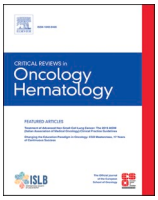
Critical Reviews in Oncology / Hematology 192 (2023) 104157

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc



Personalized medicine for metastatic prostate cancer: The paradigm of PARP inhibitors☆

Brigida Anna Maiorano [a,*], Vincenza Conteduca [b], Martina Catalano [c], Lorenzo Antonuzzo [d,e], Evaristo Maiello [a], Ugo De Giorgi [f], Giandomenico Roviello [c]

[a] Oncology Unit, IRCCS Foundation Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy
[b] Department of Medical and Surgical Sciences, Unit of Medical Oncology and Biomolecular Therapy, University of Foggia, Policlinico Riuniti, Foggia, Italy
[c] Department of Health Sciences, University of Florence, Florence, Italy
[d] Clinical Oncology Unit, and Medical Oncology Unit, Careggi University Hospital, Florence, Italy
[e] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, and Medical Oncology Unit, Careggi University Hospital, Florence, Italy
[f] Department of Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

ARTICLE INFO

Keywords:
BRCA
Biomarker
Olaparib
Rucaparib
PARP inhibitor
Prostate cancer

ABSTRACT

Despite remarkable progress in the last decade, metastatic prostate cancer (mPCa) remains incurable. The approval of PARP inhibitors (PARPis) represents a milestone in this field, which definitively enters the era of precision medicine, as mPCa is often enriched for defects of homologous recombination repair genes. PARPis are now used as single agents for patients with metastatic castration-resistant PCa. Moreover, combinations of PARPis plus androgen-receptor targeted agents and immune checkpoint inhibitors, and earlier applications of PARPis in the metastatic hormone-sensitive PCa are under evaluation, representing the possible upcoming applications of these agents. Mechanisms of sensitization and resistance have been only partially elucidated. In our review, we summarize the current clinical evidence regarding PARPis in mPCa and the future directions of these targeted agents.

1. Introduction

Despite significant improvements in our therapeutic armamentarium over the last ten years, prostate cancer (PCa) still holds the record for the most common tumor and the second leading cancer-related death cause among men worldwide (Siegel et al., 2022). Androgen-deprivation therapy (ADT) still represents the cornerstone of PCa treatment, with solid evidence for the use of taxanes (docetaxel, cabazitaxel), androgen-receptor targeting agents (ARTA – enzalutamide, apalutamide, abiraterone), and radiometabolic therapies in the metastatic setting (Chen et al., 2022). It has been recently demonstrated that around one out of four patients with metastatic castration-resistant PCa (mCRPC) carries mutations in breast cancer gene (*BRCA*)− 1 and − 2 or other Homologous recombination repair (*HRR*) genes, with a negative prognostic role for survival and disease progression, but good sensitivity to Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis) (Conteduca et al., 2021; Cui et al., 2017; Robinson, 2015; Farmer et al., 2005). Two PARPis, olaparib, and rucaparib, are currently Food and Drug Administration (FDA)- and European Medical Agency (EMA)-approved for mCRPC patients (FDA olaparib online; EMA olaparib online; FDA rucaparib online). HRR alterations have also been found in metastatic hormone-sensitive prostate cancer (mHSPC), where they exert a negative prognostic role for survival and time to conversion towards mCRPC. However, the potential targetability of these findings has not been completely understood (Lee et al., 2022). More recent studies are focusing on the potential synergism of PARPis with other drugs, such as ARTA, trying to approach the *HRR* pathway earlier, as it could modulate the androgen receptor (AR) signaling.

Herein, we review the role of PARPis in the metastatic setting of PCa, aiming to resume the current results and the possible future directions of these agents and their pioneering role in the era of personalized medicine in this disease.

☆ Twitter handle: Prostate cancer often carries HR genes alterations. PARP inhibitors are safe and effective in the mCRPC setting, and further developments are expected in this field.

* Corresponding author.
E-mail address: b.maiorano@operapadrepio.it (B.A. Maiorano).

https://doi.org/10.1016/j.critrevonc.2023.104157
Received 6 May 2023; Received in revised form 8 September 2023; Accepted 6 October 2023
Available online 18 October 2023

2. DNA damage and PARPis mechanism

Five major Deoxyribonucleic acid (DNA) repair pathways, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), HR, and non-homologous end splicing (NHEJ), are active during different phases of the cell cycle to repair DNA damage and guarantee genetic stability (Chatterjee and Walker, 2017) (Fig. 1).

Alterations that modify or remove a single base are repaired by DNA glycosylases belonging to the BER pathway that remove the altered bases, allowing the induction of single-stranded DNA breaks (SSBs) by specific endonucleases, recruited by PARP1 (Bednarz-Knoll et al., 2019; David et al., 2007). The NER system repairs a broad spectrum of SSBs that impair proper DNA coiling, removing an oligonucleotide and using the opposite DNA strand as a template for excision repair (Hoeijmakers, 2001; Ogi et al., 2010). The MMR system is involved in the repair per base pair mismatch and the regulation of the HR pathway for improved functioning of DNA double-strand breaks (DSBs) repair (Spies and Fishel, 2015). HR, a high-fidelity pathway, represents the principal repair mechanism of DSBs. This mechanism begins with the MRE11 Homolog (*MRE11*)-RAD50 homolog (*RAD50*)-Nibrin (*NBS1*) (MRN) complex that recognizes and senses DSBs, activating Ataxia-telangiectasia mutated (*ATM*) kinase. This results in the activation of several proteins, including BRCA1 and BRCA2, that induce sister chromatid use as models for stretching DNA filaments (Li and Heyer, 2008). An alternative repair process for DSBs is NHEJ which, unlike HR, does not require an intact template (Chang et al., 2017). However, this repair mechanism is less faithful than the previous one, resulting in more prone to errors such as deletions and consequent loss of genetic information (Shrivastav et al., 2008).

The principle of using HRR-targeting agents is to induce cell death by blocking a complementary pathway in cells lacking HR, disrupting two biological processes involved in DNA repair, defined as 'synthetic lethality' (Lord and Ashworth, 2017; Gourley et al., 2019). In particular, the inhibition of PARP1 and PARP2 favors the accumulation of errors in DSBs. Without a functioning HR pathway, DSBs can be repaired by a poorly faithful process such as NHEJ, with a significant possibility of errors (Ashworth and Lord, 2018).

The cytotoxic action of PARPis depends on two main mechanisms: the catalytic inhibition of PARP and the trapping of PARP-DNA complexes. In the first case, the catalytic inhibition of PARylation, essential for the activation of BER, prevents the repair of SSBs, determining the blockage and damage of the replication fork. The resolution of this block requires a functioning HR pathway, otherwise leading to apoptosis. Moreover, PARPis mediate the second mechanism after binding the catalytic domain. The allosteric effect mediated by the entrapment of PARP-DNA ('PARP trapping') changes the binding affinity for DNA, preventing it from dissociating and resulting in DSBs (Murai et al., 2012; Murai et al., 2014; Fong et al., 2009).

3. HRR mutations incidence and detection in metastatic PCa

The incidence of germline mutations in HRR genes in patients with metastatic PCa ranges from 11% to 33%. *BRCA2* is the most frequently detected aberration (5.3–13%), followed by *ATM* (1.6–7.3%), Checkpoint kinase 2 (*CHEK2*-1.9%), *BRCA1* (0.3–0.9%), and Rad51 recombinase (*RAD51*-0.4%) (Pritchard, 2016; Mateo, 2015). Some studies have reported a difference in the incidence of genomic alterations between metastatic and localized disease, increasing from 10% to 27%, resulting from the selective pressure of treatments on tumor evolution (Robinson, 2015). However, a retrospective study conducted by Mateo

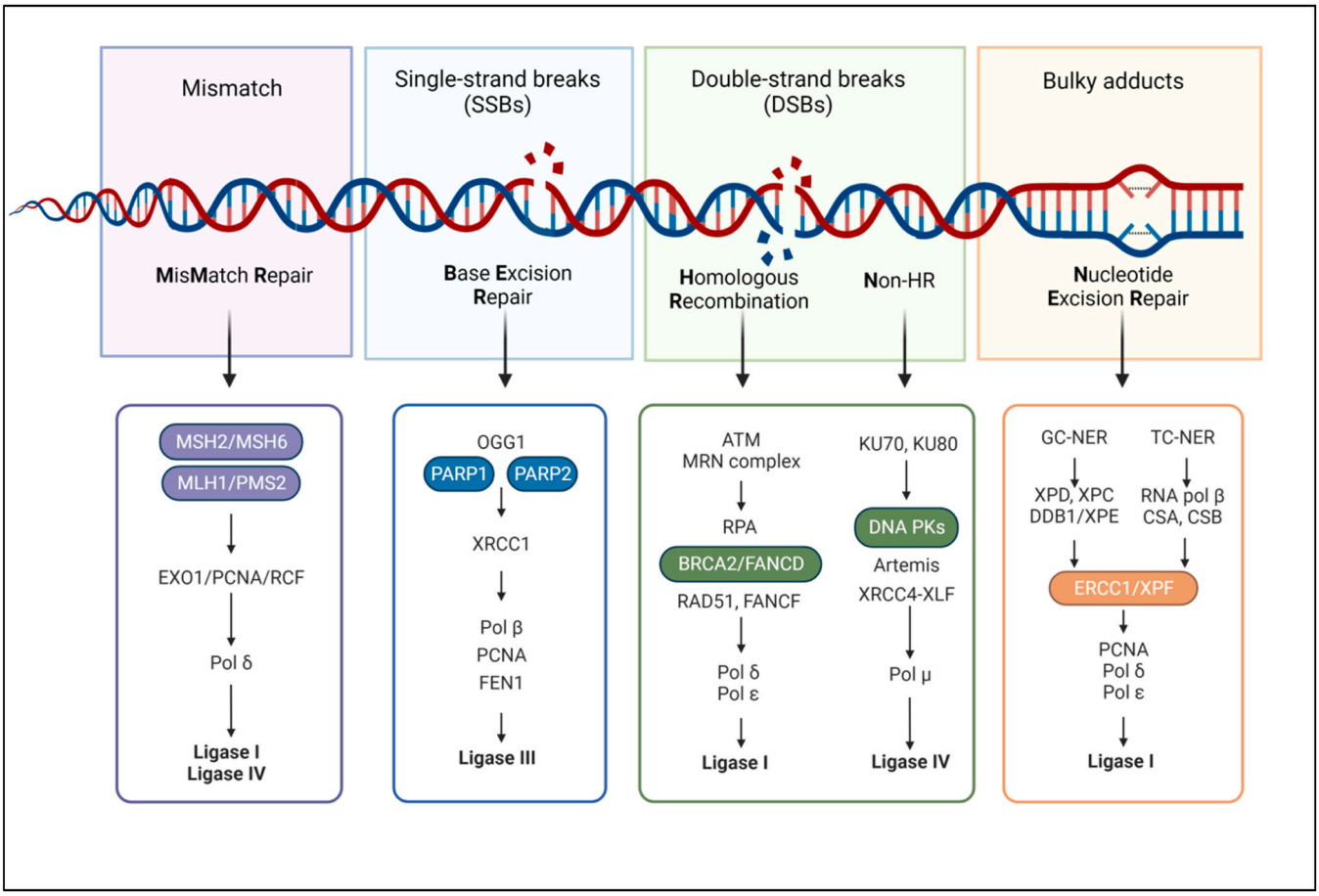


Fig. 1. Mechanisms for DNA damage repair.

et al. showed that, out of 470 biopsies from treatment-naïve PC patients who developed mCRPC, the most frequently detected aberrations were *BRCA2* (7%), Cyclin-dependent kinase 12 (*CDK12*-5%), *ATM* (4%), *TP53* (27%), and Phosphatase and tensin homolog (*PTEN*-12%). These mutations had a similar prevalence between the primary and metastatic samples, suggesting that they were already present from the early stages of PCa development, and implying that prostate specimens could be sufficient for patient profiling without resorting to further biopsies (Mateo, 2020b). However, the heterogeneity of primary tumors mainly limits data, and further studies are needed to validate these findings.

Two genetic tests for identifying HRR alterations can be performed: germinal or somatic. The germline test, mainly carried out on blood, evaluates the hereditary DNA pathogenic or probably pathogenic mutations of all types of body cells, being also useful to identify hereditary mutations. Unlike the germline test, the somatic test identifies the tumor DNA alterations, and, although occasionally, it can detect germline mutations, its use is inadequate to draw conclusions about germline status. It requires germline confirmation (Capoluongo et al., 2017). More recently, liquid biopsy has emerged as a promising surrogate for tumor biopsy, which is also helpful in overcoming spatial and temporal heterogeneity by allowing longitudinal disease monitoring (Alix-Panabières and Pantel, 2021). Circulating tumor DNA (ctDNA), the plasmatic DNA derived from tumor sites or circulating tumor cells, is an FDA-approved liquid biopsy biomarker analyzed with next-generation sequencing (NGS) on plasma samples (Alix-Panabières and Pantel, 2021). The US National Comprehensive Cancer Network (NCCN) guidelines recommend genetic testing (somatic and/or germline) for patients with high-risk, regional, and metastatic PCa (mPCa) or with a significant family history of cancer (Mohler, 2019). The European Society for Medical Oncology (ESMO) guidelines recommend germline testing for all patients with mPCa and genetic testing in patients with localized PCa and a family history supporting a hereditary predisposition to cancer (Parker et al., 2020). The Philadelphia Consensus Conference recommends testing all patients with mPCa and a significant family history of PCa or malignancies in the hereditary breast and ovarian cancer (HBOC) syndrome or Lynch syndrome spectrum. The test can be performed on blood or tissue in metastatic disease, preferably using NGS. Identification of somatic mutations in *BRCA2* or *BRCA1* results in need for germline testing due to familial implications. For patients with localized PCa, the Philadelphia consensus suggests using an initial test evaluating priority genes (*BRCA1/2* and *MMR*), possibly followed by an extended test (Giri, 2020). Finally, the European Association of Urology (EAU) considers genetic testing on ctDNA as an alternative option (Mottet, 2021) (Table 1).

A deal to concern with is represented by the choice of the optimal detection method for HRR testing. So far, tumor testing from a fresh biopsy is considered the gold standard. If not available, archival samples from the primary tumor or metastatic sites could be obtained, with some drawbacks: the heterogeneity within the tumor tissue, sometimes with a small number of representative cells, especially in case of multifocal disease, or with high tumor-infiltrating lymphocytes which reduce the detection capability. Moreover, paraffin could lead to DNA degradation in older samples, and some sites are more challenging to analyze. For example, bone tissue requires prior decalcification. In this regard, a recent consensus of Italian scientific societies recommended performing the somatic test primarily due to a higher probability of finding a mutation. Moreover, histological samples not over seven years should be used, preferably different tissues from bone metastases for the somatic testing, with specialized laboratories and expert pathologists to identify the most representative tumor areas (Russo et al., 2022).

4. PARPis monotherapy in mPCa

After a significant survival impact in other tumor subtypes, especially ovarian cancer, several PARPis have been tested also in mPCa (Table 2).

Table 1
Recommendations for genomic testing in prostate cancer.

Guidelines	Tumor testing	Germline Testing
NCCN, 2019	Recommended for *HRR* and consider for MSI/MMR alterations for all metastatic patients. Consider testing at earlier stages.	Recommend for any patients with PCa and Ashkenazi Jewish ancestry or strong family history of cancer and for all patients with high-risk localized or mPCa.
ESMO, 2020	Consider for *HRR* genes and MMR defects and MSI in patients with mCRPC	Recommended in patients with a family history of cancer; should be considered in all patients with mPCa.
Philadelphia Consensus Conference, 2019	Recommended in all patients with mPCa and in patients with a significant family history of PCa or malignancies in the HBOC syndrome or Lynch syndrome spectrum.	Recommended in mHSPC and mCRPC. To consider in patients in with non-mPCa and one of the following: Ashkenazi Jewish ancestry; T3a or higher; intraductal/ductal pathology; Grade Group 4 or above. a family history of PCa; a family history of PCa.
EAU, 2021	Recommended for HRR and MMR defects in all mPCa preferably on metastatic carcinoma tissue, or alternatively on primary tumor. To consider, although still less common, genetic testing on ctDNA.	To consider for patients with: mPCa; high risk PCa and a family history of PCa.

ctDNA: circulating tumor DNA; EAU: European Association of Urology; ESMO: European Society of Medical Oncology; HBOC: hereditary breast and ovarian cancer; HRR: homologous recombination repair; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; (m)PCa: (metastatic) prostate cancer; MMR: mismatch repair; MSI: microsatellite instability; NCCN: National Comprehensive Cancer Network

Olaparib showed promising results in a single-arm phase II trial, TOPARP, enrolling patients with mCRPC. In the first part of the study (TOPARP-A, NCT01682772), patients were included regardless of the presence of HRR mutations for the absence of a validated biomarker. However, the study required archival tissue or fresh tumor biopsies for HRR sequencing. Primary endpoints included response rate (RR), objective response, reduction in prostatic specific antigen (PSA) levels $\geq$ 50% (PSA50) from baseline, or conversion of circulating tumor cell (CTC) count from $\geq$ 5 at baseline to $<$ 5 in 7.5 mL of blood during treatment confirmed four weeks later. RR was 33% in the overall population, reaching 88% among patients with deleterious mutations in DNA repair genes and only 6% in those without the mutations. Secondary endpoints, radiographic progression-free survival (rPFS), and overall survival (OS) were also significantly longer in patients with HRR mutations (9.8 vs. 13.8 months, respectively) than in negative patients (2.7 vs. 7.5 months, respectively) (Mateo, 2015).

The next part of the study, TOPARP-B (NCT01682772), evaluated the anticancer effects of olaparib in mCRPC patients with HRR mutations progressing to platinum-based chemotherapy. Patients received olaparib 300 or 400 mg twice daily. *BRCA1/2* mutation predicted more significant responses and a longer median rPFS, with an overall response rate (ORR) of 83.3%, while in patients with *ATM* and Partner and localizer of BRCA2 (*PALB2*) alterations, radiographic ORR was 8.3% and 33.3%, respectively; PSA50 was reached in 5.2% and 66.6% of cases, respectively (Mateo, 2020a).

Based on these positive results, the phase III trial PROfound (NCT02987543) was designed. In this study, patients with mCRPC and genetic alteration in prespecified 15 HRR-related genes were randomized 2:1 to olaparib versus abiraterone or enzalutamide, after a first-line ARTA failure. Patients were divided into two prospective cohorts: cohort A included 245 patients with at least one alteration in *BRCA1*, *BRCA2*, or *ATM*; cohort B included 142 patients with alterations in any of 12 other

Table 2
Studies of PARP inhibitors monotherapy in metastatic prostate cancer.

Study	Phase	Experimental arm	Number of Patients	Previously treatment	Setting	Genes evaluated; used samples	Evaluation samples	Primary endpoint	Results of primary endpoint
TOPARP-A (NCT01682772)	II	Olaparib	49	mCRPC, ≥ 1 taxane	Unselected	113 genes panel (including *BRCA1, BRCA2, ATM, FANCA, CHEK2, PALB2, HDAC2, RAD51, MLH3, ERCC3, MRE11, NBN*)	Tumor	RR	RR 33% ITT, 88% HRR mutations
TOPARP-B (NCT01682772)	II	Olaparib 300 mg Olaparib 400 mg	49 49	mCRPC, ≥ 1 taxane	≥ 1 HRR mutations	NGS on genes related to HRR or PARP sensitivity (*BRCA1, BRCA2, ATM, CDK12, PALB2, CHECK1, CHEK2, ARID1A, ATRX, FANCA, FANCF, FANCG, FANCI, FANCM, MSH2, NBN, RAD50, WRN*)	Tumor	RR	54.3% in 400 mg group, 39.1% in 300 mg group (*BRCA1/2* 83%, *PALB2* 57%, *ATM* 37%, *CDK12* 25%)
PROfound (NCT02987543)	III	Olaparib (vs. ARTA)	162 (cohort A) 83 (cohort B)	mCRPC, ≥ 1 ARTA; prior taxane allowed	≥ 1 HRR mutations	Cohort A (*BRCA1, BRCA2, ATM)*; Cohort B *(BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2RA, RAD51B, RAD51C, RAD51D, RAD54L)*	Tumor	rPFS	Cohort A: 7.4 vs 3.6 months (HR=0.34; 95% CI, 0.25–0.47) Cohort B: 5.8 vs. 3.5 months (HR=0.49; 95% CI, 0.38–0.63)
TRITON-2 (NCT02952534)	II	Rucaparib	115	mCRPC, ≥ 1 ARTA, and > 1 taxane	*g/sBRCA1/2* mutations	*BRCA1, BRCA2*	Tumor or plasma	ORR, PSA-RR	ORR: *sBRCA1/2* 43.9%, *gBRCA1/2* 42.9% PSA-RR: *sBRCA1/2* 50.7%, *gBRCA1/2* 61.4%
			78		*g/s non-BRCA* HRR mutations	*ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54*			ORR: *ATM* 10.5%, *CDK12* 0%, *CHEK2* 11.1%, other mutations 28.6% PSA-RR: *ATM* 4.1%, *CDK12* 6.7%, *CHEK2* 16.7%
TRITON-3 (NCT02975934)	III	Rucaparib		mCRPC, > 1 ARTA; taxane for mHSPC allowed	*BRCA1/2* or *ATM* mutations	*BRCA1, BRCA2, ATM*	Tumor or plasma	Imaging-based PFS	10.2 vs. 6.4 mos (overall) 11.2 vs. 6.4 mos (BRCAm) 8.1 vs. 6.8 mos (ATMm)
TALAPRO-1 (NCT03148795)	II	Talazoparib	75	mCRPC, ≥ 1 taxane and ≥ 1 ARTA	HRR mutations	*ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, NBN, PALB2, RAD51C, MLH1, MRE11A*	Tumor	ORR	*BRCA1/2* 43.9%, *PALB2* 33.3%, *ATM* 11.8%
GAHALAD (NCT02854436)	II	Niraparib	81	mCRPC, ≥ 1 taxane and ≥ 1 ARTA	HRR mutations	*BRCA1/2, ATM, FANCA, CHEK2, PALB2, BRIP1, HDAC*	Tumor or plasma	ORR	*BRCA1/2* 41%, non-*BRCA* 9%

ARTA: androgen receptor targeted agent; ATM: ataxia-telangiectasia mutated; ATR: ATR serine/threonine kinase gene; BARD1: BRCA1 associated RING domain 1; (s/g)BRCA1/2: (somatic/germline) breast cancer gene 1/2; BRIP1: BRCA1 interacting protein 1; CDK12: cyclin-dependent kinase 12; CHEK2: Checkpoint kinase 2; CT: chemotherapy; FANCA/L: Fanconi anemia complementation group A/L; HDAC: histone deacetylase; HR: hazard ratio; HRR: homologous recombination repair; ITT: intention to treat; MLH1: MutL homolog 1; MRE11: meiotic recombination 11 homolog A; NBN: nibrin; NGS: next generation sequencing; ORR: overall response rate; PALB2: partner and localizer of BRCA2; PPP2RA: protein phosphatase 2 A; PSA-RR: PSA response rate; RAD51/54: RAD51/54 recombinase; rPFS: radiographic progression-free survival; RR: compete response rate

genes including *CDK12*, *CHEK2*, Protein phosphatase 2 A (*PPP2R2A*), *RAD51B*, *RAD54L*, *BRCA1* associated ring domain 1 (*BARD1*), *BRCA1* interacting protein (*BRIP1*). In cohort A, the median PFS (primary endpoint) was 7.4 versus 3.6 months in the control arm (hazard ratio [HR] 0.34; 95% confidence interval [CI], 0.25–0.47; $p < 0.001$); OS was 19.1 months in the olaparib arm and 14.7 months in the control arm (HR 0.69; 95% CI, 0.5–0.97; $p = 0.02$). In cohort B, PFS was 5.8 versus 3.5 months (HR 0.49; 95% CI, 0.38–0.63; $p < 0.001$) (de Bono et al., 2020; Hussain et al., 2020). In the overall population, OS was 17.3 versus 14.0 months in olaparib and control arms, respectively, without a statistically significant difference. Main ≥ grade (G)3 adverse events (AEs) were anemia (21%) and fatigue (3%). Based on these results, FDA approved olaparib for mCRPC patients with germline or somatic HRR gene mutations [FDA Olaparib online]. However, the number of participants with a mutation such as *BARD1*, *BRIP1*, *RAD51* was minimal, and for others with substantial numbers of mutation cases (i.e., *CDK12*, and *CHEK2*), results looked disappointing. Thus, EMA limited olaparib to mCRPC patients with *BRCA1* and *BRCA2* mutations, after ARTA progression [EMA olaparib online].

The second PARPi approved in PCa treatment, rucaparib, has been evaluated in the single-arm, open-label phase II study TRITON2 (NCT02952534) in patients with mCRPC and HRR gene alteration (15 genes panel) who had received one prior taxane-based chemotherapy and at least one ARTA. The results were reported for patients with *BRCA1* or *BRCA2* mutations ($n = 115$) and those with a non-*BRCA* HRR gene alteration ($n = 78$) separately (Abida and Campbell, 2020a; Abida and Patnaik, 2020b). In patients with *BRCA1/2* alterations, the primary endpoints, ORR for patients with soft-tissue disease and PSA response for patients with non-measurable disease, were 43.5% and 54.8%, respectively. Median rPFS was 9.0 months (Abida and Patnaik, 2020b). Among patients with a non-*BRCA* alteration, responses to rucaparib were minimal. No differences were found between somatic and germline *BRCA* mutations (Abida and Campbell, 2020a). These data led to the breakthrough FDA approval of rucaparib for mCRPC patients with somatic or germline *BRCA1/2* mutation after progression to one taxane and at least one ARTA [FDA rucaparib online]. Rucaparib was subsequently compared with ARTA or taxanes in the randomized phase III TRITON3 (NCT02975934), enrolling mCRPC patients with a germline or somatic *BRCA1/2* or *ATM* mutation, after a previous ARTA. Imaging-based PFS was the primary endpoint, OS and ORR were key secondary outcomes. A total of 297 patients received rucaparib, and 135 ARTA or taxanes (56% docetaxel). After a median follow up (mFU) of 62 months, mPFS was 10.2 versus 6.4 months in the overall population (HR 0.61; 95% CI, 0.47–0.8; $p < 0.001$), 11.2 vs. 6.4 months in the *BRCA*-mutant (HR 0.50; 95% CI, 0.36–0.69; $p < 0.001$), and 8.1 vs. 6.8 months in the *ATM*--mutant subgroup (HR 0.95; 95% CI, 0.59–1.52; exploratory analysis). At an interim analysis, mOS was 24.3 vs. 20.8 months (HR 0.81; 95% CI, 0.58–1.12; $p = 0.21$). ORR was 35% vs. 16% in the overall population, 45% vs. 17% in the *BRCA*-mutant subgroup, no response was recorded in the *ATM*-mutant subgroup. The median treatment duration was 8.1 vs. 5.1 months. Most commonly, rucaparib caused fatigue, nausea, and anemia, whereas in the control group, fatigue, diarrhea, and neuropathy occurred more frequently. Treatment discontinuation occurred in 15% of patients treated with rucaparib, versus 22% of the control group. 5 (2%) and 3 (2%) patients died in the two arms, respectively (Fizazi, 2023).

Talazoparib was evaluated in the single-arm, open-label phase II TALAPRO-1 trial, enrolling mCRPC patients after progression to at least one taxane-based regimen and one ARTA. The primary endpoint was ORR. 127 patients with a mutation tested in an 11 HRR genes panel received talazoparib. ORR was 29.8%, higher in *BRCA2*-mutant patients (46%) than *BRCA1*, *ATM*, and *PALB2*, without differences between germline and somatic mutations. Median rPFS and OS were 5.6 and 26.4 months in the overall population, 11.2 and 24 months in *BRCA1/2* mutated patients ($n = 61$), and 3.5 and 12.0 months in case of *ATM* mutation ($n = 11$), respectively. The *PALB2*-mutant groups reached a mOS of 12.2 months. Hematological toxicity was confirmed as the most common AE, with ≥G3 anemia in 31%, thrombocytopenia in 9%, and neutropenia in 8% of patients (de Bono et al., 2021).

The open-label phase II GALAHAD study tested niraparib in HRR-positive mCRPC patients (8 genes panel) who received at least one taxane and at least one ARTA. In patients with biallelic *BRCA1* or *BRCA2* mutations, there was an ORR of 41.4% and a CTC < 5 rate of 49% with a conversion rate (≥5–0 CTC) of 20%. Anemia (35%), neutropenia (10%), thrombocytopenia (8.3%), and hypertension (5.3%) were the most reported ≥G3 AEs. Two deaths from urosepsis and seizure were related to the study drug (Smith, 2022).

5. Combination studies with PARPis

After improving response and survival in monotherapy, PARPis started to be tested in combination with agents having different mechanisms of action. So far, the principal combinations of PARPis involve ARTA and immune checkpoint inhibitors (ICIs). However, other studies investigate combinations with chemotherapy and other targeted agents (Table 3).

5.1. PARPis plus ARTA

There is a strong rationale for combining ARTA and PARPis, as blocking the AR downregulates genes involved in DNA repair, enhancing DNA damage (Asim, 2017; Li et al., 2017a; 2017b). In fact, PARP promotes the transcription of the AR gene; therefore, AR blocking causes PARP overexpression, increasing sensitivity to PARPis (Li et al., 2017a; 2017b).

In the NCT01972217 phase II study, 141 mCPRC patients - previously treated with docetaxel, received abiraterone and were randomized to add olaparib versus placebo (PBO). HRR alterations were detected in 56% of cases. Median rPFS (the primary endpoint) was 13.8 months with olaparib versus 8.2 months with PBO (HR 0.65; 95% CI, 9.44–0.97; $p = 0.034$). Nausea (37% vs. 18%), constipation (25% vs. 11%), and pain (24% vs. 18%) were the most common AEs. ≥G3 AEs occurred in 54% vs. 28% of patients, more frequently anemia (21% vs. 0%), pneumonia (6% vs. 4%), and myocardial infarction (6% vs.0%). One treatment-related death due to pneumonia was reported in the olaparib + abiraterone group (Clarke et al., 2018). No significant differences in Health-related quality of life (HR-QoL) were reported (Saad et al., 2022b). Retrospective biomarkers analyses did not show significant differences between patients carrying *HRR* mutations and wild-type patients (Saad et al., 2018).

MAGNITUDE (NCT03748641) was a randomized phase III study including 670 naïve mCRPC patients randomized to abiraterone plus niraparib versus PBO. Patients were not selected for HRR status, even if they were assigned to a pre-specified positive ($n = 423$) or negative ($n = 247$) cohort. Patients could be included if abiraterone was started no more than four months before. rPFS was the primary endpoint, which had to be hierarchically tested first in the *BRCA1/2*-mutant subgroup, then in the other *HRR* patients; OS, time-to-chemotherapy, and time-to-symptomatic progression were the secondary endpoints. The *HRR*-negative cohort was judged in a pre-specified interim analysis for futility, and enrollment was stopped in this cohort. In the *HRR*-positive cohort, adding niraparib plus abiraterone significantly prolonged rPFS compared to abiraterone + PBO (median rPFS 16.5 vs. 13.7 months; HR 0.53; 95% CI, 0.36–0.79; $p = 0.0014$). Also, secondary endpoints benefitted from the addition of niraparib to abiraterone. OS data were immature, but a trend towards longer OS was suggested. ORR was higher in the combination cohort (52% vs. 31% in *BRCA*-mutant; 60% vs. 28% in *HRR*-positive patients), and the rate of complete responses was 18% vs. 14% in *BRCA*-mutant, and 22% vs. 11% in *HRR*-positive patients. AEs were reported in 99.1% vs. 94.1% of patients, severe AEs in 11.3% vs. 2.8%, and dose reduction was requested by 19.8% vs. 3.3% of cases, with a discontinuation rate of 10.8% vs. 4.7%. However, QoL

Table 3
Studies of PARPis combination in metastatic prostate cancer.

Study	Phase	Administered agents	Nr of patients	Setting	Primary endpoint	Efficacy results	Safety
PARPis plus ARTA							
NCT01972217	II	Abiraterone + Olaparib/PBO	141	mCRPC (after docetaxel)	rPFS	Median rPFS: 13.8 vs. 8.2 months ($p = 0.034$)	Most common AEs: nausea (37% vs. 18%), constipation (25% vs. 11%), pain (24% vs. 18%); ≥G3 AEs: 54% vs. 28%, more frequently anemia (21% vs. 0%), pneumonia (6% vs. 4%), myocardial infarction (6% vs.0%); 1 TRAE death in the combo group; No QoL differences
MAGNITUDE (NCT03748641)	III	Abiraterone + niraparib/PBO	670 (413 HRR^+)	mCRPC (naïve)	rPFS (hierarchic test: HRR^+ then HRR^-)	HRR^+: Median rPFS 16.5 vs. 13.7 months ($p = 0.0014$); ORR 60% vs. 28%; CRR 22% vs. 11% *BRCA*m: ORR 52% vs. 31% in *BRCA*m; CRR 18% vs. 14% HRR^- cohort: closed for futility	AEs: 99.1% vs. 94.1%; severe AEs: 11.3% vs. 2.8%; dose reduction: 19.8% vs. 3.3%; discontinuation rate;10.8% vs. 4.7%. Comparable QoL questionaries between the two cohorts
PROpel (NCT03732820)	III	Abiraterone + prednisone/PBO	796	mCRPC (docetaxel as mHSPC allowed)	rPFS	Median rPFS: ITT 24.8 vs. 16.6 months ($p < 0.0001$), in HRR^+: NR vs. 13.9 months, in HRR^-: 24 vs. 19 months, in *BRCA*m: NR vs. 8.4 months. OS: HR= 0.86; $p = 0.29$	AEs: 47% vs. 38%, discontinuation rate 13.8% vs. 7.8%, comparable QoL between the two cohorts
BRCAAway (NCT03012321)	II	Olaparib vs. Olaparib + abiraterone vs. abiraterone	161	mCRPC (naïve, *BRCA1/2* or *ATM* mut)	PFS	mPFS NR (olaparib + abiraterone), 11.3 months (olaparib; HR=0.14), 11 months (abiraterone; HR=0.19) PSA-RR 85% olaparib + abiraterone, 67% olaparib, 79% abiraterone	43 TRAEs: 23 fatigue, 17 nausea, 9 anemia
TALAPRO2 (NCT03395197)	III	Talazoparib/PBO + enzalutamide	805	mCRPC (naïve)	rPFS	median rPFS: NR vs. 21.9 months ($p < 0.001$). rPFS 27.9 in HRD vs. 16.4 months in HRP ($p < 0.001$). ORR 61.7% vs. 43.9%	≥G3 AEs: 71.9% vs. 40.6%; median time to QoL deterioration 30.8 vs. 25.0 mos ($p = 0.04$)
PARPis plus ICIs							
CheckMate 9KD (NCT03338790)	II	Olaparib + Nivolumab	88 (Cohort 1) 75 (Cohort 2)	mCRPC: after CT and ARTA (Cohort A1); after ARTA, CT naïve (Cohort A2)	ORR, PSA50-RR	Cohort A1: ORR 10.3% (HRR+ 17.2%, HRR- 3.4%), PSA50-RR 11.9% (HRR+ 18.2%, HRR- 5.0%); median rPFS 4.9 months, mOS 13.9 months. Cohort A2: ORR 15.4% (HRR+ 25%, HRR- 5.1%), PSA50-RR 27.3% (HRR+ 41.9%, HRR- 14.3%), median rPFS 8.1 months, mOS 20.2 months.	Most common AEs in the two cohorts: nausea (40%), fatigue, anemia; ≥G3 AEs (50%): anemia, neutropenia, and ALT increase the most frequent
KEYNOTE-365 (NCT02861573) cohort A	Ib/II	Olaparib + pembrolizumab	102	mCRPC after docetaxel	Safety, PSA-RR, ORR	PSA-RR: 15%, ORR: 8.5%, mPFS: 4.5 months, mOS: 14 months	AEs: 91%; ≥G3 AEs 48%. 6 TRAEs-related deaths
KEYLINK-010	III	Pembrolizumab + Olaparib vs. ARTA	739	mCRPC after docetaxel and ARTA	rPFS	Stopped for futility at interim analysis: median rPFS 4.4 vs. 4.2 months ($p = 0.55$); mOS 15.8 vs. 14.6 months ($p = 0.26$)	
MEDI4736 (NCT02484404)	I/II	Olaparib + durvalumab	14	mCRPC after ARTA	ORR, RP2D	Median rPFS 16.1 months, 12-mos rPFS 51.5%	Most common >G3 AEs were anemia (24%), lymphopenia (12%), infection (12%), nausea (12%)
Other combinations							
TRAP (NCT03787680)	II	Olaparib + ceralasertib (ATR inhibitor)	35?	mCRPC		HRR^+/ATMm: PSA-RR 40%	
NCT02893917	II	Olaparib vs. olaparib + cediranib (anti-VEGFR)	90	mCRPC		Median rPFS 8.5 (combo) vs. 4.0 months (mono) ($p = 0.359$) HRR^+ 10.6 vs. 3.8 months (HR=0.64,	
NCT01085422		Veliparib + temozolomide	26	mCRPC (after ≥2 lines of therapy)	PSA-RR	PSA-RR 8%, ORR 0%, mPFS/TTP 9wks, mPFS 39.6 wks 25/26 patients reported AEs, more	

(*continued on next page*)

Table 3 (*continued*)

Study	Phase	Administered agents	Nr of patients	Setting	Primary endpoint	Efficacy results	Safety
						frequently nausea, fatigue, and thrombocytopenia. ≥G3 AEs were: thrombocytopenia (23.1%), anemia (15.4%), colitis, fatigue, and neutropenia (all 7.7%)	

AEs: adverse events; ARTA: androgen receptor targeted agent; ATM: ATM: ataxia-telangiectasia mutated; ATR: Ataxia telangiectasia and Rad3-related; BRCAm: BRCA mutant; CRR: compete response rate; CT: chemotherapy;: hazard ratio; HRR: homologous recombination repair; ICIs: immune checkpoint inhibitors; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; mOS: median overall survival; mPFS: median progression-free survival; NR: not reached; ORR: overall response rate; PARPis: PARP-inhibitors; PBO: placebo; PSA-RR: PSA response rate; QoL: quality of life; rPFS: radiographic progression-free survival; TTP: time to progression; TRAE: treatment-related adverse event; VEGFR: vascular endothelial growth factor receptor

questionaries yielded comparable results between the two cohorts (Chi et al., 2022). At the second interim analysis presented at the American Society for Clinical Oncology Genito-Urinary (ASCO-GU) 2023 symposium, niraparib plus abiraterone prolonged rPFS to 19.5 months in the *BRCA* mutant subgroup, with a trend toward longer OS (Efstathiou et al., 2023).

PROpel (NCT03732820) was a randomized phase III trial. Patients were eligible if they had not previously received abiraterone; they could have been treated with another ARTA but must have stopped treatment over 12 months before enrollment; docetaxel in the hormone-sensitive setting was allowed. Patients were randomized to abiraterone plus olaparib 300 mg twice daily vs. PBO. Overall, 796 were randomized, of which around 1 out of 3 had *HRR* mutations (10% were *BRCA* mutant). Adding olaparib to abiraterone prolonged rPFS (the primary endpoint) compared to PBO, with a median rPFS of 24.8 vs. 16.6 months (HR 0.66; 95% CI, 0.54–0.81; $p < 0.0001$). The benefit was consistent among all the subgroups, although it was more significant in patients carrying HRR alterations (not reached [NR] vs. 13.9 months; HR 0.50; 95% CI, 0.34–0.73) than in those without *HRR* alteration (24 vs. 19 months; HR 0.76; 95% CI, 0.60–0.97), and in patients carrying *BRCA* mutations (NR vs. 8.4 months; HR 0.23; 95% CI, 0.12–0.43) (Saad et al., 2022a, 2022b; Clarke, 2022). At the final analysis run in December 2022, there was a trend towards OS benefit in the abiraterone plus olaparib group (mOS 42.1 mos) than PBO plus olaparib (34.7 mos), with medians NR in the *HRR/BRCA* mutant subgroups (Clarke et al., 2023). No safety concerns emerged from the study, even if a higher AEs rate was reported in the combination group (47%) than in the abiraterone + PBO cohort (38%), and a higher discontinuation rate emerged if patients received olaparib (13.8%) than PBO (7.8%). QoL results were comparable between the two cohorts (Saad et al., 2022a, 2022b; Clarke, 2022).

In the randomized BRCAAway (NCT03012321) phase II trial, mCRPC patients were selected for carrying *BRCA1/2*, or *ATM* mutations. 161 patients were randomized in first line 1:1:1 to abiraterone alone vs. olaparib vs. abiraterone plus olaparib. mPFS - the primary endpoint - was NR in the combination group, 11.3 months in the olaparib group (HR 0.14; 95% CI, 0.04–0.43), and 11.0 months in the abiraterone group (HR 0.19; 95% CI, 0.06–0.61). PSA-RR was 85%, 67%, and 79% in the olaparib + abiraterone, olaparib and abiraterone groups, respectively. 43 patients developed AEs, most commonly fatigue ($n = 23$), nausea ($n = 17$), and anemia ($n = 9$) (Hussain et al., 2022).

The phase III TALAPRO-2 (NCT03395197) randomized mCRPC not selected for *HRR* status to enzalutamide plus talazoparib/PBO. The primary endpoint was rPFS in patients with evaluable soft tissue or bone lesions. At a median follow-up of 25 months, median rPFS was NR in 402 patients treated with talazoparib plus enzalutamide versus 21.9 months in the 403 PBO plus enzalutamide group (HR 0.63; 95% CI, 0.51–0.78; $p < 0.001$). The benefit was more considerable in patients with *HRR* alterations (rPFS 27.9 vs. 16.4 months; HR 0.46; 95% CI, 0.30–0.70; $p < 0.001$). Adding talazoparib to enzalutamide increased ORR (61.7% vs. 43.9%). OS data were still immature at the time of the ASCO-GU presentation. 71.9% versus 40.6% of patients reported ≥G3 AEs, mainly anemia, hypertension, and fatigue. Discontinuation rates did not significantly differ between the two groups; however, the median time to deterioration in the quality of life was significantly longer in the talazoparib plus enzalutamide (30.8 mos) than in the PBO plus enzalutamide group (25.0 mos, HR 0.78; 95% CI, 0.62–0.99; $p = 0.04$) (Agarwal et al., 2023).

Together, the results of these studies have two major implications: the overcoming of PCa patients' selection based on *HRR* status, as there is evidence of PARPis benefit both in *HRR* defective and in *HRR* wild type patients; and secondly, the anticipation of PARPis in the earlier phases of the disease, moving from mCRPC to mHSPC. Further studies are ongoing (Rao et al., 2021; Agarwal et al., 2022; Rathkopf et al., 2021) (Table 4).

5.2. PARPis plus immune checkpoint inhibitors

In pre-clinical models, PARPis synergize with anti-Programmed Death-1 (PD-1)/PD-Ligand 1 (PD-L1) agents, resulting in reciprocal potentiation of antitumor efficacy (Jiao et al., 2017; Shen et al., 2019; Wang et al., 2019; Maiorano et al., 2022; Catalano et al., 2022). Some effects include increased DSBs on DNA, PD-L1 upregulation, and Stimulation of Interferon Gene (STING) signaling activation (Maiorano et al., 2022). As ICIs, such as pembrolizumab, have already demonstrated preliminary antitumor activity in mCRPC patients as monotherapy, several studies tried to investigate the association of PARPis and ICIs, starting from the mCRPC setting (Hansen et al., 2018; Antonarakis, 2020).

In cohorts A1 and A2 of the phase II CheckMate 9KD (NCT03338790) trial, patients with mCRPC received olaparib plus nivolumab. Cohort A1 included patients already treated with chemotherapy and ARTA; cohort A2 enrolled chemotherapy-naïve and ARTA-pretreated patients. The co-primary endpoints were ORR and PSA50-RR in the intention-to-treat (ITT) population and patients with HRR-positive tumors. rPFS, OS, and safety were the secondary endpoints. Cohort A1 included 88 patients, and cohort A2 included 77 patients (HRR alterations presented in around half of the cases). In cohort A1, ORR was 10.3%, PSA50-RR 11.9%, median rPFS 4.9 months, and mOS 13.9 months. ORR reached 17.2% in *HRR*-positive versus 3.4% in *HRR*-negative patients. PSA50-RR was 18.2% in *HRR*-positive versus 5.0% in *HRR*-negative patients. In cohort A2, ORR was 15.4%, and PSA50-RR 27.3%. Median rPFS was 8.1 months and mOS 20.2 months. In HRR-positive patients, ORR was 25% versus 5.3% in HRR-negative, and PSA50-RR was 41.9% versus 14.3%. The most common AEs in the two cohorts were nausea (around 40% of patients), fatigue, and anemia. Around half of the patients developed ≥G3 AEs, anemia, neutropenia, and alanine transaminase (ALT) increase being the most frequent (Fizazi, 2022). Therefore, although the results of combining nivolumab and rucaparib were dismal in unselected patients, better response rates and survival outcomes were recorded among *HRR*-positive patients.

In cohort A of the phase Ib/II KEYNOTE-365 (NCT02861573), 102 patients with docetaxel-pretreated mCRPC were treated with pembrolizumab plus olaparib 400 mg or 300 mg twice daily. The primary endpoints were safety, PSA-RR, and ORR; the secondary endpoints were

Table 4
Ongoing trials of PARPis combination in mPCa.

Clinical trial name	Phase	Drug combination	Setting	Biomarker Selection at enrollment	Primary Endpoint	Target number
CASPAR (NCT04455750)	III	Rucaparib/PBO + enzalutamide	mCRPC	No	rPFS, OS	984
QUEST (NCT03431350)	I/II	Niraparib + cetrelimab or abiraterone	mCRPC	No	Safety, ORR	60
LuPARP (NCT03874884)	I	Olaparib + 177LuPSMA	mCRPC	No	DLT, MTD, RP2D	52
COMRADE (NCT03317392)	I/II	Olaparib + Radium223	mCRPC	No	MTD, rPFS	133
NiraRad (NCT03076203)	I	Niraparib + Radium223	mCRPC	No	MTD	6
COBRA (NCT04038502)	II	Olaparib + Carboplatin	mCRPC	Yes	PFS	100
NCT04824937	II	Talazoparib + Telaglenastat (glutaminase inhibitor)	mCRPC	No	OR, type of response	30
REPAIR (NCT05425862)	I	Talazoparib + pidnarulex (Polymerase I inhibitor)	mCRPC	No	MTD	48
NCT04846478	I	Talazoparib + tazemetostat	mCRPC	No	DLT, safety	38
RAMP (NCT04179396)	I	Rucaparib + abiraterone/ enzalutamide	mCRPC	No	PK, safety	60
NCT04253262	I/II	Rucaparib + Copanlisib	mCRPC	No	MTD, overall response	44
NCT03442556	II	Rucaparib maintenance after docetaxel and carboplatin induction	mCRPC	Yes	rPFS	20
NCT03840200	I	Rucaparib + ipatasertib (AKTi)	mCRPC	No	Safety, DLT, PSA-RR	54
TALAPRO-3 (NCT04821622)	III	Talazoparib/PBO + enzalutamide	mHSPC	Yes	rPFS	550
AMPLITUDE (NCT04497844)	III	Niraparib/PBO + Abiraterone	mHSPC	Yes	rPFS	788
ZZ-First (NCT04332744)	II	Talazoparib + Enzalutamide	mHSPC	No	PSA-CR	54

DLT: dose limiting toxicities; mCRPC: metastatic castration-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; MTD: maximum tolerated doses; ORR: overall response rate; OS: overall survival; PBO: placebo; PK: pharmacokinetics; PSA-CR: PSA-complete response; rPFS: radiographic progression-free survival; RP2D: recommended phase 2 dose

PFS and OS. 28% of patients were PD-L1 positive (defined as a combined proportional score [CPS]≥1). This was a heavily pre-treated population, as 92% of patients had previously received both docetaxel and enzalutamide or abiraterone, 39% cabazitaxel, and 45% both abiraterone and enzalutamide. 33% of patients had a visceral disease; the median PSA was 109 ng/mL. PSA-RR was 15%, ORR 8.5%, mPFS 4.5 months, and mOS 14 months. 91% of patients developed AEs, and in 48% of cases, they were ≥G3 AEs. 6 deaths related to the drugs were reported (Yu and Piulats, 2022).

The combination of PARPis and ICIs was further explored in the KEYLYNK-010 phase III trial, with 793 mCRPC patients progressing to ARTA and docetaxel receiving pembrolizumab plus olaparib versus another ARTA. At the time of the interim analysis, the trial did not meet its primary endpoints of rPFS (median rPFS 4.4 vs. 4.2 months; HR 1.02; 95% CI, 0.82–1.25, p = 0.55) and OS (mOS 15.8 vs. 14.6 months; HR 0.94; 95% CI, 0.77–1.14, p = 0.26) and therefore was stopped for futility (Yu and Sun, 2022).

In the MEDI4736 (NCT02484404) phase I/II trial, 17 mCRPC patients progressing to abiraterone or enzalutamide were treated with olaparib and durvalumab. ORR and recommended phase 2 dose (RP2D) were the primary endpoints. Median rPFS was 16.1, with 12-mos rPFS 51.5%. The most common ≥G3 AEs were anemia (24%), lymphopenia (12%), infection (12%), and nausea (12%) (Karzai, 2018). Currently, the QUEST (NCT03431350) phase I/II study is ongoing, testing the triple combination of niraparib plus abiraterone plus cetrelimab (an anti-PD-1 agent) (Table 4).

5.3. Other combinations

In the TRAP (NCT03787680) phase II trial, mCRPC patients received the combination of olaparib and ceralasertib, an Ataxia Telangiectasia and Rad3-related (*ATR*) inhibitor. The *ATR* pathway is involved in DNA stabilization. Therefore, its activity is synergic with PARP (Wilson et al., 2022). In the cohort of patients with *HRR* or *ATM* mutations (n = 35), the PSA-RR was 40% (Reichert et al., 2022). Similarly, the Phosphatidylinositol-3 kinase (*PI3K*)-*AKT* pathway can synergize with PARP, as PARP inhibition induces AKT activation after downstream effects on ATM and AKT. In the phase Ib NCT03840200 study, the mCRPC group achieved a PSA response in 50% of cases harboring *HRR*, and in 25% not harboring HRR (Pook et al., 2022).

In the NCT01085422 trial, 26 mCRPC patients progressing to ≥ 2 previous lines of therapy received the PARPi veliparib plus temozolomide. PSA-RR (the primary endpoint) was 8%, ORR was 0%, mPFS and time-to-progression (TTP) were 9 weeks, and mOS 39.6. 25/26 patients reported AEs, more frequently nausea, fatigue, and thrombocytopenia. ≥G3 AEs were: thrombocytopenia (23.1%), anemia (15.4%), colitis, fatigue, and neutropenia (all 7.7%) (Hussain et al., 2014).

The anti-Vascular endothelial growth factor receptor (VEGFR) cediranib downregulates *BRCA1/2* and *RAD5q* expression. In a phase II study (NCT02893917), 90 mCRPC patients were randomized to olaparib alone or plus cediranib. The combination group achieved a median rPFS of 8.5 vs. 4.0 months (HR 0.62; 95% CI, 0.39–0.97; p = 0.359), that was 10.6 vs. 3.8 months in case of HRR alterations (HR 0.64; 95% CI, 0.27–1.50) (Kim, 2022). A phase I/II study, including durvalumab, olaparib, and/or cediranib, is ongoing (NCT02484404). Finally, the combination of PARPis and radiotherapy is under evaluation (Table 4).

6. Biomarkers of response to PARPis

HRR alterations do not behave similarly. Molecular analyses of the published studies evidence that *BRCA1/2* alterations reach higher objective responses (34–52%) compared to non-*BRCA* alterations (10–12%) (Lozano et al., 2020; Hussain et al., 2020; de Bono et al., 2020; Carreira, 2021; Abida, 2012 and 2014; McNevin et al., 2022). This difference was apparent in subgroup analyses from the PROfound and TOPARP-B trials, in which *BRCA* mutations conferred a more robust benefit than *ATM* or *CDK12* alterations (Hussain et al., 2020; de Bono et al., 2020). As a result, the FDA approval of olaparib for mCRPC men with *HRR* alterations was restricted by EMA to only *BRCA*-mutant cancers. In case of *ATM* mutations, patients with germline mutations and loss of *ATM* achieve long response and survival after PARPis; this datum emerged initially in the TOPARP-B trial (Carreira, 2021). *ATM* mutations led to response rates in around one out of three patients in the PROfound trial (Abida, 2012 and 2014). Regarding *PALB2*, for which a prognostic role for PARPis emerges from TOPARP-B, and TRITON2 trials, the main limitation is represented by the low prevalence of the

mutation. This is also true for *CHEK2*, Fanconi anemia complementation group A (*FANCA*), and *RAD51* genes (McNevin, 2022).

A difference seems to exist also between the two *BRCA* genes. Some studies have shown better responses to PARPis in mCRPC patients carrying *BRCA2* than *BRCA1* mutations. As proof, a pooled analysis from TOPARP-A and -B, PROfound, TRITON2, and TALAPRO-1 studies showed a higher PSA-RR, ORR, and rPFS for *BRCA2* than *BRCA1* patients (Markowski and Antonarakis, 2020) (Table 5).

This evidence may be partially due to the different roles that *BRCA1* and *BRCA2* play in the HRR pathway, as *BRCA2* is involved in the reparation mechanism. At the same time, *BRCA1* exerts multiple functions over HR, such as recruitment to DNA damage sites, resection of DNA end, checkpoint at G2/M and S-phase, and DNA repairing (Roy et al., 2012).

No differences seem to be evidenced in somatic versus germline mutations, both in the TRITON2 and in TALAPRO-1 and TOPARP-B studies (Loehr, 2021; de Bono et al., 2021; Carreira, 2021). On the contrary, different alterations of the same gene could be associated with different magnitudes of response and survival. Indeed, in the TOPARP-B study, patients carrying *BRCA* homozygous deletions reached longer responses than frameshifts of stop-gain mutations, with an rPFS of 16.4 months. Regarding biallelic vs. monoallelic *BRCA* mutations, in TRITON2, PSA responses were higher in biallelic alterations (75%) than monoallelic (11.1%). A possible explanation is that monoallelic alterations determine an incomplete HR function, while in case of biallelic deletions, PARPis resistance mechanisms, such as reversion mutations, emerge with more difficulty. However, according to TOPARP-B, unless in case of a low tumor content, even in the absence of a second hit mutation, a monoallelic pathogenic variant of *BRCA* should be sufficient for selecting patients for PARPis treatment (Carreira, 2021).

DNA damage repair mutations, such as *BRCA1/2* or *ATM*, also seem to play a role in response to the combination of ICIs and PARPis, even if studies need to be improved (Antonarakis, 2020). In fact, in the CheckMate 9KD, the advantage in the response rate of nivolumab plus olaparib among *BRCA*-mutant patients did not translate into a survival advantage. Nevertheless, after the KEYLINK-010 trial was stopped for futility, we may abandon the hypothesis of using the combination of PARPis and ICIs in unselected patients [Merck KEYLINK-010 online]. Further studies will better answer this question: the NCT04169841 phase II trial will test the efficacy of the triple combination of olaparib, durvalumab, and tremelimumab, in *HRR*-positive patients with many solid cancers, PCa included (Fumet et al., 2020).

In the TOPARP-A trial, and other retrospective cases, circulating cell-free DNA (cfDNA) analyses identified somatic *BRCA2* mutations that restored the standard open reading frame, the so-called 'reversion mutations', after olaparib progression, as a possible resistance mechanism (Goodall, 2017; Quigley, 2017; Norquist et al., 2011; Afghahi et al., 2017; Barber et al., 2013; Lin, 2019; Pettitt et al., 2020). The largest casuistry comes from the TRITON2 study, in which NGS analyses demonstrated that *BRCA* reversion mutations were absent at baseline, whereas 39% of patients developed them after rucaparib progression. Moreover, in 2 out of 3 cases, *BRCA* reversion mutations occurred sub-clonally at a lower allele frequency than the original mutation (Loehr et al., 2022). Only the *BRCA2* homozygous deletion seems unable to generate reversion mutations (Carreira, 2021). Other mutations of *HRR* genes and surface transporters that restore the DNA repair mechanisms, such as the loss of *PARP1* or *53BP1*, or increase PARPis efflux, such as the P-glycoprotein (Pgp) upregulation, or block PARP degradation, such as the PARP-glycohydrolase (*PARG*) enzyme mutations, or also epigenetic changes such as the promoter demethylation of *BRCS1* and *RAD51C*, are associated with PARPis resistance (Lord and Ashworth, 2013; D'Andrea, 2018). Another hypothesized mechanism for PARPis resistance is the presence at baseline, or the occurrence during treatment, of neuroendocrine features, for example, identified by Retinoblastoma1 (*RB1*) loss (Liu et al., 2019; Horak, 2019; Akamatsu et al., 2018). Some other factors have been studied as potentially causing PARPis resistance, as they are related to DNA repair pathways in various ways, such as the Polo-like kinase 1 (*Plk1*), Nitrogen permease regulator-like 2 (*NPRL2*), High mobility group A2 (*HMGA2*) mutations (Li, 2017; Chen et al., 2019; Hombach-Klonisch et al., 2019).

Conversely, in 'in vitro' models, loss of Chromodomain helicase DNA-binding protein 1 (*CDH1*) has been identified as a sensitizing mechanism for DNA-damaging therapies such as PARPis. This is a chromatin remodeler onco-suppressor whose loss seems to identify PCa subtypes carrying increased genomic instability and defect in DNA damage repair pathways (Kari et al., 2016; Shenoy, 2017). More studies on sensitizing and resistance mechanisms are needed to define treatment selection and sequencing strategies better.

Alternative methods could enter the path for HRR testing in the future. Liquid biopsy is the forerunner, being a minimally invasive procedure. Liquid biopsy appears to be very useful in a disease such as mPCa, often characterized by a long history and, therefore, a risk of old and scant specimens to analyze or with a particular propensity to bone metastases, whose biopsies result in discomfort for patients. In many studies, liquid biopsy, especially with circulating tumor DNA (ctDNA) analysis, has been addressed to identify genomic alterations with good sensitivity and concordance with tissue findings (ranging from 80% to 94%) (Catalano et al., 2023). The main advantage of this test is that ctDNA could better represent the heterogeneity of tumor compared to biopsy; moreover, it allows following longitudinal modifications of gene mutations, for example, in case of reversion mutations or other resistance mutations appearing. A limitation of this technique is represented by those cases with a low circulating tumor fraction (Catalano, 2023; Trujillo et al., 2022). The usefulness and accuracy of liquid biopsy have yet to be prospectively tested; therefore, future studies are warranted to validate the use of this method to find *HRR* alterations, preferably in selected centers.

Table 5
Differences in response and survival between *BRCA1* and *BRCA2* mutations.

	PSA50-RR (*nr. pts/total*)		ORR (*nr. pts/total*)		rPFS (*months*)	
	BRCA1	BRCA2	BRCA1	BRCA2	BRCA1	BRCA2
TOPARP-A	0/1	7/7	NE	5/5	NE	NR
TOPARP-B	1/2	22/28	0/1	11/20	NE	8.2
PROFOUND	NR	NR	0/5	24/43	2.1	10.8
TRITON-2	2/13	61/102	3/9	24/53	8.7	9.7
TALAPRO-1	2/5	26/41	2/4	15/37	NR	8.8

BRCA1/2: BReast CAncer gene 1/2; NE: not estimable; NR: not reached; ORR: overall response rate; PSA50-RR: PSA response rate with reduction > 50%; rPFS: radiographic progression-free survival

7. Conclusions

Metastatic PCa remains a challenging disease, with an urgent need for improving outcomes and tailoring treatments. Currently, PARPis represent a new standard of care in mCRPC patients with *BRCA* alterations. FDA approved olaparib also for *HRR* defects, even if the predictive role of HRR does not seem similar among the mutations. More recently, the combination of PARPis and ARTA demonstrated efficacy in mHSPC. However, the combination has been approved by EMA independently from *BRCA* status and with only PFS data. Further studies are warranted for new combinations and prognostic biomarkers identification. Ideal future trials should include molecular subtyping to go deeper into patterns of response and resistance. Furthermore, more accurate molecular profiling could help personalize PCa therapy progress. Finally, choosing the most appropriate time for treatment starting will be of primary importance shortly, for optimizing treatment sequencing and maximizing clinical benefit.

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors did not declare any conflict of interest concerning the preparation of this manuscript entitled.

Acknowledgements

Fig. 1 was created with *BioRender.com*.

References

Abida, W., Campbell, D., Patnaik, A., Shapiro, J.D., Sautois, B., Vogelzang, N.J., Voog, E. G., Bryce, A.H., McDermott, R., Ricci, F., Rowe, J., Zhang, J., Piulats, J.M., Fizazi, K., Merseburger, A.S., Higano, C.S., Krieger, L.E., Ryan, C.J., Feng, F.Y., Simmons, A.D., Loehr, A., Despain, D., Dowson, M., Green, F., Watkins, S.P., Golsorkhi, T., Chowdhury, S., 2020a. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study. Clin. Cancer Res. 26, 2487–2496. https://doi.org/10.1158/1078-0432.CCR-20-0394.

Abida, W., Patnaik, A., Campbell, D., Shapiro, J., Bryce, A.H., McDermott, R., Sautois, B., Vogelzang, N.J., Bambury, R.M., Voog, E., Zhang, J., Piulats, J.M., Ryan, C.J., Merseburger, A.S., Daugaard, G., Heidenreich, A., Fizazi, K., Higano, C.S., Krieger, L. E., Sternberg, C.N., Watkins, S.P., Despain, D., Simmons, A.D., Loehr, A., Dowson, M., Golsorkhi, T., Chowdhury, S., on behalf of the TRITON2 investigators, 2020b. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a *BRCA1* or *BRCA2* gene alteration. JCO 38, 3763–3772. https://doi.org/10.1200/JCO.20.01035.

Afghahi, A., Timms, K.M., Vinayak, S., Jensen, K.C., Kurian, A.W., Carlson, R.W., Chang, P.-J., Schackmann, E., Hartman, A.-R., Ford, J.M., Telli, M.L., 2017. Tumor *BRCA1* reversion mutation arising during neoadjuvant platinum-based chemotherapy in triple-negative breast cancer is associated with therapy resistance. Clin. Cancer Res. 23, 3365–3370. https://doi.org/10.1158/1078-0432.CCR-16-2174.

Agarwal, N., Azad, A., Fizazi, K., Mateo, J., Matsubara, N., Shore, N.D., Chakrabarti, J., Chen, H.-C., Lanzalone, S., Niyazov, A., Saad, F., For the TALAPRO-3 investigational group, 2022. Talapro-3: a phase 3, double-blind, randomized study of enzalutamide (ENZA) plus talazoparib (TALA) versus placebo plus enza in patients with DDR gene mutated metastatic castration-sensitive prostate cancer (mCSPC). TPS221–TPS221 JCO 40. https://doi.org/10.1200/JCO.2022.40.6_suppl.TPS221.

Agarwal, N., Azad, A., Carles, J., Fay, P.A., Matsubara, N., Heinrich, D., Szczylik, C., De Giorgi, U., Joung, J.Y., Fong, P.C.C., Voog, E., Jones, R.J., Shore, N.D., Dunshee, C., Zschaebitz, S., Lin, X., Healy, C.G., Di Santo, N., Zohren, F., Fizazi, K., 2023. LBA17. TALAPRO-2: Phase 3 Study of Talazoparib (TALA) + Enzalutamide (ENZA) versus Placebo (PBO) + ENZA as First-Line (1L) Treatment in Patients (pts) with Metastatic Castration-Resistant Prostate Cancer (mCRPC), presented at ASCO GU 2023.

Akamatsu, S., Inoue, T., Ogawa, O., Gleave, M.E., 2018. Clinical and molecular features of treatment-related neuroendocrine prostate cancer. Int. J. Urol. 25, 345–351. https://doi.org/10.1111/iju.13526.

Alix-Panabières, C., Pantel, K., 2021. Liquid biopsy: from discovery to clinical application. Cancer Discov. 11, 858–873. https://doi.org/10.1158/2159-8290.CD-20-1311.

Antonarakis, E.S., Piulats, J.M., Gross-Goupil, M., Goh, J., Ojamaa, K., Hoimes, C.J., Vaishampayan, U., Berger, R., Sezer, A., Alanko, T., de Wit, R., Li, C., Omlin, A., Procopio, G., Fukasawa, S., Tabata, K., Park, S.H., Feyerabend, S., Drake, C.G., Wu, H., Qiu, P., Kim, J., Poehlein, C., de Bono, J.S., 2020. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. JCO 38, 395–405. https://doi.org/10.1200/JCO.19.01638.

Ashworth, A., Lord, C.J., 2018. Synthetic lethal therapies for cancer: what's next after PARP inhibitors? Nat. Rev. Clin. Oncol. 15, 564–576. https://doi.org/10.1038/s41571-018-0055-6.

Asim, M., Tarish, F., Zecchini, H.I., Sanjiv, K., Gelali, E., Massie, C.E., Baridi, A., Warren, A.Y., Zhao, W., Ogris, C., McDuffus, L.-A., Mascalchi, P., Shaw, G., Dev, H., Wadhwa, K., Wijnhoven, P., Forment, J.V., Lyons, S.R., Lynch, A.G., O'Neill, C., Zecchini, V.R., Rennie, P.S., Baniahmad, A., Tavaré, S., Mills, I.G., Galanty, Y., Crosetto, N., Schultz, N., Neal, D., Helleday, T., 2017. Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. Nat. Commun. 8, 374 https://doi.org/10.1038/s41467-017-00393-y.

Barber, L.J., Sandhu, S., Chen, L., Campbell, J., Kozarewa, I., Fenwick, K., Assiotis, I., Rodrigues, D.N., Reis-Filho, J.S., Moreno, V., Mateo, J., Molife, L.R., De Bono, J., Kaye, S., Lord, C.J., Ashworth, A., 2013. Secondary mutations in *BRCA2* associated with clinical resistance to a PARP inhibitor: clinical PARP inhibitor resistance. J. Pathol. 229, 422–429. https://doi.org/10.1002/path.4140.

Bednarz-Knoll, N., Eltze, E., Semjonow, A., Brandt, B., 2019. BRCAness in prostate cancer. Oncotarget 10, 2421–2422. https://doi.org/10.18632/oncotarget.26818.

Capoluongo, E., Ellison, G., López-Guerrero, J.A., Penault-Llorca, F., Ligtenberg, M.J.L., Banerjee, S., Singer, C., Friedman, E., Markiefka, B., Schirmacher, P., Büttner, R., van Asperen, C.J., Ray-Coquard, I., Endris, V., Kamel-Reid, S., Percival, N., Bryce, J., Röthlisberger, B., Soong, R., de Castro, D.G., 2017. Guidance statement on BRCA1/2 tumor testing in ovarian cancer patients. Semin Oncol. 44, 187–197. https://doi.org/10.1053/j.seminoncol.2017.08.004.

Carreira, S., Porta, N., Arce-Gallego, S., Seed, G., Llop-Guevara, A., Bianchini, D., Rescigno, P., Paschalis, A., Bertan, C., Baker, C., Goodall, J., Miranda, S., Riisnaes, R., Figueiredo, I., Ferreira, A., Pereira, R., Crespo, M., Gurel, B., Nava Rodrigues, D., Pettitt, S.J., Yuan, W., Serra, V., Rekowski, J., Lord, C.J., Hall, E., Mateo, J., de Bono, J.S., 2021. Biomarkers associating with PARP inhibitor benefit in prostate cancer in the TOPARP-B trial. Cancer Discov. 11, 2812–2827. https://doi.org/10.1158/2159-8290.CD-21-0007.

Catalano, M., Iannone, F.L., Cosso, F., Generali, D., Mini, E., Roviello, G., 2022. Combining inhibition of immune checkpoints and PARP: rationale and perspectives in cancer treatment. Expert Opin. Ther. Targets 26, 923–936. https://doi.org/10.1080/14728222.2022.2158813.

Catalano, M., Generali, D., Gatti, M., Riboli, B., Paganini, L., Nesi, G., Roviello, G., 2023. DNA repair deficiency as circulating biomarker in prostate cancer. Front Oncol. 13, 1115241 https://doi.org/10.3389/fonc.2023.1115241.

Chang, H.H.Y., Pannunzio, N.R., Adachi, N., Lieber, M.R., 2017. Non-homologous DNA end joining and alternative pathways to double-strand break repair. Nat. Rev. Mol. Cell Biol. 18, 495–506. https://doi.org/10.1038/nrm.2017.48.

Chatterjee, N., Walker, G.C., 2017. Mechanisms of DNA damage, repair, and mutagenesis: DNA damage and repair. Environ. Mol. Mutagen. 58, 235–263. https://doi.org/10.1002/em.22087.

Chen, K., O'Brien, J., McVey, A., Jenjitranant, P., Kelly, B.D., Kasivisvanathan, V., Lawrentschuk, N., Murphy, D.G., Azad, A.A., 2022. Combination treatment in metastatic prostate cancer: is the bar too high or have we fallen short? Nat. Rev. Urol. https://doi.org/10.1038/s41585-022-00669-z.

Chen, X., Chen, Z., Zheng, B., Tang, W., 2019. Targeting NPRL2 to enhance the efficacy of olaparib in castration-resistant prostate cancer. Biochem. Biophys. Res. Commun. 508, 620–625. https://doi.org/10.1016/j.bbrc.2018.11.062.

Chi, K.N., Rathkopf, D.E., Smith, M.R., Efstathiou, E., Attard, G., Olmos, D., Lee, J.Y., Small, E.J., Gomes, A.J., Roubaud, G., Saad, M., Zurawski, B., Sakalo, V., Mason, G., del Corral, A., Wang, G.C., Wu, D., Diorio, B., Lopez- Gitlitz, A.M., Sandhu, S.K., 2022. Phase 3 MAGNITUDE study: first results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations, 12–12 JCO 40. https://doi.org/10.1200/JCO.2022.40.6_suppl.012.

Clarke, N., Wiechno, P., Alekseev, B., Sala, N., Jones, R., Kocak, I., Chiuri, V.E., Jassem, J., Fléchon, A., Redfern, C., Goessl, C., Burgents, J., Kozarski, R., Hodgson, D., Learoyd, M., Saad, F., 2018. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 19, 975–986. https://doi.org/10.1016/S1470-2045(18)30365-6.

Clarke, N.W., Armstrong, A.J., Thiery-Vuillemin, A., Oya, M., Shore, N., Loredo, E., Procopio, G., de Menezes, J., Girotto, G., Arslan, C., Mehra, N., Parnis, F., Brown, E., Schlürmann, F., Joung, J.Y., Sugimoto, M., Virizuela, J.A., Emmenegger, U., Navratil, J., Buchschacher, G.L., Poehlein, C., Harrington, E.A., Desai, C., Kang, J., Saad, F., 2022. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. NEJM Evid. 1 https://doi.org/10.1056/EVIDoa2200043.

Clarke, N.W., Armstrong, A.J., Thiery-Vuillemin, A., Oya, M., Shore, N.D., Procopio, G., Cardoso Guedes, J.D., Arslan, C., Mehra, N., Parnis, F., Brown, E., Schlurmann, F., Joung, J.Y., Sugimoto, M., Oliver Sartor, A., Liu, Y., Poehlein, C.H., Barker, L., del Rosario, P.M., Saad, F., 2023. Final Overall Survival (OS) in Propel: Abiraterone (Abi) and Olaparib (Ola) versus Abiraterone and Placebo (Pbo) as First-Line (1L) Therapy for Metastatic Castration-Resistant Prostate Cancer (mCRPC), presented at ASCO-GU 2023.

Conteduca, V., Mosca, A., Brighi, N., de Giorgi, U., Rescigno, P., 2021. New prognostic biomarkers in metastatic castration-resistant prostate cancer. Cells 10, 193. https://doi.org/10.3390/cells10010193.

Cui, M., Gao, X.S., Gu, X., Guo, W., Li, X., Ma, M., Qin, S., Qi, X., Xie, M., Peng, C., Bai, Y., 2017. BRCA2 mutations should be screened early and routinely as markers of poor prognosis: evidence from 8,988 patients with prostate cancer. Oncotarget 8, 40222–40232. https://doi.org/10.18632/oncotarget.16712.

D'Andrea, A.D., 2018. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair 71, 172–176. https://doi.org/10.1016/j.dnarep.2018.08.021.

David, S.S., O'Shea, V.L., Kundu, S., 2007. Base-excision repair of oxidative DNA damage. Nature 447, 941–950. https://doi.org/10.1038/nature05978.

de Bono, J., Mateo, J., Fizazi, K., Saad, F., Shore, N., Sandhu, S., Chi, K.N., Sartor, O., Agarwal, N., Olmos, D., Thiery-Vuillemin, A., Twardowski, P., Mehra, N., Goessl, C., Kang, J., Burgents, J., Wu, W., Kohlmann, A., Adelman, C.A., Hussain, M., 2020. Olaparib for metastatic castration-resistant prostate cancer. N. Engl. J. Med 382, 2091–2102. https://doi.org/10.1056/NEJMoa1911440.

de Bono, J.S., Mehra, N., Scagliotti, G.V., Castro, E., Dorff, T., Stirling, A., Stenzl, A., Fleming, M.T., Higano, C.S., Saad, F., Buttigliero, C., van Oort, I.M., Laird, A.D., Mata, M., Chen, H.-C., Healy, C.G., Czibere, A., Fizazi, K., 2021. Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): an open-label, phase 2 trial. Lancet Oncol. 22, 1250–1264. https://doi.org/10.1016/S1470-2045(21)00376-4.

Efstathiou, E., Smith, M.R., Sandhu, S., Attard, G., Saad, M., Olmos, D., Castro, E., Roubaud, G., Gomes, A.J., Small, E.J., Rathkopf, D.E., Gurney, H., Jung, W., Mason, G., St. John Francis, P., Wang, G.C., Wu, D., Diorio, B., Lopez-Gitlitz, A.M., Chi, K.N., 2023. 170, Niraparib (NIRA) with Abiraterone Acetate and Prednisone (AAP) in

Patients (Pts) with Metastatic Castration-Resistant Prostate Cancer (Mcrpc) and Homologous Recombination Repair (HRR) Gene Alterations: Second Interim Analysis (IA2) of MAGNITUDE, presented at ASCO-GU 2023.

Farmer, H., McCabe, N., Lord, C.J., Tutt, A.N.J., Johnson, D.A., Richardson, T.B., Santarosa, M., Dillon, K.J., Hickson, I., Knights, C., Martin, N.M.B., Jackson, S.P., Smith, G.C.M., Ashworth, A., 2005. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434, 917–921. https://doi.org/10.1038/nature03445.

Fizazi, K., Retz, M., Petrylak, D.P., Goh, J.C., Perez-Gracia, J., Lacombe, L., Zschäbitz, S., Burotto, M., Mahammedi, H., Gravis, G., Bastos, D.A., McCune, S.L., Vázquez Limón, J.C., Kwan, E.M., Castellano, D., Fléchon, A., Saad, F., Grimm, M.-O., Shaffer, D.R., Armstrong, A.J., Bhagavatheeswaran, P., Amin, N.P., Ünsal-Kaçmaz, K., Wang, X., Li, J., Loehr, A., Pachynski, R.K., 2022. Nivolumab plus rucaparib for metastatic castration-resistant prostate cancer: results from the phase 2 checkmate 9KD trial. J. Immunother. Cancer 10, e004761. https://doi.org/10.1136/jitc-2022-004761.

Fizazi, K., Piulats, J.M., Reaume, M.N., Ostler, P., McDermott, R., Gingerich, J.R., Pintus, E., Sridhar, S.S., Bambury, R.M., Emmenegger, U., Lindberg, H., Morris, D., Nolè, F., Staffurth, J., Redfern, C., Sáez, M.I., Abida, W., Daugaard, G., Heidenreich, A., Krieger, L., Sautois, B., Loehr, A., Despain, D., Heyes, C.A., Watkins, S.P., Chowdhury, S., Ryan, C.J., Bryce, A.H., TRITON3 Investigators, 2023. Rucaparib or physician's choice in metastatic prostate cancer. N. Engl. J. Med. 388, 719–732. https://doi.org/10.1056/NEJMoa2214676.

Fong, P.C., Boss, D.S., Yap, T.A., Tutt, A., Wu, P., Mergui-Roelvink, M., Mortimer, P., Swaisland, H., Lau, A., O'Connor, M.J., Ashworth, A., Carmichael, J., Kaye, S.B., Schellens, J.H.M., de Bono, J.S., 2009. Inhibition of Poly(ADP-Ribose) polymerase in tumors from *BRCA* mutation carriers. N. Engl. J. Med. 361, 123–134. https://doi.org/10.1056/NEJMoa0900212.

Fumet, J.-D., Limagne, E., Thibaudin, M., Truntzer, C., Bertaut, A., Rederstorff, E., Ghiringhelli, F., 2020. Precision medicine phase II study evaluating the efficacy of a double immunotherapy by durvalumab and tremelimumab combined with olaparib in patients with solid cancers and carriers of homologous recombination repair genes mutation in response or stable after olaparib treatment. BMC Cancer 20, 748. https://doi.org/10.1186/s12885-020-07253-x.

Giri, V.N., Knudsen, K.E., Kelly, W.K., Cheng, H.H., Cooney, K.A., Cookson, M.S., Dahut, W., Weissman, S., Soule, H.R., Petrylak, D.P., Dicker, A.P., AlDubayan, S.H., Toland, A.E., Pritchard, C.C., Pettaway, C.A., Daly, M.B., Mohler, J.L., Parsons, J.K., Carroll, P.R., Pilarski, R., Blanco, A., Woodson, A., Rahm, A., Taplin, M.-E., Polascik, T.J., Helfand, B.T., Hyatt, C., Morgans, A.K., Feng, F., Mullane, M., Powers, J., Concepcion, R., Lin, D.W., Wender, R., Mark, J.R., Costello, A., Burnett, A.L., Sartor, O., Isaacs, W.B., Xu, J., Weitzel, J., Andriole, G.L., Beltran, H., Briganti, A., Byrne, L., Calvaresi, A., Chandrasekar, T., Chen, D.Y.T., Den, R.B., Dobi, A., Crawford, E.D., Eastham, J., Eggener, S., Freedman, M.L., Garnick, M., Gomella, P.T., Handley, N., Hurwitz, M.D., Izes, J., Karnes, R.J., Lallas, C., Languino, L., Loeb, S., Lopez, A.M., Loughlin, K.R., Lu-Yao, G., Malkowicz, S.B., Mann, M., Mille, P., Miner, M.M., Morgan, T., Moreno, J., Mucci, L., Myers, R.E., Nielsen, S.M., O'Neil, B., Pinover, W., Pinto, P., Poage, W., Raj, G.V., Rebbeck, T.R., Ryan, C., Sandler, H., Schiewer, M., Scott, E.M.D., Szymaniak, B., Tester, W., Trabulsi, E.J., Vapiwala, N., Yu, E.Y., Zeigler-Johnson, C., Gomella, L.G., 2020. Implementation of germline testing for prostate cancer: philadelphia prostate cancer consensus conference 2019. JCO 38, 2798–2811. https://doi.org/10.1200/JCO.20.00046.

Goodall, J., Mateo, J., Yuan, W., Mossop, H., Porta, N., Miranda, S., Perez-Lopez, R., Dolling, D., Robinson, D.R., Sandhu, S., Fowler, G., Ebbs, B., Flohr, P., Seed, G., Rodrigues, D.N., Boysen, G., Bertan, C., Atkin, M., Clarke, M., Crespo, M., Figueiredo, I., Riisnaes, R., Sumanasuriya, S., Rescigno, P., Zafeiriou, Z., Sharp, A., Tunariu, N., Bianchini, D., Gillman, A., Lord, C.J., Hall, E., Chinnaiyan, A.M., Carreira, S., de Bono, J.S., 2017. Circulating cell-free DNA to guide prostate cancer treatment with PARP inhibition. Cancer Discov. 7, 1006–1017. https://doi.org/10.1158/2159-8290.CD-17-0261.

Gourley, C., Balmaña, J., Ledermann, J.A., Serra, V., Dent, R., Loibl, S., Pujade-Lauraine, E., Boulton, S.J., 2019. Moving from poly (ADP-Ribose) polymerase inhibition to targeting DNA repair and DNA damage response in cancer therapy. J. Clin. Oncol. 37, 2257–2269. https://doi.org/10.1200/JCO.18.02050.

Hansen, A.R., Massard, C., Ott, P.A., Haas, N.B., Lopez, J.S., Ejadi, S., Wallmark, J.M., Keam, B., Delord, J.-P., Aggarwal, R., Gould, M., Yang, P., Keefe, S.M., Piha-Paul, S. A., 2018. Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. Ann. Oncol. 29, 1807–1813. https://doi.org/10.1093/annonc/mdy232.

Hoeijmakers, J.H., 2001. Genome maintenance mechanisms for preventing cancer. Nature 411, 366–374. https://doi.org/10.1038/35077232.

Hombach-Klonisch, S., Kalantari, F., Medapati, M.R., Natarajan, S., Krishnan, S.N., Kumar-Kanojia, A., Thanasupawat, T., Begum, F., Xu, F.Y., Hatch, G.M., Los, M., Klonisch, T., 2019. HMGA 2 as a functional antagonist of PARP 1 inhibitors in tumor cells. Mol. Oncol. 13, 153–170. https://doi.org/10.1002/1878-0261.12390.

Horak, P., Weischenfeldt, J., von Amsberg, G., Beyer, B., Schütte, A., Uhrig, S., Gieldon, L., Klink, B., Feuerbach, L., Hübschmann, D., Kreutzfeldt, S., Heining, C., Maier, S., Hutter, B., Penzel, R., Schlesner, M., Eils, R., Sauter, G., Stenzinger, A., Brors, B., Schröck, E., Glimm, H., Fröhling, S., Schlomm, T., 2019. Response to olaparib in a *PALB2* germline mutated prostate cancer and genetic events associated with resistance. Cold Spring Harb. Mol. Case Stud. 5, a003657 https://doi.org/10.1101/mcs.a003657.

Hussain, M., Carducci, M.A., Slovin, S., Cetnar, J., Qian, J., McKeegan, E.M., Refici-Buhr, M., Chyla, B., Shepherd, S.P., Giranda, V.L., Alumkal, J.J., 2014. Targeting DNA repair with combination veliparib (ABT-888) and temozolomide in patients with metastatic castration-resistant prostate cancer. Invest N. Drugs 32, 904–912. https://doi.org/10.1007/s10637-014-0099-0.

Hussain, M., Mateo, J., Fizazi, K., Saad, F., Shore, N., Sandhu, S., Chi, K.N., Sartor, O., Agarwal, N., Olmos, D., Thiery-Vuillemin, A., Twardowski, P., Roubaud, G., Özgüroğlu, M., Kang, J., Burgents, J., Gresty, C., Corcoran, C., Adelman, C.A., de Bono, J., 2020. Survival with olaparib in metastatic castration-resistant prostate cancer. N. Engl. J. Med 383, 2345–2357. https://doi.org/10.1056/NEJMoa2022485.

Hussain, M.H.A., Kocherginsky, M., Agarwal, N., Zhang, J., Adra, N., Paller, C.J., Picus, J., Reichert, Z.R., Szmulewitz, R.Z., Tagawa, S.T., Whang, Y.E., Dreicer, R., Kuzel, T., Bazzi, L., Gerke, T.A., Daignault-Newton, S., Chinnaiyan, A., Antonarakis, E.S., 2022. BRCAAWAY: a randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) with DNA repair defects, 5018–5018 JCO 40. https://doi.org/10.1200/JCO.2022.40.16_suppl.5018.

Jiao, S., Xia, W., Yamaguchi, H., Wei, Y., Chen, M.-K., Hsu, J.-M., Hsu, J.L., Yu, W.-H., Du, Y., Lee, H.-H., Li, C.-W., Chou, C.-K., Lim, S.-O., Chang, S.-S., Litton, J., Arun, B., Hortobagyi, G.N., Hung, M.-C., 2017. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin. Cancer Res. 23, 3711–3720. https://doi.org/10.1158/1078-0432.CCR-16-3215.

Kari, V., Mansour, W.Y., Raul, S.K., Baumgart, S.J., Mund, A., Grade, M., Sirma, H., Simon, R., Will, H., Dobbelstein, M., Dikomey, E., Johnsen, S.A., 2016. Loss of *CHD1* causes DNA repair defects and enhances prostate cancer therapeutic responsiveness. EMBO Rep. 17, 1609–1623. https://doi.org/10.15252/embr.201642352.

Karzai, F., VanderWeele, D., Madan, R.A., Owens, H., Cordes, L.M., Hankin, A., Couvillon, A., Nichols, E., Bilusic, M., Beshiri, M.L., Kelly, K., Krishnasamy, V., Lee, S., Lee, M.-J., Yuno, A., Trepel, J.B., Merino, M.J., Dittamore, R., Marté, J., Donahue, R.N., Schlom, J., Killian, K.J., Meltzer, P.S., Steinberg, S.M., Gulley, J.L., Lee, J.-M., Dahut, W.L., 2018. Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations. J. Immunother. Cancer 6, 141. https://doi.org/10.1186/s40425-018-0463-2.

Kim, J.W., McKay, R.R., Radke, M.R., Zhao, S., Taplin, M.-E., Davis, N.B., Monk, P., Appleman, L.J., Lara, P.N., Vaishampayan, U.N., Zhang, J., Paul, A.K., Bubley, G., Van Allen, E.M., Unlu, S., Huang, Y., Loda, M., Shapiro, G.I., Glazer, P.M., LoRusso, P.M., Ivy, S.P., Shyr, Y., Swisher, E.M., Petrylak, D.P., 2022. Randomized trial of olaparib with or without cediranib for metastatic castration-resistant prostate cancer: the results from national cancer institute 9984. JCO.21.02947 JCO. https://doi.org/10.1200/JCO.21.02947.

Lee, A.M., Saidian, A., Shaya, J., Nonato, T., Cabal, A., Randall, J.M., Millard, F., Stewart, T., Rose, B., Tamayo, P., McKay, R.R., 2022. The prognostic significance of homologous recombination repair pathway alterations in metastatic hormone sensitive prostate cancer. Clin. Genitourin. Cancer 20, 515–523. https://doi.org/10.1016/j.clgc.2022.06.016.

Li, J., Wang, R., Kong, Y., Broman, M.M., Carlock, C., Chen, L., Li, Z., Farah, E., Ratliff, T. L., Liu, X., 2017a. Targeting Plk1 to enhance efficacy of olaparib in castration-resistant prostate cancer. Mol. Cancer Ther. 16, 469–479. https://doi.org/10.1158/1535-7163.MCT-16-0361.

Li, L., Karanika, S., Yang, G., Wang, J., Park, S., Broom, B.M., Manyam, G.C., Wu, W., Luo, Y., Basourakos, S., Song, J.H., Gallick, G.E., Karantanos, T., Korentzelos, D., Azad, A.K., Kim, J., Corn, P.G., Aparicio, A.M., Logothetis, C.J., Troncoso, P., Heffernan, T., Toniatti, C., Lee, H.-S., Lee, J.-S., Zuo, X., Chang, W., Yin, J., Thompson, T.C., 2017b. Androgen receptor inhibitor–induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. Sci. Signal. 10, eaam7479 https://doi.org/10.1126/scisignal.aam7479.

Li, X., Heyer, W.-D., 2008. Homologous recombination in DNA repair and DNA damage tolerance. Cell Res. 18, 99–113. https://doi.org/10.1038/cr.2008.1.

Lin, K.K., Harrell, M.I., Oza, A.M., Oaknin, A., Ray-Coquard, I., Tinker, A.V., Helman, E., Radke, M.R., Say, C., Vo, L.-T., Mann, E., Isaacson, J.D., Maloney, L., O'Malley, D.M., Chambers, S.K., Kaufmann, S.H., Scott, C.L., Konecny, G.E., Coleman, R.L., Sun, J.X., Giordano, H., Brenton, J.D., Harding, T.C., McNeish, I.A., Swisher, E.M., 2019. *BRCA* reversion mutations in circulating tumor DNA predict primary and acquired resistance to the PARP inhibitor rucaparib in high-grade ovarian carcinoma. Cancer Discov. 9, 210–219. https://doi.org/10.1158/2159-8290.CD-18-0715.

Liu, B., Li, L., Yang, G., Geng, C., Luo, Y., Wu, W., Manyam, G.C., Korentzelos, D., Park, S., Tang, Z., Wu, C., Dong, Z., Sigouros, M., Sboner, A., Beltran, H., Chen, Y., Corn, P.G., Tetzlaff, M.T., Troncoso, P., Broom, B., Thompson, T.C., 2019. PARP inhibition suppresses GR–MYCN–CDK5–RB1–E2F1 signaling and neuroendocrine differentiation in castration-resistant prostate cancer. Clin. Cancer Res. 25, 6839–6851. https://doi.org/10.1158/1078-0432.CCR-19-0317.

Loehr, A., Hussain, A., Patnaik, A., Bryce, A.H., Castellano, D., Font, A., Shapiro, J., Zhang, J., Sautois, B., Vogelzang, N.J., Chatta, G., Courtney, K., Harzstark, A., Ricci, F., Despain, D., Watkins, S., King, C., Nguyen, M., Simmons, A.D., Chowdhury, S., Abida, W., 2022. Emergence of BRCA reversion mutations in patients with metastatic castration-resistant prostate cancer after treatment with rucaparib. S0302283822026392 Eur. Urol.. https://doi.org/10.1016/j.eururo.2022.09.010.

Loehr, A., Patnaik, A., Campbell, D., Shapiro, J., Bryce, A.H., McDermott, R., Sautois, B., Vogelzang, N.J., Bambury, R.M., Voog, E., Zhang, J., Piulats, J.M., Hussain, A., Ryan, C.J., Merseburger, A.S., Daugaard, G., Heidenreich, A., Fizazi, K., Higano, C.S., Krieger, L.E., Sternberg, C.N., Watkins, S.P., Despain, D., Simmons, A.D., Dowson, M., Golsorkhi, T., Chowdhury, S., Abida, W., 2021. Response to rucaparib in BRCA-mutant metastatic castration-resistant prostate cancer identified by genomic testing in the TRITON2 study. Clin. Cancer Res. 27, 6677–6686. https://doi.org/10.1158/1078-0432.CCR-21-2199.

Lord, C.J., Ashworth, A., 2017. PARP inhibitors: synthetic lethality in the clinic. Science 355, 1152–1158. https://doi.org/10.1126/science.aam7344.

Lord, C.J., Ashworth, A., 2013. Mechanisms of resistance to therapies targeting BRCA-mutant cancers. Nat. Med. 19, 1381–1388. https://doi.org/10.1038/nm.3369.

Lozano, R., Castro, E., Aragon, I., Thorne, H., López-Campos, F., Sanz, A., Alonso, C., Anido, U., maria Jose, J., Gutierrez Pecharroman, A., Ramirez-Backhaus, M., Balmana Gelpi, J., Chirivella, I., Llort, G., Romero-Laorden, N., Arevalo, S., Rubio, J., Di Domenico, T., Sandhu, S.K., Olmos, D., 2020. PROREPAIR-A: clinical and molecular characterization study of prostate cancer (PC) patients with and without previously known germline *BRCA1/2* mutations, 5511–5511 JCO 38. https://doi.org/10.1200/JCO.2020.38.15_suppl.5511.

Maiorano, B.A., Lorusso, D., Maiorano, M.F.P., Ciardiello, D., Parrella, P., Petracca, A., Cormio, G., Maiello, E., 2022. The interplay between PARP inhibitors and immunotherapy in ovarian cancer: the rationale behind a new combination therapy. IJMS 23, 3871. https://doi.org/10.3390/ijms23073871.

Markowski, M.C., Antonarakis, E.S., 2020. *BRCA1* versus *BRCA2* and PARP inhibitor sensitivity in prostate cancer: more different than alike? JCO 38, 3735–3739. https://doi.org/10.1200/JCO.20.02246.

Mateo, J., Carreira, S., Sandhu, S., Miranda, S., Mossop, H., Perez-Lopez, R., Nava Rodrigues, D., Robinson, D., Omlin, A., Tunariu, N., Boysen, G., Porta, N., Flohr, P., Gillman, A., Figueiredo, I., Paulding, C., Seed, G., Jain, S., Ralph, C., Protheroe, A., Hussain, S., Jones, R., Elliott, T., McGovern, U., Bianchini, D., Goodall, J., Zafeiriou, Z., Williamson, C.T., Ferraldeschi, R., Riisnaes, R., Ebbs, B., Fowler, G., Roda, D., Yuan, W., Wu, Y.-M., Cao, X., Brough, R., Pemberton, H., A'Hern, R., Swain, A., Kunju, L.P., Eeles, R., Attard, G., Lord, C.J., Ashworth, A., Rubin, M.A., Knudsen, K.E., Feng, F.Y., Chinnaiyan, A.M., Hall, E., de Bono, J.S., 2015. DNA-repair defects and olaparib in metastatic prostate cancer. N. Engl. J. Med. 373, 1697–1708. https://doi.org/10.1056/NEJMoa1506859.

Mateo, J., Porta, N., Bianchini, D., McGovern, U., Elliott, T., Jones, R., Syndikus, I., Ralph, C., Jain, S., Varughese, M., Parikh, O., Crabb, S., Robinson, A., McLaren, D., Birtle, A., Tanguay, J., Miranda, S., Figueiredo, I., Seed, G., Bertan, C., Flohr, P., Ebbs, B., Rescigno, P., Fowler, G., Ferreira, A., Riisnaes, R., Pereira, R., Curcean, A., Chandler, R., Clarke, M., Gurel, B., Crespo, M., Nava Rodrigues, D., Sandhu, S., Espinasse, A., Chatfield, P., Tunariu, N., Yuan, W., Hall, E., Carreira, S., de Bono, J. S., 2020a. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol. 21, 162–174. https://doi.org/10.1016/S1470-2045(19)30684-9.

Mateo, J., Seed, G., Bertan, C., Rescigno, P., Dolling, D., Figueiredo, I., Miranda, S., Nava Rodrigues, D., Gurel, B., Clarke, M., Atkin, M., Chandler, R., Messina, C., Sumanasuriya, S., Bianchini, D., Barrero, M., Petermolo, A., Zafeiriou, Z., Fontes, M., Perez-Lopez, R., Tunariu, N., Fulton, B., Jones, R., McGovern, U., Ralph, C., Varughese, M., Parikh, O., Jain, S., Elliott, T., Sandhu, S., Porta, N., Hall, E., Yuan, W., Carreira, S., de Bono, J.S., 2020b. Genomics of lethal prostate cancer at diagnosis and castration resistance. J. Clin. Invest 130, 1743–1751. https://doi.org/10.1172/JCI132031.

McNevin, C.S., Cadoo, K., Baird, A.-M., Finn, S.P., McDermott, R., 2022. PARP inhibitors in advanced prostate cancer in tumors with DNA damage signatures. Cancers 14, 4751. https://doi.org/10.3390/cancers14194751.

Mohler, J.L., Antonarakis, E.S., Armstrong, A.J., D'Amico, A.V., Davis, B.J., Dorff, T., Eastham, J.A., Enke, C.A., Farrington, T.A., Higano, C.S., Horwitz, E.M., Hurwitz, M., Ippolito, J.E., Kane, C.J., Kuettel, M.R., Lang, J.M., McKenney, J., Netto, G., Penson, D.F., Plimack, E.R., Pow-Sang, J.M., Pugh, T.J., Richey, S., Roach, M., Rosenfeld, S., Schaeffer, E., Shabsigh, A., Small, E.J., Spratt, D.E., Srinivas, S., Tward, J., Shead, D.A., Freedman-Cass, D.A., 2019. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. J. Natl. Compr. Cancer Netw. 17, 479–505. https://doi.org/10.6004/jnccn.2019.0023.

Mottet, N., van den Bergh, R.C.N., Briers, E., Van den Broeck, T., Cumberbatch, M.G., De Santis, M., Fanti, S., Fossati, N., Gandaglia, G., Gillessen, S., Grivas, N., Grummet, J., Henry, A.M., van der Kwast, T.H., Lam, T.B., Lardas, M., Liew, M., Mason, M.D., Moris, L., Oprea-Lager, D.E., van der Poel, H.G., Rouvière, O., Schoots, I.G., Tilki, D., Wiegel, T., Willemse, P.-P.M., Cornford, P., 2021. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur. Urol. 79, 243–262. https://doi.org/10.1016/j.eururo.2020.09.042.

Murai, J., Huang, S.N., Das, B.B., Renaud, A., Zhang, Y., Doroshow, J.H., Ji, J., Takeda, S., Pommier, Y., 2012. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res 72, 5588–5599. https://doi.org/10.1158/0008-5472.CAN-12-2753.

Murai, J., Huang, S.-Y.N., Renaud, A., Zhang, Y., Ji, J., Takeda, S., Morris, J., Teicher, B., Doroshow, J.H., Pommier, Y., 2014. Stereospecific PARPtrapping by BMN 673 and comparison with olaparib and rucaparib. Mol. Cancer Ther. 13, 433–443. https://doi.org/10.1158/1535-7163.MCT-13-0803.

Norquist, B., Wurz, K.A., Pennil, C.C., Garcia, R., Gross, J., Sakai, W., Karlan, B.Y., Taniguchi, T., Swisher, E.M., 2011. Secondary somatic mutations restoring *BRCA1/2* predict chemotherapy resistance in hereditary ovarian carcinomas. JCO 29, 3008–3015. https://doi.org/10.1200/JCO.2010.34.2980.

Ogi, T., Limsirichaikul, S., Overmeer, R.M., Volker, M., Takenaka, K., Cloney, R., Nakazawa, Y., Niimi, A., Miki, Y., Jaspers, N.G., Mullenders, L.H.F., Yamashita, S., Fousteri, M.I., Lehmann, A.R., 2010. Three DNA polymerases, recruited by different mechanisms, carry out NER repair synthesis in human cells. Mol. Cell 37, 714–727. https://doi.org/10.1016/j.molcel.2010.02.009.

Parker, C., Castro, E., Fizazi, K., Heidenreich, A., Ost, P., Procopio, G., Tombal, B., Gillessen, S., ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org, 2020. Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 31, 1119–1134. https://doi.org/10.1016/j.annonc.2020.06.011.

Pettitt, S.J., Frankum, J.R., Punta, M., Lise, S., Alexander, J., Chen, Y., Yap, T.A., Haider, S., Tutt, A.N.J., Lord, C.J., 2020. Clinical *BRCA1/2* reversion analysis identifies hotspot mutations and predicted neoantigens associated with therapy resistance. Cancer Discov. 10, 1475–1488. https://doi.org/10.1158/2159-8290.CD-19-1485.

Pook, D.W., Geynisman, D.M., Carles, J., De Braud, F.G., Joshua, A.M., Perez-Gracia, J.L., Llácer Pérez, C., Shin, S.J., Fang, B., Barve, M.A., Maruzzo, M., Bracarda, S., Kim, M., Kerloeguen, Y., Gallo, J.D., Maund, S., Harris, A., Huang, K.-C., Sutaria, D.S., Gurney, H., 2022. A phase Ib, open-label study evaluating the safety and efficacy of ipatasertib + rucaparib in patients with metastatic castration-resistant prostate cancer (mCRPC), 95–95 JCO 40. https://doi.org/10.1200/JCO.2022.40.6_suppl.095.

Pritchard, C.C., Mateo, J., Walsh, M.F., De Sarkar, N., Abida, W., Beltran, H., Garofalo, A., Gulati, R., Carreira, S., Eeles, R., Elemento, O., Rubin, M.A., Robinson, D., Lonigro, R., Hussain, M., Chinnaiyan, A., Vinson, J., Filipenko, J., Garraway, L., Taplin, M.-E., AlDubayan, S., Han, G.C., Beightol, M., Morrissey, C., Nghiem, B., Cheng, H.H., Montgomery, B., Walsh, T., Casadei, S., Berger, M., Zhang, L., Zehir, A., Vijai, J., Scher, H.I., Sawyers, C., Schultz, N., Kantoff, P.W., Solit, D., Robson, M., Van Allen, E.M., Offit, K., de Bono, J., Nelson, P.S., 2016. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N. Engl. J. Med 375, 443–453. https://doi.org/10.1056/NEJMoa1603144.

Quigley, D., Alumkal, J.J., Wyatt, A.W., Kothari, V., Foye, A., Lloyd, P., Aggarwal, R., Kim, W., Lu, E., Schwartzman, J., Beja, K., Annala, M., Das, R., Diolaiti, M., Pritchard, C., Thomas, G., Tomlins, S., Knudsen, K., Lord, C.J., Ryan, C., Youngren, J., Beer, T.M., Ashworth, A., Small, E.J., Feng, F.Y., 2017. Analysis of circulating cell-free DNA identifies multiclonal heterogeneity of *BRCA2* reversion mutations associated with resistance to PARP inhibitors. Cancer Discov. 7, 999–1005. https://doi.org/10.1158/2159-8290.CD-17-0146.

Rao, A., Ryan, C.J., VanderWeele, D.J., Heller, G., Lewis, L.D., Watt, C., Chen, R.C., Grubb, R., Hahn, O.M., Beltran, H., Morris, M.J., 2021. CASPAR (Alliance A031902): a randomized, phase III trial of enzalutamide (ENZ) with rucaparib (RUCA)/Placebo (PBO) as a novel therapy in first-line metastatic castration-resistant prostate cancer (mCRPC). TPS181–TPS181 JCO 39. https://doi.org/10.1200/JCO.2021.39.6_suppl.TPS181.

Rathkopf, D.E., Chi, K.N., Olmos, D., Cheng, H.H., Agarwal, N., Graff, J.N., Sandhu, S.K., Hayreh, V., Lopez-Gitlitz, A., Francis, P.St.J., Attard, G., 2021. AMPLITUDE: a study of niraparib in combination with abiraterone acetate plus prednisone (AAP) versus AAP for the treatment of patients with deleterious germline or somatic homologous recombination repair (HRR) gene-altered metastatic castration-sensitive prostate cancer (mCSPC). TPS176–TPS176 JCO 39. https://doi.org/10.1200/JCO.2021.39.6_suppl.TPS176.

Reichert, Z.R., Devitt, M.E., Alumkal, J.J., Smith, D.C., Caram, M.V., Palmbos, P., Vaishampayan, U.N., Alva, A.S., Braun, T., Yentz, S.E., Tsao, P.A., Dreicer, R., Cackowski, F.C., Shah, N., Dean, E., Smith, S., Heath, E.I., 2022. Targeting resistant prostate cancer, with or without DNA repair defects, using the combination of ceralasertib (ATR Inhibitor) and olaparib (the TRAP Trial), 88–88 JCO 40. https://doi.org/10.1200/JCO.2022.40.6_suppl.088.

Robinson, D., Van Allen, E.M., Wu, Y.-M., Schultz, N., Lonigro, R.J., Mosquera, J.-M., Montgomery, B., Taplin, M.-E., Pritchard, C.C., Attard, G., Beltran, H., Abida, W., Bradley, R.K., Vinson, J., Cao, X., Vats, P., Kunju, L.P., Hussain, M., Feng, F.Y., Tomlins, S.A., Cooney, K.A., Smith, D.C., Brennan, C., Siddiqui, J., Mehra, R., Chen, Y., Rathkopf, D.E., Morris, M.J., Solomon, S.B., Durack, J.C., Reuter, V.E., Gopalan, A., Gao, J., Loda, M., Lis, R.T., Bowden, M., Balk, S.P., Gaviola, G., Sougnez, C., Gupta, M., Yu, E.Y., Mostaghel, E.A., Cheng, H.H., Mulcahy, H., True, L. D., Plymate, S.R., Dvinge, H., Ferraldeschi, R., Flohr, P., Miranda, S., Zafeiriou, Z., Tunariu, N., Mateo, J., Perez-Lopez, R., Demichelis, F., Robinson, B.D., Sboner, A., Schiffman, M., Nanus, D.M., Tagawa, S.T., Sigaras, A., Eng, K.W., Elemento, O., Sboner, A., Heath, E.I., Scher, H.I., Pienta, K.J., Kantoff, P., de Bono, J.S., Rubin, M. A., Nelson, P.S., Garraway, L.A., Sawyers, C.L., Chinnaiyan, A.M., 2015. Integrative clinical genomics of advanced prostate cancer. Cell 162, 454. https://doi.org/10.1016/j.cell.2015.06.053.

Roy, R., Chun, J., Powell, S.N., 2012. BRCA1 and BRCA2: different roles in a common pathway of genome protection. Nat. Rev. Cancer 12, 68–78. https://doi.org/10.1038/nrc3181.

Russo, A., Incorvaia, L., Capoluongo, E., Tagliaferri, P., Gori, S., Cortesi, L., Genuardi, M., Turchetti, D., De Giorgi, U., Di Maio, M., Barberis, M., Dessena, M., Del Re, M., Lapini, A., Luchini, C., Jereczek-Fossa, B.A., Sapino, A., Cinieri, S., 2022. Italian scientific societies. implementation of preventive and predictive BRCA testing in patients with breast, ovarian, pancreatic, and prostate cancer: a position paper of italian scientific societies. ESMO Open 7, 100459. https://doi.org/10.1016/j.esmoop.2022.100459.

Saad, F., Armstrong, A.J., Thiery-Vuillemin, A., Oya, M., Loredo, E., Procopio, G., Janoski de Menezes, J., Girotto, G.C., Arslan, C., Mehra, N., Parnis, F., Brown, E., Schlürmann, F., Joung, J.Y., Sugimoto, M., Poehlein, C.H., Harrington, E., Desai, C., Kang, J., Clarke, N., 2022a. PROpel: phase III trial of olaparib (ola) and abiraterone (abi) versus placebo (pbo) and abi as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC), 11–11 JCO 40. https://doi.org/10.1200/JCO.2022.40.6_suppl.011.

Saad, F., Chi, K.N., Shore, N., Graff, J.N., Posadas, E.M., Freeman, S., Tryon, J., Trudel, G. C., de Jong, J., Meltzer, J., Zhao, X., Tran, N., Rezazadeh, A., 2018. Interim results of a phase Ib study of niraparib plus androgen receptor-targeted therapy in men with metastatic castration-resistant prostate cancer. Ann. Oncol. 29, viii292. https://doi.org/10.1093/annonc/mdy284.043.

Saad, F., Thiery-Vuillemin, A., Wiechno, P., Alekseev, B., Sala, N., Jones, R., Kocak, I., Chiuri, V.E., Jassem, J., Fléchon, A., Redfern, C., Kang, J., Burgents, J., Gresty, C., Degboe, A., Clarke, N.W., 2022b. Patient-reported outcomes with olaparib plus

abiraterone versus placebo plus abiraterone for metastatic castration-resistant prostate cancer: a randomised, double-blind, phase 2 trial. S1470204522004983 Lancet Oncol.. https://doi.org/10.1016/S1470-2045(22)00498-3.

Shen, J., Zhao, W., Ju, Z., Wang, L., Peng, Y., Labrie, M., Yap, T.A., Mills, G.B., Peng, G., 2019. PARPi triggers the STING-dependent immune response and enhances the therapeutic efficacy of immune checkpoint blockade independent of BRCAness. Cancer Res. 79, 311–319. https://doi.org/10.1158/0008-5472.CAN-18-1003.

Shenoy, T.R., Boysen, G., Wang, M.Y., Xu, Q.Z., Guo, W., Koh, F.M., Wang, C., Zhang, L. Z., Wang, Y., Gil, V., Aziz, S., Christova, R., Rodrigues, D.N., Crespo, M., Rescigno, P., Tunariu, N., Riisnaes, R., Zafeiriou, Z., Flohr, P., Yuan, W., Knight, E., Swain, A., Ramalho-Santos, M., Xu, D.Y., de Bono, J., Wu, H., 2017. CHD1 loss sensitizes prostate cancer to DNA damaging therapy by promoting error-prone double-strand break repair. Ann. Oncol. 28, 1495–1507. https://doi.org/10.1093/annonc/mdx165.

Shrivastav, M., De Haro, L.P., Nickoloff, J.A., 2008. Regulation of DNA double-strand break repair pathway choice. Cell Res. 18, 134–147. https://doi.org/10.1038/cr.2007.111.

Siegel, R.L., Miller, K.D., Fuchs, H.E., Jemal, A., 2022. Cancer statistics, 2022. CA A Cancer J. Clin. 72, 7–33. https://doi.org/10.3322/caac.21708.

Smith, M.R., Scher, H.I., Sandhu, S., Efstathiou, E., Lara, P.N., Yu, E.Y., George, D.J., Chi, K.N., Saad, F., Ståhl, O., Olmos, D., Danila, D.C., Mason, G.E., Espina, B.M., Zhao, X., Urtishak, K.A., Francis, P., Lopez-Gitlitz, A., Fizazi, K., Parnis, F., Joshua, A. M., Horvath, L.G., Steer, C., Marx, G., Sandhu, S., Gurney, H., Ferguson, T., Van Bruwaene, S., Luyten, D., Schatteman, P., Lumen, N., Dirix, L., Goeminne, J.-C., Gil, T., Seront, E., Vulsteke, C., Kussumoto, C., Franke, F.A., Martinelli de Oliveira, F. A., Pereira de Santana Gomes, A.J., Pinczowski, H., Preto, D.D., Zucca, L.E., Borges, G.S., Murad, A.M., Saad, F., Chi, K.N., Fradet, Y., Fleshner, N.E., Emmenegger, U., Brasso, K., Fizazi, K., Culine, S., Thiery-Vuillemin, A., Joly, F., Fléchon, A., Hilgers, W., Eymard, J.-C., Borchiellini, D., Barthélémy, P., Berger, R., Leibowitz-Amit, R., Mermershtain, W., Rouvinov, K., Peer, A., Kovel, S., Sella, A., Lolkema, M.P., van den Eertwegh, A.J.M., Voortman, J., Aarts, M.J., Gietema, J.A., Kim, C.-S., Choi, Y.-D., Chung, B.-H., Gafanov, R.A., Kopyltsov, E., Usynin, E.A., Carles, J., Mellado, B., Maroto, J.P., García-Donás, J., Rodríguez Moreno, J.F., Durán, I., Pérez-Valderrama, B., Castro, E., Olmos, D., Méndez-Vidal, M.J., Estellés, D.L., Sarrió, R.G., Muñoz-Langa, J., Herranz, U.A., Puente Vázquez, J., Castellanos, E., Hellström, M., Widmark, A., Lissbrant, I.F., Jellvert, Å., Külich, C., Blom, R., Ståhl, O., Chiang, P.-H., Kang, C.-H., Ou, Y.-C., Wang, S.-S., Wu, H.-C., Lu, Y.-C., Attard, G., Khoo, V., Bahl, A., Kellati, P., Parikh, O., Srinivasan, R., Lester, J.F., Staffurth, J.N., Cheng, H.H., Efstathiou, E., Pilié, P.G., George, D.J., Karsh, L.I., Kelly, W.K., Danila, D.C., Sieber, P.R., Smith, M.R., Heath, E.I., Vaishampayan, U.N., Flaig, T.W., Emamekhoo, H., Pinski, J.K., Kalebasty, A.R., Maly, J.J., Moon, H., 2022. Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial. Lancet Oncol. 23, 362–373. https://doi.org/10.1016/S1470-2045(21)00757-9.

Spies, M., Fishel, R., 2015. Mismatch repair during homologous and homologous recombination. Cold Spring Harb. Perspect. Biol. 7, a022657 https://doi.org/10.1101/cshperspect.a022657.

Trujillo, B., Wu, A., Wetterskog, D., Attard, G., 2022. Blood-based liquid biopsies for prostate cancer: clinical opportunities and challenges. Br. J. Cancer 127, 1394–1402. https://doi.org/10.1038/s41416-022-01881-9.

Wang, Z., Sun, K., Xiao, Y., Feng, B., Mikule, K., Ma, X., Feng, N., Vellano, C.P., Federico, L., Marszalek, J.R., Mills, G.B., Hanke, J., Ramaswamy, S., Wang, J., 2019. Niraparib activates interferon signaling and potentiates anti-PD-1 antibody efficacy in tumor models. Sci. Rep. 9, 1853 https://doi.org/10.1038/s41598-019-38534-6.

Wilson, Z., Odedra, R., Wallez, Y., Wijnhoven, P.W.G., Hughes, A.M., Gerrard, J., Jones, G.N., Bargh-Dawson, H., Brown, E., Young, L.A., O'Connor, M.J., Lau, A., 2022. ATR inhibitor AZD6738 (Ceralasertib) exerts antitumor activity as a monotherapy and in combination with chemotherapy and the PARP inhibitor olaparib. Cancer Res 82, 1140–1152. https://doi.org/10.1158/0008-5472.CAN-21-2997.

Brigida Anna Maiorano, MD, PhD, works as medical oncologist at IRCCS "Casa Sollievo della Sofferenza", with experience in genitourinary oncology, preclinical and clinical research.

Vincenza Conteduca is Associate Professor at the Department of Medical and Surgical Sciences, Unit of Medical Oncology and Biomolecular Therapy, University of Foggia, Italy. Since 2011 she has been involved in several clinical trials and translation oncology research projects in urological tumours, particularly, in prostate cancer. Her research is mainly focused on the identification of novel biological profiles of sensitivity and/or resistance to treatments by plasma DNA analysis, in collaboration with some of the most influential research institutes in Europe and United States.

Martina Catalano, MD, is Research Investigator in Oncology with experience in genito-urinary oncology and clinical research working at the Florence University.

Lorenzo Antonuzzo, MD, PhD, is Professor of Medical Oncology at the Florence University, with experience in gastrointestinal and genitourinary cancers and neuroendocrine tumors.

Evaristo Maiello is the Head of Oncology Unit at IRCCS "Casa Sollievo della Sofferenza". He participated in more than 50 multicenter clinical trials as principal investigator. He is an active member of the Italian Society of Medical Oncology (AIOM) and has served as President of Gruppo Oncologico dell'Italia Meridionale (GOIM). Furthermore, he has been recently elected President of Federation of Italian Cooperative Oncology Groups (FICOG). He authored about 150 scientific publications.

Ugo De Giorgi is Director of Clinical and Experimental Oncology Unit of IRCCS Istituto Romagnolo studio tumori (IRST) Meldola, Italy. He is Coordinator of the uro-gynecologic oncology multidisciplinary team of Ausl Romagna and Professor of Medical Oncology. He is Secretary and past President of Meet-URO (Italian Network for Research in Urologic Oncology), member of international scientific associations on GU tumors and coordinator of national/international studies.

Giandomenico Roviello, MD, PhD, is Professor of Medical Oncology with experience in genitourinary oncology, preclinical and clinical research at the Florence University.