared abiraterone with or without olaparib. Abiraterone was seen to inhibit androgen synthesis by inhibition of CYP17 steroidogenesis enzymes. Irrespective of HRR status, combination therapy increased the median rPFS by 5.6 months, and may be considered as a new type of synthetic lethality [86]. Enzalutamide is a second-generation antiandrogen that inhibits key stages of AR signalling. Preclinical research shows that PARPi and enzalutamide change the expression of apoptosis-related signalling pathways, and the most promising therapeutic strategy is enzalutamide following enzalutamide and olaparib therapy [87]. In 2018, Clarke et al. published the results of a randomised, double-blind, placebo-controlled, phase II trial that provided clinical efficacy of combining therapy for patients with mCRPC who received docetaxel and were candidates for abiraterone treatment. Patients (n = 142) were randomly assigned to olaparib + abiraterone or placebo + abiraterone arms. Median rPFS was significantly longer in the abiraterone plus olaparib group than in the abiraterone plus placebo group (13.8 vs. 8.2 months; HR 0.65; 95% CI 0.44–0.97, P = 0.034), and this was independent of genetic status. The study BRCAAway is an ongoing randomised phase II trial in mCRPC with DNA repair defects (loss of ATM, BRCA1, BRCA2). Patients who want to take part in the study will have to provide new material for biopsy. Enrolled patients are randomised to abiraterone + prednisone (arm I), olaparib (arm II), or abiraterone + prednisone and olaparib (arm III). If patients have non-canonical DNA-repair gene alterations, they will receive olaparib in monotherapy. Patients in olaparib or abiraterone arms may cross over to the combination therapy arm at progression. The primary end-point is radiographical and clinical PFS. The secondary end-points are objective disease and PSA response rates. PROpel is the first phase III trial (NCT03732820) designed to compare abiraterone + placebo to abiraterone or olaparib in patients with BRCA1,2 or ATM mutations with progressive mCRPC in the first-line setting of mCRPC. The aim of the TALAPRO-2 phase III trial (NCT03395197) is to compare rPFS in patients with asymptomatic or minimally asymptomatic patients with mCRPC treated with talazoparib or talazoparib with enzalutamide. Part I of the study determined the starting dose for talazoparib. Part II of the study will evaluate the efficacy, safety and pharmacokinetics of combination therapy. Patients are stratified by prior treatment and DDR mutation status.

An interesting proposal is combining PARPi with immunotherapy (anti PD-1 and PD-L1 inhibitors). PARP increases the tumoral immunogenicity by accumulation of neoantigens, epigenetic changes, and affecting the immune response and tumour microenvironment, which explains the possibility of increasing the efficacy of anti-PD-1/L1 inhibitors. The Keynote-365 phase Ib/II trial showed that median radiographic rPFS for pembrolizumab and olaparib was 4.3 months, and median overall survival (OS) was 14 months [88]. The Keylink-010 study (NCT03834519) with olaparib and pembrolizumab is designed to test if combinations of these drugs increase OS and rPFS. Unselected patients enrolled into the study were pre-treated with enzalutamide/abiraterone and chemotherapy. The comparator will be a next-generation hormonal agent. Another phase II study is underway with durvalumab and olaparib for patients with biochemically recurrent (PSA double time < 9 months), non-metastatic CSPC with DDR mutations (NCT03810105). In addition, a phase Ib/II trial of anti PD-L1 avelumab and talazoparib will be tested to assess dose-liming toxicity and overall response in patients with locally advanced, metastatic solid tumours, including CRPC (NCT03330405).

Docetaxel is an old chemotherapeutic agent that is currently used in castration-sensitive and CRPC patients. Patients with mCRPC with homologous HRR DNA deficiency (BRCA2, BRCA1, ATM, PALB2) will be enrolled in the PLATI-PARP study to receive four cycles of docetaxel and a carboplatin chemotherapy regimen, with rucaparib as a maintenance therapy (NCT03442556, PLATI-PARP).

In addition, there are clinical data that show that patients with BRCAmut are better responders to radiation therapy and, surprisingly, Radium-223 therapy [89]. The ASCLEPlus trial (NCT04194554) is a phase II/II trial that will be evaluating dose-limiting toxicities and the proportion of patients experiencing biochemical failure. The inclusion criteria include node-positive PCa and/or high-risk PCa. Patients will receive niraparib, leuprolide, abiraterone, and stereotactic body radiotherapy at a total dose of 37.5–40 Gy. The ongoing clinical trials with radioligands include the combination of olaparib or niraparib with radium-223 in mCRPC (COMRADE, NCT03317392; NiraRAD, NCT03076203). 177 Lu-PSMA is a new innovative radioligand that demonstrates activity in heavily pretreated PCa. The LuPARP study is a phase I dose-escalation and dose-expansion study that will evaluate the safety and tolerability of olaparib in combination with 177Lu-PSMA (NCT03874884). A new concept in therapy includes combining PARPi with ATR inhibitor (AZD 6738, NCT03787680) or antiangiogenic drugs like cediranib (NCT02893917). ATR is a kinase of DNA damage response and modulates the ATR checkpoint kinase 1 signalling pathway [90]. Cediranib is an orally active, small molecule inhibitor of VEGFR (vascular endothelial growth factor receptor).

6.4 PARPi Toxicity

Compared to chemotherapy, the toxicity of PARP inhibitors is low; however, there is a lack of mature data about the long-term safety of PARPi in PCa populations. According to the PROFOUND trial, the most common adverse events were haematological (anaemia 46%), gastrointestinal (nausea

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41%, loss of appetite (30%) and fatigue or asthenia (41%).
Twenty-two percent of the patients required dose reduction
due to adverse events [76]. The GALAHAD and TRITON2
studies confirmed data from previous studies, with the most
common adverse event being anaemia (17.9–25%) [65, 79].
It is important to remain aware of patients who received
Radium-223 or taxane chemotherapy regimens, as these
patients may be more prone to developing myelosuppression
during PARPi therapy. Anaemia remains the most common
grade 3 toxicity adverse event [76]. In the PROFOUND trial,
myelodysplastic syndrome was not reported, despite initial
reports and published case reports [91]. A recently published
meta-analysis of 14 trials showed that PARPi in combined
therapy may be associated with myelodysplastic syndrome,
but the incidence of that complication is low [92].

7 Conclusions

Androgen-deprivation therapy is the mainstay of treat-
ment for metastatic PCa. Despite the initial responsiveness
to androgen-deprivation therapy, PCa transforms into an
incurable castration-resistant stage of the disease. During
cancerogenesis and the development of castration resistance
the genomic landscape of PCa changes. DNA-repair path-
way mutations are one of the classes of clinically actionable
mutations that occur more frequently in CRPC than primary
PCa [13].

Approximately 20% of CRCP patients harbour germline
or somatic mutations in one of the HRR genes, which sup-
ports the mechanism of synthetic lethality. PARP inhibitors
are the first registered treatment options for patients with
mCRPC based on the genetic concept of synthetic lethal-
ty. The FDA has approved olaparib in HRR-mutated and
rucaparib in BRCA-mutated mCRPC. PARPi should be
considered in patients who have HRR mutations and have
progressed on enzalutamide and/or abiraterone, regardless of
prior docetaxel therapy. The main doubts concerning PARPi
include proper genetic analysis and its clinical relevance.
In the majority of clinical trials, the stratification to treatment
arms depends on the HRR status. Genetic testing (next-
generation sequencing) should be performed, optimally, in
fresh collected tumour biopsies, because of the highest rate
of detected mutations. Less optimal sources for genetic test-
ing are circulating tumour DNA, primary tumour tissue, and
blood or saliva samples. There are some doubts concerning
the sensitivity of drugs in relationship to specific genetic
mechanisms leading to gene alterations. It is not yet clear
which patients achieve the greatest benefit. The meta-analy-
sis by Mohyuddin et al. indicates that the response rates and
survival for patients with somatic and germline mutations
are similar [93]. There is a suggestion that patients with
biallelic BRCA2 inactivation achieved the greatest benefit
in comparison to non-BRCA mutated patients. Results from
the TOPARP-B and TRITON-2 studies suggest that patients
with ATM alteration achieved much less benefit than those
with BRCA altered tumours [14, 75].

Many clinical trials are ongoing to determine the effi-
cy of PARPi monotherapy, polytherapy at different tumour
stages and independent of the castration status of the PCa.
The strongest clinical data indicate the use of PARPi in ca-
stration resistant phases of disease, however, ongoing trials
may change the indications for PARPi in castration-sensitive
PCa, similar to docetaxel or novel antiandrogens. The data
from preclinical and clinical trials support the use of PARPi
in combination therapy.

PARPi are not the only new genomically defined phar-
macologicals. Immunotherapy has significantly changed the
way many cancers are managed; however, in PCa the use of
immunotherapy remains low. Pembrolizumab was the first
anti-PD1-directed therapy registered by the FDA for PCa
with MMR deficiency (MSH2, MSH6, MLH2 or PMS2)
or microsatellite instability (MSI). There is a need to clarify
the biomarkers of immune responsiveness and DNA damage
repair to indicate the appropriate guidelines [94]. PARPi and
anti PD-1 therapy are approved therapies by NCCN, how-
ever, with a higher level of evidence for olaparib (category
1) than pembrolizumab (category 2B) [95]. The results of
clinical trial data regarding OS are immature, although heav-
ily pretreated patients who receive PARPi have a 66% lower
risk of progression or death [76]. PARPi are breakthrough
therapies in oncology and key components of a new era of
targeted therapies and molecular tumour boards [96]. Impor-
tant issues that remain are the determination of prognostic
and predictive factors to facilitate personalised therapy to
achieve more effective results from treatment.

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Iżycka-Świeszewska and Lubomir Bodnar declare that they have no
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