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UROLOGICAL ONCOLOGY

Role of PARP inhibitors in prostate cancer

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Introduction Olaparib, rucaparib, niraparib, and talazoparib are poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) targeted at recombination. To gain a comprehensive understanding of the mechanism of action of PARPi, scientists conducted research involving numerous studies that provided evidence regarding their efficacy and safety.

Material and methods A literature review was performed using the PubMed® and Google Scholar databases. Articles were reviewed and categorized based on the most crucial and current information regarding the pharmacological properties and use of PARPi in treating metastatic castration-resistant prostate cancer (mCRPC), while also indicating the future therapeutic direction toward which these pharmaceuticals are progressing. Data were extracted, analyzed and summarized.

Results PARP inhibitors like olaparib, rucaparib, niraparib, and talazoparib show promise in mCRPC, particularly for patients with specific genetic mutations (*BRCA1/2*, *ATM*). While they extend PFS and sometimes OS, side effects – especially anemia – are prevalent and impact treatment continuation.

Conclusions Despite PARPi already being recognized as the standard treatment for mCRPC, further research is crucial to optimize their efficacy and safety, particularly in the context of combination therapies and use in the early stages of the disease.

Key Words: PARP inhibitors ‹› mCRPC ‹› olaparib ‹› rucaparib ‹› niraparib ‹› talazoparib

INTRODUCTION

Prostate cancer (PCa) is the second most common type of cancer diagnosed and the fifth most common reason for cancer deaths in men worldwide [1]. The activation of oncogenes and the inhibition of tumour suppressor genes are the 2 main molecular cascades that start the complex process of carcinogenesis [2]. These types of genes regulate the stability of the genome, cellular growth, and apoptosis. *BRCA1* and *BRCA2*, among others, play a significant role in regulating genomic stability as tumour suppressor genes [3]. They are key members of the homologous recombination repair (HRR) family of genes, playing a central role in repairing double-strand breaks (DSB) of the DNA. Loss of function mutations of the *BRCA* genes have been linked to genomic instability, which results in elevated mutation burden and accelerated tumourigenesis [2]. It has been proven that PCa is several times more prevalent in people with inherited *BRCA2* mutations than in the general population [4, 5]. Although these mutations increase the risk of developing PCa, they can also be a target for emerging precision oncology therapies

– poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) [6, 7]. These agents are tumour-selective, exploiting the genetic vulnerabilities of cancer cells with *BRCA1* or *BRCA2* mutations, resulting in cell death while sparing normal cells – a phenomenon called synthetic lethality [8]. They are one of the most recognised and promising medication classes among several types of targeted therapy [9]. Three representatives of this group received approval from the Food and Drug Administration (FDA); these are olaparib, rucaparib, and talazoparib (in combination with enzalutamide) [10–12]. In addition, olaparib has been approved by the European Medicines Agency (EMA). Others, including niraparib, are under intensive investigation.

The available evidence suggests that PARPi are a promising new treatment option for PCa [7]. However, more research is needed to fully understand their mechanism of action and to determine their safety and efficacy. The aim of this narrative review is to provide valuable insights into the role of PARPi in the treatment of PCa and to give an overview for clinicians of future research directions.

A literature review was conducted to identify relevant studies concerning PARPi for PCa. The search was carried out using PubMed as the primary database, and the studies collected formed the foundation for a narrative analysis of literature published within the last 10 years. Only prospective studies were included.

PARP INHIBITORS

Each cell cycle results in hundreds of DNA breaks, and every cell, including tumour cells, needs to repair these breaks to avoid cell death [13, 14]. There are several types of DNA damage, such as base modifications, and single- (SSB) and double-strand breaks (DSB), which are repaired by specific proteins including DNA glycosylases, PARP1, and Ku70/Ku80, respectively [15, 16]. DSB may develop as a result of DNA replication if SSB goes unrepaired [17]. Because replication forks can break when they come into contact with a SSB, homologous recombination is an essential mechanism for repairing replication forks and preventing fork collapse [18]. In tumours with *BRCA1/2* mutations, these double-strand breaks cannot be effectively repaired, resulting in cell death [19]. However, the homologous repair is still active in healthy cells (not cancerous) with no mutation in *BRCA1* or *BRCA2*, allowing them to withstand PARP suppression [20].

PARPi are oral medications that affect replication at the DNA level by building a complex with the PARP1 and PARP2 enzymes [21–23]. They specifically target *BRCA*- or HRR-deficient cancer cells [7]. DNA breaks that are typically repaired by the HRR during the late S to G2 phase of the cell cycle are not repaired as a result of PARP inhibition with PARPi [21]. They prevent SSB repair and inhibit PARylation, which increases the amount of SSB in the cell. SSB that is not corrected turns into DSB during replication [23]. When cancer cells with harmful *BRCA1* or *BRCA2* mutations are treated with PARPi, the unrepaired DNA will eventually cause the cancer cells to die, a process known as synthetic lethality [22]. A single gene deficiency has just a little impact on a cell's ability to survive; however, the simultaneous loss of 2 functioning genes causes cell death [7]. Recently, it has been demonstrated that PARPi can trap the PARP1 and PARP2 enzymes in the damaged DNA. Contrary to unrepaired single-strand breaks brought on by PARP inactivation, trapped PARP-DNA complexes were more cytotoxic [21]. Due to the suppression of its enzymatic activity, which is necessary for the repulsion between auto-PARylated PARP1 and DNA, PARP1 cannot separate from DNA once it has been trapped [24].

CURRENT APPLICATIONS AND STUDY RESULTS OF PARP INHIBITORS

Olaparib

In December 2014, olaparib (Lynparza, Astra Zeneca AB, and Merck) was approved in the European Union and the United States for the treatment of advanced ovarian cancer and breast cancer with *BRCA1/2* gene mutations [25]. Patients with deleterious or suspected deleterious g*BRCA*m, HER2-negative (no human epidermal growth factor receptor type 2) metastatic breast cancer who have received chemotherapy in the neoadjuvant, adjuvant, or metastatic setting are eligible for treatment with Lynparza [26].

In monotherapy, it is used for maintenance treatment in adult patients with advanced low-differentiation epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with *BRCA1/2* mutations, who have achieved a response (complete or partial) after completion of platinum compound-based first-line chemotherapy.

Its efficacy has also been confirmed in patients with platinum-sensitive, recurrent, low-differentiated ovarian cancer, and metastatic pancreatic adenocarcinoma with inherited *BRCA1/2* [10].

The randomised phase 3 PROfound trial, initiated in 2017, evaluated the PARPi olaparib in men with metastatic castration-resistant prostate cancer (mCRPC) who experienced disease progression while

receiving ARSI (androgen-receptor signalling inhibitor). Patients were randomly assigned in a 2:1 ratio to receive either olaparib 300 mg twice daily or enzalutamide 160 mg once daily/abiraterone 1,000 mg. All the included patients harboured somatic or germline mutations of the HRR genes. Participants were divided into 2 cohort groups. Cohort A included patients with *BRCA1/2* or *ATM* (ataxia telangiectasia mutated) mutations, and cohort B included patients with a mutation in at least one of 12 other HRR genes *(BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D*, or *RAD54L*) [27].

The primary and secondary endpoints of the study were as follows: The olaparib arm demonstrated a significantly longer median imaging-based progression-free survival (PFS) of 7.4 months compared to 3.6 months in the control group. The hazard ratio (HR) for progression or death was 0.34, with a 95% confidence interval (CI): 0.25–0.47 ($p < 0.001$). Furthermore, the objective response rate (ORR) in the olaparib arm was 33% vs 2% in the control group. A 50% reduction in prostate-specific antigen (PSA) levels was observed in 43% of patients in the olaparib group compared to 8% in the control group. The clearance of circulating tumour cells (CTCs) was achieved in 30% of patients treated with olaparib vs 11% in the control group. Lastly, the median overall survival (OS) was 18.5 months for patients in the olaparib arm compared to 15.1 months for those in the control group [28].

In cohort A, radiographic PFS (rPFS) significantly favoured olaparib (HR: 0.49, 95% CI: 0.38–0.63). Furthermore, the results for OS showed a significant improvement among men with *BRCA1/2* or *ATM* mutations (cohort A) (HR: 0.69, 95% CI: 0.50–0.97, $p = 0.018$). This effect was not significant in men with any (other) HRR aberrations (cohort B) (HR = 0.96, 95% CI: 0.63–1.49). Interestingly, 66% (n = 86/131) of patients on physician-recommended enzalutamide/abiraterone who progressed switched to olaparib [27]. Considering toxicity, patients receiving olaparib compared to ARSI more often developed anaemia (46.1% vs 15.4%), including those requiring transfusions. Other prevalent side effects included nausea (41.4% vs 19.2%) or vomiting, decreased appetite (30.1% vs 17.7%), anorexia, weight loss, diarrhoea, thrombocytopaenia, creatinine elevation, cough and dyspnea, and fatigue (26.2% vs 20.8%) for olaparib vs enzalutamide/abiraterone. Among men receiving olaparib, 16.4% discontinued treatment due to side effects, compared to 8.5% of patients receiving enzalutamide.

In addition, 4.3% of olaparib-treated patients developed pulmonary embolism, compared with 0.8% of enzalutamide/abiraterone-treated patients, none of whom were fatal.

A randomised phase III trial (PROfound) has been the first study to confirm the clinical utility of genetic testing and precision medicine in the mCRPC setting [7].

On 19 May 2020, the U.S. Food and Drug Administration expanded existing guidelines to monotherapy during the treatment of adult men with mCRPC with *BRCA1/2* mutations (germline and/or somatic) who have experienced disease progression after prior therapy with an ARSI new hormone-activated drug [10, 29]. Olaparib can be used in the treatment of deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC patients who have progressed after prior treatment with enzalutamide or abiraterone [12].

In 2022, the EMA expanded the indication of olaparib in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated [10, 29].

There have been 2 more studies using olaparib in patients with castration-resistant PCa: TOPARP-A and TOPARP-B.

TOPARP-A was an open-label, two-stage, phase 2 study. Olaparib tablets were given to all patients twice daily at a dose of 400 mg. Response to olaparib treatment was to be assessed 6 months after the start of the trial in responding patients: Objective response by modified RECIST, PSA decline of ≥ 50% according to the Prostate Cancer Working Group 2, and conversion of circulating tumour cell count from ≥5 cells/7.5 ml blood at baseline to <5 cells/7.5 ml blood confirmed by at least 2 readings 4 weeks apart [30]. Twelve patients received the study medication for more than 6 months, and 16 of the 49 patients who could be evaluated had a response. In 16 of the 49 patients that could be analysed (33%), next-generation sequencing revealed homozygous deletions, harmful mutations, or both in DNA-repair genes, such as *BRCA1/2*, *ATM*, Fanconi's anaemia genes, and CHEK2. Fourteen of these 16 patients (88%) responded to olaparib, including 4 of 5 patients with *ATM* abnormalities and 7 with *BRCA2* deletion. The most frequent side effects were anaemia (20%) and fatigue (12%) [31].

TOPARP-B was an open-label, multicentre, randomised phase 2 trial. Olaparib was administered twice daily at doses of 300 mg or 400 mg to eligible patients in a random order. This study found that mCRPC with DDR (DNA damage response) gene alterations is responsive to the antitumour drug olaparib. A total of 711 patients agreed to targeted screening, and 25 of the 46 evaluable patients in the

400 mg cohort and 18 of the 46 evaluable patients in the 300 mg cohort experienced confirmed composite responses. In the 400 mg cohort, 24.2% of patients evaluated achieved a radiological response, while in the 300 mg cohort, it was 16.2% of patients. Anaemia (31% in the 300 mg cohort and 37% in the 400 mg cohort) was the most prevalent grade 3–4 side effect in both cohorts. Thirteen patients reported 19 significant adverse reactions. After 11 days of treatment, one myocardial infarction fatality, which may have been due to the medication, occurred in the 300 mg cohort [30].

Rucaparib

Rucaparib (Rubraca, Pharmaand GmbH), under the name Rubraca, received accelerated approval in the United States in December 2016 for the treatment of patients with advanced ovarian cancer with *BRCA1/2* gene mutations who had previously been treated with both a new hormonal drug (enzalutamide or abiraterone) and one taxane-containing chemotherapy [27]. It is also used for maintenance treatment of ovarian cancer.

In May 2020, the FDA approved the use of the drug during therapy in patients with mCRPC [27].

On 21 July 2022, the EMA's human medicines committee, the CHMP, recommended that Rubraca no longer be used as a third-line treatment for *BRCA*-mutated ovarian, fallopian tube, or peritoneal cancer in patients whose cancer has returned after at least 2 platinum-based chemotherapies and who cannot have further platinum-based therapy [32]. The recommendation was based on the results of the ARIEL4 trial, which showed that rucaparib was inferior to chemotherapy (OS: 19.4 vs 25.4 months).

In the open-label TRITON3 phase 3 trial, the primary endpoint of achieving a significant improvement in rPFS was achieved when using rucaparib monotherapy (Rubraca) to treat patients with mCRPC with *BRCA* mutations not requiring chemotherapy. Somatic analysis of *BRCA1* and *BRCA2* using a sample of circulating tumor DNA was the preferred method for selecting patients for rucaparib treatment [27]. Among 405 participants, the median rPFS was 11.2 months (95% CI: 9.2–13.8) with rucaparib vs 6.4 months (95% CI: 5.4–8.3) for physician selection of therapy in mCRPC patients with *BRCA* mutations (HR = 0.50; 95% CI: 0.36–0.69; p <0.001).

In the intention-to-treat (ITT) population, which also included those with *ATM* mutations, the median rPFS was 10.2 months (95% CI: 8.3–11.2) with rucaparib vs 6.4 months (95% CI: 5.6–8.2) using physician-selected treatment including docetaxel, abiraterone acetate, or enzalutamide (HR, 0.61; 95% CI: 0.47–0.80; p <0.001) [27, 33]. The secondary endpoint of OS indicated better efficacy of rucaparib. The median OS in the *BRCA* subgroup reached 24.3 months (95% CI: 19.9–25.7) compared to 20.8 months (95% CI: 16.3–23.1) in the control group. The HR was 0.81 with a 95% CI: 0.58–1.12 (p = 0.21) [34].

According to claims by Pharmaand GmbH, rucaparib reduces the risk of progression or death, based on imaging studies, by 50% in patients with *BRCA* mutations, and was more effective than docetaxel and ARSI in the *BRCA* subgroup and ITT populations [35].

Treatment-related adverse events (TEAEs) of grade 3 or higher during rucaparib use included anaemia or decreased haemoglobin (23.7%), neutropaenia (7.4%), chronic fatigue (7.0%), thrombocytopaenia (5.9%), and increased alanine and aspartate aminotransferase activity (5.2%). Therapy with rucaparib was discontinued due to adverse effects in 14.8% compared to 21.5% of the control group.

Niraparib

In March 2017, niraparib was approved by the FDA for maintenance therapy in patients with recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer.

The purpose of the GALAHAD trial is to evaluate niraparib as monotherapy in men with mCRPC and abnormalities in deoxyribonucleic acid (DNA) repair. The study included 289 patients. Study participants received 300 mg of niraparib (3 capsules of 100 mg each) orally once a day. In total, 223 (77%) patients underwent an overall efficacy analysis. Patients were divided into 2 cohort groups: a *BRCA* cohort (n = 142) and a non-*BRCA* cohort (n = 81).

In the final analysis, with a median follow-up of 10-0 months (IQR: 6.6–13.3), the ORR in the *BRCA* (n = 76) measurable cohort was 34.2% (95% CI: 23.7–46.0) [36].

Among the most common adverse reactions were nausea (57.79%), anaemia (53.29%), vomiting (37.72%), weakness (36.33%), constipation (33.91%), thrombocytopaenia (32.53%), decreased appetite (32.18%), and back pain (20.42%) [37].

The study showed that niraparib is tolerable and has antitumour activity in heavily treated patients with mCRPC and DRD, particularly in patients with *BRCA* mutations [36].

The MAGNITUDE trial is a phase 3 study that aims to compare the effectiveness and safety of combining niraparib and AAP (abiraterone acetate plus prednisone) vs placebo and AAP in treating mCRPC

as a first-line therapy. Cohort 1 consisted of patients positive for *HRR* gene alteration (in ≥1 of the following: *ATM*, *BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2*, or *PALB2*). Cohort 2 comprised men with no positive result for DRD. Open cohort 3 was made up of those eligible based on HRR status. Patients in the HRR+ and HRR– cohorts were randomly assigned in a 1:1 ratio to receive niraparib 200 mg once daily with AA 1000 mg once daily and prednisone 5 mg twice daily (niraparib + AAP group) or placebo + AAP. They took the drugs in 28-day cycles until unequivocal clinical progression, unacceptable toxicity, or death.

In the study, cohort 1 included 423 patients (212 in the niraparib + AAP group and 211 in the placebo + AAP group).

Cohort 2 consisted of 247 patients receiving niraparib + AAP (n = 123) and placebo + AAP (n = 124). Cohort 3, which is ongoing, involves patients eligible based on HRR status (n = 95). They will receive a new formulation of niraparib 200 mg, AAP 1000 mg tablets, and prednisone 10 mg, with results to be reported later.

Initially, the evaluation of rPFS took place in the *BRCA1/2* subgroup, followed by the examination in the broader HRR+ cohort. The median follow-up duration for the HRR+ cohort was 18.6 months. Within the *BRCA1/2* subgroup, the median rPFS was notably extended in the niraparib + AAP group compared to the placebo + AAP group (16.6 vs 10.9 months; HR = 0.53; 95% CI: 0.36–0.79; p = 0.001). Similarly, HRR+ individuals in the niraparib + AAP group had a significantly prolonged rPFS (16.5 vs 13.7 months; HR = 0.73; 95% CI: 0.56–0.96; p = 0.022). Furthermore, the combination of niraparib and AAP resulted in an extended duration until PSA progression and yielded a higher ORR in both the HRR+ and *BRCA1/2* subgroups. There was a substantial correlation between time to PSA progression and rPFS, with a strong overall correlation coefficient of 0.67 (95% CI: 0.56–0.75). Within the HRR+ cohort, changes in patient-reported quality of life over time were comparable between treatment arms. Following the predetermined criteria, the analysis concluded futility for the HRR– cohort.

The most common grade 3 adverse events were anaemia (28.3% vs 7.6%) and hypertension (14.6% vs 12.3%), for niraparib + AAP vs placebo + AAP [38].

Talazoparib

Talazoparib is qualified for use as monotherapy in the treatment of adult patients with germline mutations in the *BRCA1/2* genes who have HER2-negative locally advanced or metastatic breast cancer [39].

Talazoparib was evaluated in an open-label phase II trial (TALAPRO-1) in patients with mCRPC and DDR-HRR mutations.

Between 2017 and 2020, 128 patients were enrolled in the study. In total, 127 patients received at least one dose of talazoparib, and 104 had measurable soft tissue disease [40].

The primary endpoint was ORR [41]. Among patients who met the relevant criteria, 50% had *BRCA2* mutations, while alterations in *BRCA1, ATM*, or *PALB2* accounted for 4, 1.4, and 4% of male subjects, respectively.

After a median follow-up period of 16.4 months, the radiological RR was 29.8% (95% CI: 21.2–39.6). In addition, patients with *BRCA1/2* mutations had a higher RR (response rate) (46% radiological RR, 66% PSA50 RR, 72% CTC conversion RR).

Therefore, talazoparib showed durable anti-tumour activity in these heavily treated patients with mCRPC and DDR-HHR gene mutations [42].

The predominant grade 3-4 treatment-emergent adverse events included anaemia (affecting 39 out of 127 patients, 31%), thrombocytopaenia (observed in 11 patients, 9%), and neutropaenia (reported in 10 patients, 8%) [40].

In TALAPRO-2 (phase III randomised, double-blind, placebo-controlled trial), the experts evaluated the combination of talazoparib and enzalutamide in the first-line treatment setting for mCRPC patients. Men were divided into 2 groups. The first group received talazoparib 0.5 mg once daily (reduced dose from a standard of 1.0 mg) plus enzalutamide 160 mg once daily, and the second group was taking placebo + enzalutamide. Randomisation was stratified by *HRR* gene alteration status (deficient vs non-deficient or unknown).

The median follow-up for rPFS was 24.9 months (IQR: 21.9–30.2) in the talazoparib group and 24.6 months (14.4–30.2) in the placebo group. At the time of the planned primary analysis, the median rPFS had not been reached (95% CI: 27.5 months-not reached) in the talazoparib plus enzalutamide group and was 21.9 months (16.6–25.1) in the placebo plus enzalutamide group, showing a HR of 0.63 (95% CI: 0.51–0.78; p <0.0001) [43]. The OS and prolonged safety monitoring will provide additional insights into the clinical advantages of the treatment combination both in patients with tumour HRR gene alterations and those without.

The most common severe or life-threatening treatment-emergent side effect during treatment with talazoparib/enzalutamide was anaemia (65.8%). Because of this, 8.3% of patients discontinued the treatment. Due to anaemia, 43.2% of patients received dose reduction.

Table 1. *Summary of progress in clinical studies of PARPi for the treatment of mCRPC*

Treatment		Study	Phase	Study results	Patients (n)			Pharmacokinetics	The most common adverse event
S_{arm}	C_{arm}				T	K_A	K_B		
Olaparib	Enzalutamide or abiraterone plus prednisone	PROfound (NCT02987543)	3	The median time to disease progression in the study group was 9.8 months. The risk of disease progression or death relative to the control group is 78% lower OS time: 38% reduction in the risk of death during treatment with olaparib compared to hormonal drugs. OS time for the study group was 20.1 months and 14.4 months for the control group [28]	387	245	142	Dosage: 300 mg twice daily Olaparib is metabolized by cytochrome P450 (CYP) 3A4/5 *in vitro* The protein binding of olaparib is approximately 82% *in vitro* About 44% of the drug is excreted via the urine and 42% of the dose is excreted via the feces. Half-life is 6.10 hours The mean apparent plasma clearance is 4.55 l/h Take with or without food. Food does not significantly alter the extent of olaparib absorption [45]	Anaemia 46.1%, nausea 41.4% or vomiting, decreased appetite 30.1%, fatigue 26.2%
Olaparib	n/a	TOPARP-A	2	No results posted	148			Olaparib is metabolized by cytochrome P450 (CYP) 3A4/5 *in vitro* The protein binding of olaparib is approximately 82% *in vitro* About 44% of the drug is excreted via the urine and 42% of the dose is excreted via the faeces Half-life is 6.10 hours The mean apparent plasma clearance is 4.55 l/h Take with or without food. Food does not significantly alter the extent of olaparib absorption	Anaemia (grade 3–4: in the 300 mg cohort – 31%, in the 400 mg cohort – 37%), fatigue (grade 1–2: in the 300 mg cohort – 39%, in the 400 mg cohort – 55%)
	n/a	(NCT01682772) TOPARP-B	2	mCRPC with DDR gene alterations is responsive to the antitumor drug Olaparib	711	46 patients in the 400 mg cohort	46 patients in the 300 mg cohort		
					T	S_{arm}	C_{arm}		
Rucaparib	Enzalutamide or abiraterone or docetaxel	TRITON3 (NCT02975934)	3	The HR for rPFS was 0.50 (95% CI: 0.36–0.69) for patients with *BRCA*	405	270	135	Dosage: 600 mg twice daily Rucaparib is 70% bound to human plasma proteins *in vitro* Following a single oral dose of radiolabelled rucaparib, unchanged rucaparib accounted for 64% of the radioactivity. Rucaparib accounted for 45% and 95% of the radioactivity in urine and faeces, respectively Half-life is 26 hours The mean apparent total clearance at steady state is 44.2 l/h (45%) Take with or without food. High-fat meals increase drug exposure but not to a clinically significant extent [46, 47]	Grade 3 or higher: anaemia or decreased haemoglobin (23.7%), neutropenia (7.4%), chronic fatigue (7.0%), thrombocytopenia (5.9%), and increased ALT and AST activity (5.2%)

Table 1. *Continued*

Treatment		Study	Phase	Study results	Patients (n)			Pharmacokinetics	The most common adverse event
S_{arm}	C_{arm}				T	K_A	K_B		
Niraparib	n/a	GALAHAD (NCT02854436)	2	With a median follow-up of 10–0 months (IQR: 6.6–13.3), the ORR in the *BRCA* measurable cohort (n = 76) was 34.2% (95% CI: 23.7–46.0) [36]	223 (77%) of 289 patients were included in the overall efficacy analysis population	*BRCA* cohort (n = 142)	non-*BRCA* cohort (n = 81) [36]	Dosage: 300 mg once daily The absolute bioavailability of niraparib is approximately 73% Food does not appear to affect drug exposure Niraparib is 83% bound to human plasma proteins The average percent recovery of the administered dose over 21 days was 47.5% in urine and 38.8% in faeces The mean half-life ($t_{1/2}$) is 36 hours The apparent total clearance (CL/F) of niraparib was 16.2 l/h 45 [48]	Nausea (57.79%), anaemia (53.29%), vomiting (37.72%), weakness (36.33%), constipation (33.91%), thrombocytopenia (32.53%), decreased appetite (32.18%), or back pain (20.42%)
Niraparib	Abiraterone acetate plus prednisone	Magnitude (NCT03748641)	3	Median for the HRR+ cohort: 18.6 months The median rPFS for the *BRCA1/2* subgroup was extended in the niraparib + AAP group compared to the placebo + AAP group (16.6 vs 10.9 months) The combination of niraparib and AAP resulted in an extended duration until PSA progression and yielded a higher ORR in both the HRR+ and *BRCA1/2* subgroups A futility analysis was in the HRR– cohort [38]	670	HRR+ cohort n = 423 (212 in the niraparib + AAP group and 211 in the placebo + AAP group)	HRR– cohort n = 247 (123 in the niraparib + AAP group and 124 in the placebo + AAp group)	Dosage: 200 mg once daily The absolute bioavailability of niraparib is approximately 73% Food does not appear to affect drug exposure Niraparib is 83% bound to human plasma proteins The average percent recovery of the administered dose over 21 days was 47.5% in urine and 38.8% in faeces The mean half-life ($t_{1/2}$) is 36 hours The apparent total clearance (CL/F) of niraparib was 16.2 l/h 45 [48]	Grade 3 adverse events were anaemia (28.3% vs 7.6%) and hypertension (14.6% vs 12.3%), for niraparib + AAP vs placebo + AAP
Talazoparib	n/a	TALAPRO-1 (NCT03148795)	2	Median follow-up of 16.4 months Radiological RR in the study was 29.8% (95% CI: 21.2–39.6) Patients with *BRCA1/2* mutations had a higher RR (46% radiological RR, 66% PSA50 RR, 72% CTC conversions RR) [42]	128 patients enrolled	127 received talazoparib	104 had soft tissue disease	Dosage: 1 mg once daily talazoparib is 74% bound to plasma proteins 64.7% of talazoparib is excreted in the urine 19.7% is eliminated in the faeces The mean apparent oral clearance of talazoparib is 6.45 l/h with an inter-individual variability of 31.1% [48, 49]	Anaemia (42.5%) and nausea (32.7%)
Talazoparib	Enzalutamide	TALAPRO-2 (NCT03395197)	3	Talazoparib/enzalutamide was associated with a 37% decrease in the rPFS risk, compared to placebo/ enzalutamide (median: not reached vs 22 months; HR: 0.63, 95% CI: 0.51–0.78, p <0.001) [50]	399 patients enrolled [51]	200 received talazoparib + enzalutamide	199 received enzalutamide + placebo	Dosage: 1 mg once daily Talazoparib is 74% bound to plasma proteins 64.7% of talazoparib is excreted in the urine, 19.7% is eliminated in the faeces The mean apparent oral clearance of talazoparib is 6.45 l/h with an inter-individual variability of 31.1% [48, 49]	Anaemia (65.8%), neutropenia (35.7%), thrombocytopenia (24,6%), fatigue (33.7%), back pain (22.1%), decreased appetite (21,6%) [44]

AAP – abiraterone acetate plus; ALT – alanine minotransferaze; AST – aspartate aminotransferaze; Carm – control group; HRR – homologous recombination repair; KA – cohort group A; KB – cohort group B; mCRPC – metastatic castration-resistant prostate cancer; n/a – not applicable; ORR – objective response rate; OS – overall survival; PSA – prostate-specific antigen; rPFS – radiographic progression-free survival; RR – response rate; Sarm – study group; T – total number of patients

Other common side effects in the all-comers cohort included neutropaenia, which was observed in 35.7% of patients, and thrombocytopaenia, which was observed in 24.6% of patients.
Among non-haematological treatment-emergent side effects, fatigue (33.7%), back pain (22.1%), and decreased appetite (21.6%) were the most common. A similar incidence of all-cause treatment-emergent side effects was seen between the all-comers cohort and the homologous recombination repair deficient only cohort [44] (Table 1).

FUTURE DIRECTIONS

Recent studies have shown that the ATR (ataxia telangiectasia and Rad3-related protein) inhibitor (ATRi) AZD6738 tends to increase the effect of PARPi, which motivates further research into the combination of PARPi and ATRi in HRR-deficient cells without *BRCA1/2* mutations. There is a chance that this combination will be profitable in the treatment of patients without *BRCA1/2* germline mutations. Nonetheless, combining these two groups of inhibitors may result in greater damage to normal cells. Thus, in order to be able to use the combination of PARPi and ATRi effectively and safely, further research is needed [52]. Ongoing trial summaries are listed in Table 2. However, with the increasing introduction of PARPi into cancer treatment, a growing problem with resistance occurring in many patients might be noticed [6]. Rebuilding the HR pathway, by reversion mutations and regulations of genes responsible for replication fork stability (mostly genes in the *ATR*/*CHK1* pathway) may affect the mechanism of resistance in PC [53]. It is therefore appropriate to consider using ATRi, as a potential therapy, to defeat the resistance of PARPi in cancers with *BRCA*-deficiency [54]. Furthermore, understanding checkpoint inhibitors and the results of various combinations of PARPi and ATR will help to make clinical decisions expecting delayed resistance [53].
One trial involving metastatic hormone-sensitive prostate cancer (mHSPC) patients with HRR gene mutation and PARPi (olaparib) is ongoing. The study is currently recruiting 30 participants for the trial. The rPFS Per Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumours Version 1.1 is a primary outcome measure. In this study, there are 10 points in the inclusion criteria among others: age ≥18 years, confirmed adenocarcinoma of the prostate, and the subject's life expectancy must be less than 16 weeks. The exclusion criteria also involve 24 points, including prior treatment with any PARPi or any new hormone agent, including olaparib, niraparib, abiraterone, enzalutamide, apalutamide, etc., subject's participation in another clinical study with a drug or a plan to participate in another interventional clinical study within 30 days prior to enrolment, and chronic, uncontrolled hypertension present. No results have not been published yet because the study is in the process of recruiting participants [55].
The ongoing NCT03810105 trial is a study of olaparib (and durvalumab) in men with castration-sensitive biochemically recurrent non-metastatic prostate cancer harbouring mutations in DDR. Recruitment of participants for this study has not yet begun. The inclusion criteria comprise requirements such as males 18 years of age and above, a history of radical prostatectomy, and a number of specific blood test results. Selected exclusion criteria are as follows: no past use of olaparib or another PARPi, less than one month passed since the last medication regimen or radiation therapy (prostate radiotherapy before), and no medical disorders that, in the investigator's opinion, would make this procedure unsafe, such as uncontrolled hypertension, uncontrolled diabetes mellitus, or cardiac disease. This study also has no results yet [56].
There are more studies with mCRPC that have not yet been completed. Many of them are listed in Table 2. One of the trials with mCRPC (NCT03572478) was terminated due to lack of efficacy. Despite the fact that the protocol originally called for conducting a phase 1/2a trial, 12 participants were only enrolled in the phase 1 cohort. Due to their fast-progressing conditions, 2 patients were not evaluable for DLT; furthermore, no patients were included in the phase 2 group. Among adverse events (phase 1 cohort), the most frequent were anaemia, nausea, fatigue, ALT and AST increase, and anorexia. Slightly less frequent, but also occurring were vomiting, oedema limbs, pain, weight loss, arthralgia, generalised muscle weakness, and dysgeusia. Due to the small number of trials involving mHSPC patients and with non-metastatic prostate cancer, as well as the fact that in the above study, no patients were contained in phase 2, there is a need to conduct more research in these directions [57].

CONCLUSIONS

PARPi have already become a standard of care for mCPRC. Despite the already-known findings of prospective randomised trials, there is an ongoing need to analyse the real-world safety of PARPi and to test their efficacy in various clinical settings and patient populations. The main challenge currently facing researchers is how to administer PARPi in combination with a suitable drug that could support their action and improve the efficacy of the therapy, also in earlier stages of PCa.

Table 2. *Summary of ongoing clinical trials of PARP inhibitors to treat prostate cancer*

Study	Phase	Treatment	Status	Disease status	Primary outcomes/Efficacy measure	Patients (n)
NCT01972217 [58]	II	Olaparib + abiraterone or placebo + abiraterone	Active, not recruiting	mCRPC	Part A: Percentage of patients experiencing AEs Number of patients with DLTs Part B: Median rPFS time percentage of patients with progression events or death (rPFS)	158
NCT05242744 [59]		[18F] FluorThanatrace	Recruiting	Prostate cancer metastatic	Measurement of effect size	30
NCT05501548 [60]	II	Olaparib only or olaparib + vitamin C	Recruiting	PCa Castration-resistant prostate cancer	PSA50 response	15
NCT05498272 [61]	II	Olaparib + LHRH agonist	Recruiting	PCa BRCA1 mutation BRCA2 mutation Prostatic adenocarcinoma High-risk cancer	Pathological complete response (pCR) rate Minimal residual disease (MRD) rate	32
NCT03787680 [62]	II	Olaparib + AZD6738 (ATR inhibitor)	Active, not recruiting	mCRPC	RR (CR or PR) in DNA repair proficient (DRPro) patients	49
NCT04194554 [63]	I/II	Niraparib Leuprolide Abiraterone acetate Radiation: SBRT	Recruiting	High risk and node-positive prostate cancer	DLTs (Phase 1) Proportion of patients experiencing biochemical failure	1,000
NCT04030559 [64]	II	Niraparib Niraparib tosylate monohydrate Procedure: radical prostatectomy	Recruiting	High-risk prostate cancer and DNA Damage response defects	pRR	30
NCT05327621 [65]	II	Pamiparib	Recruiting	mCRPC	rPFS	50
NCT05568550 [66]	II	Pembrolizumab + androgen deprivation therapy + radiation therapy or pembrolizumab + olaparib + androgen deprivation therapy + radiation therapy	Recruiting	PCa	Clinical response rate	64
NCT04821622 [67]	III	Talazoparib + enzalutamide or placebo + enzalutamide	Active, non-recruiting	*DDR* gene mutated metastatic Castration-sensitive prostate cancer	rPFS	550
NCT03572478 [57]	I/II	Only rucaparib Only nivolumab or rucaparib + nivolumab	Terminated	mCRPC	Percentage of participants with DLTs (phase 1) Frequency of patients with T cell inflammation in the tumour compared between treatment arms (phase 2)	12

AEs – adverse events; ATR – ataxia telangiectasia and Rad3-related protein; CR – complete response; DLTs – dose limiting toxicities; LHRH – luteinizing-hormone-releasing hormone; mCRPC – metastatic castration-resistant prostate cancer; PCa – prostate cancer; PR – partial response; pRR – pathologic response rate; rPFS – radiographic progression-free survival; SBRT – stereotactic body radiotherapy

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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