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Review Article

PARP inhibitors in metastatic prostate cancer: When, who, and how?

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ABSTRACT

Carcinoma prostate is among the most common cancers worldwide and is mainly treated in metastatic settings through androgen blockade or chemotherapy. Homologous repair deficiency is fairly common (germline and somatic) and allows targeted therapy through poly ADP-ribose polymerases (PARP) inhibitors. While data backing monotherapy is strong, recent evidence seems to support frontline combination therapy as well. Genetic testing of prostate cancer patients also needs personalization. Pre-clinical and early clinical data have provided insights into mechanisms and management of therapy resistance as well. This narrative review deals with the optimal patient selection and the evidence behind PARP inhibitor therapy in cases of metastatic carcinoma prostate.

Keywords: Carcinoma prostate, Prostate cancer, Castration-resistant prostate cancer, Homologous repair, Homologous repair deficient, Olaparib, Niraparib, Rucaparib, Veliparib, Talazoparib, Poly ADP-ribose polymerases, Poly ADP-ribose polymerases inhibitors, Poly ADP-ribose polymerases inhibitors, Liquid biopsy

INTRODUCTION

Prostate cancer is among the most common solid organ tumors globally, with a marked epidemiological variation.[1] While androgen receptor (AR) directed therapies and chemotherapy remain the standard of care, targeted agents are rapidly being incorporated. In this regard, poly ADP-ribose polymerases (PARP) inhibitors and immune checkpoint inhibitors have been recently added to the therapeutic armamentarium. This review focuses on the biological rationale, patient selection, and current evidence behind PARP inhibitor therapy in metastatic castration-resistant carcinoma prostate.

DNA REPAIR AND PROSTATE CANCER

Types of DNA repair mechanisms

A plethora of endogenous/exogenous agents lead to DNA damage which is repaired, mainly by the following mechanisms: Nucleotide excision repair, Base excision repair (BER), Mismatch repair, homologous repair (HR), non-homologous end joining (NHEJ; Classical and alternate), and finally the Fanconi pathway.[2] Impairment in these pathways may lead to genomic instability, a hallmark of cancer.[3] Consequently, defects in these mechanisms lead to a multitude of inherited cancer syndromes.[4] The tumor microenvironment may potentiate these DNA repair defects through local hypoxemia, hypoglycemia, epigenetic modification, and other mechanisms.[2] In this

complex conundrum of interactions, two pathways deserve special mention when dealing with prostatic adenocarcinoma: BER and homologous recombination repair (HRR).

BER corrects lesions that typically do not alter the DNA helix structure.[5] These lesions (deamidation, oxidation, and methylation) are typically a manifestation of spontaneous decay of DNA, a process accelerated by reactive oxygen species generation in aerobic organisms.[6] DNA glycosylases, enzymes that cleave bonds between the deoxyribose backbone and the mismatched DNA base, are the key effectors. Each specific lesion covered in the BER spectrum is recognized by a specific DNA glycosylase (although many have overlapping specificities) leading to the formation of an abasic site (AP), which is subsequently repaired through the sequential activity of an AP-endonuclease, exonuclease, and a DNA polymerase as well as ligase.[7]

Double-strand breaks may be repaired by homologous recombination or non-homologous end-joining.[8,9] Homologous recombination utilizes the complementary sequence on the sister chromatid, leading to high fidelity, but a dependence on the G2 and M phases of the cell cycle (when DNA is condensed into chromosomes). NHEJ shows lesser fidelity but is available throughout the cell cycle.[10]

PARP: Functions in DNA damage repair

PARPs are a family of 17 proteins with varied functions including stress response, chromatin remodeling, DNA repair, and apoptosis. Its most well recognized member, PARP1, was initially identified as a part of BER with subsequent evidence hinting at the utility in the other aforementioned DNA repair mechanisms as well.[11] It is now known that PARP1 is pivotal for single-strand break (SSB) repair and has a role in BER since an SSB is introduced as an intermediate step.[12]

PARP1 detects DNA damage through zinc finger motifs[13] and subsequently leads to the polymerization of ADP-ribose units from NAD+ molecules onto acidic residues.[14] Auto-PARylation leads to enhanced catalytic activity and causes PARylation of histones and chromatin associated proteins as well.[15] This PARylated scaffold attracts DNA repair molecules such as x-ray repair cross-complementing protein 1 (XRCC1) to the site.[16] Persistent PARP1 activation leads to depletion of nicotinamide adenine dinucleotide (NADH+) based energy sources intracellularly and may lead to cell death. PARP2 and PARP3 have similar functions with some redundancy, but both are essential for cell survival.[15]

HOW DO PARP INHIBITORS WORK: A PRIMER ON SYNTHETIC LETHALITY

A plethora of chemical and physical agents can induce cell death in cancer cells, but a similar impact on normal cells narrows their therapeutic index and impairs clinical utility. However, epigenetic and genetic alterations within cancer cells or in the tumor microenvironment may create an opportunity for selective killing. On these lines, two genes are synthetic lethal if mutations in both are lethal, but mutation in either has no impact on viability.[17] PARP inhibitors utilize the synthetic lethality of PARP1 with the HR machinery. A multitude of mechanisms has been postulated for the same.

Accumulation of SSB was among the initial mechanisms postulated.[18] However, the following observations undermine this hypothesis. First, PARP inhibitor-exposed cells do not show accumulation of SSB.[19] Second, siRNA-mediated depletion of XRCC1 (Key component of SSBR) does not enhance sensitivity to PARP inhibitors.[20] Other postulated mechanisms with lesser evidence are NHEJ upregulation, disrupting the processing of Okazaki fragments, and disrupted transcription.[11]

The most accepted mechanism currently is replication fork stalling with PARP trapping. Cell division requires the replication fork to transverse the entire genome making an SSB encounter a statistical certainty at some point. In such situations, the replication fork is stalled and stabilized until the SSB is repaired.[21] PARP activation is required for MRE11-mediated replication restart.[18] Stalled replication forks lead to florid production of single stranded DNA since only one of the two DNA strands show continuity. PARP1 localizes to these stalled replication forks and through PARylation leads to the following corrective mechanisms: First, recruitment of (MRE11 Homolog, Double Strand Break Repair Nuclease), an endonuclease responsible for degradation of the ssDNA product, while the corrective measures are undertaken. Second, it leads to XRCC1 recruitment which provides a pivotal scaffold for SSB repair machinery. Third, it leads to Breast cancer gene 1 and 2 respectively and RAD51 colocalization at the stalled replication fork leading to stabilization until the time the SSB is repaired. However, in BRCA deficient cells, the third aspect is lacking leading to indiscriminate DNA destruction by the MRE11 endonuclease.[21] PARP trapping refers to the persistent localization of PARP1 at the stalled replication forks with no further steps since PARP inhibitors competitively bind to the NAD+ binding site and disallow auto-PARylation. This explains the higher efficacy of pharmacological inhibition when compared to PARP1 gene knockout.[22] Furthermore, when these stalled replication forks lead to DSBs, HR deficient (HRD) cells rely only on NHEJ for rejoining, leading to higher chances of genomic instability.[11]

HOMOLOGOUS DNA REPAIR AND PROSTATE CANCER

Into the precision medicine era

The advent of precision medicine in carcinoma prostate stems from the whole exome and transcriptome analysis of fresh

metastatic site tissue reported by Robinson *et al*.[23] Prior studies had focused on the specimen from primary prostate cancer and elucidated somatic mutations, copy number alterations, and chromoplexy involving, mainly the speckle - type POZ protein (SPOP), forkhead box A1 (FOXA1), and the *TP53* gene along with abundant E26-transformed specific (ETS) translocations.[24] While some of these alterations were prognostic (Copy number variations and evidence of tumor hypoxia could predict relapses), none were targetable.[25,26] Mutational landscape of metastatic disease was less well known given the technical difficulties in sequencing decalcified biopsies (since bone is the most common metastatic site).[27,28] The few studies focusing on this question did demonstrate mutations in the AR gene, as well as the androgen signaling pathway. However, these studies were based on a small number of autopsy specimens and pre-clinical models and utilized targeted sequencing, impacting both the internal and external validity of these findings.[29,30] The lack of characterization of mutational landscape in metastatic settings combined with hardly any targetable mutations in primary settings made carcinoma prostate a rather unattractive choice for targeted drug discovery.

Targetable mutations, the holy grail of personalized medicine, are best evaluated by whole-exome/transcriptome sequencing done prospectively on specimens of clinical interest (therapy naïve vs. after failure). The study by Robertson *et al*. evaluated 150 such biopsies and reported that, nearly, all cases had the presence of a pre-established biological driver mutation. About 63% of patients had a mutation in the AR pathway, showing the continued dependence on AR signaling in castration-resistant diseases. Even after excluding all AR-pathway alterations, 65% of patients had a "clinically actionable mutation" involving the phosphoinositide 3-kinases (PI3K) pathway (49%), DNA repair pathways (19%), rapidly accelerated fibrosarcoma (RAF) kinases (3%), cyclin dependent kinase (CDK) inhibitors (7%), and the wingless-related integration site (WNT) pathway (5%). In addition, 8% of cases had a pathological germline variant as well.[23]

The mutations detected in prostate cancer specimens have therapeutic implications hinting at the potential for personalized medicine in metastatic prostate cancer. A report of exceptional responders to platinum based chemotherapy reported deleterious HRR gene mutations in all three reported cases.[31] Another study evaluating blanket Olaparib therapy revealed similar enrichment in responders.[32] Thus, DNA repair pathway defects are targetable in carcinoma prostate, and studies further characterizing these lesions are detailed below.

DNA repair pathways defects are early drivers

To assess better the type, nature, and frequency of DNA repair pathway mutations, a study evaluated 504 tumor specimens from 451 patients through targeted sequencing.[33] The frequency of mutations in the PI3K, RAF kinase family, and the WNT pathway was similar to prior reports.[23] In addition, new insights regarding HRR machinery in carcinoma prostate were evident. First, around 22% of all cases had a somatic mutation in the gene involved in HRR, with mutations in the BRCA-2 gene being the most common (9%). Second, among patients undergoing germline testing, 19% had a germline pathogenic mutation in an HRR gene. Third, nearly 27% of patients had some HRR gene alteration when cotested with germline and somatic assays. Fourth, germline analysis alone accounted for only half of these patients. Fifth, although many gene mutations showed enrichment with progressive stages (AR, retinoblastoma 1 (RB1), phosphatase and tensin homolog (PTEN), and ataxia telangiectasia mutated (ATM)), the prevalence of mutations in TP53 and BRCA2 was relatively uniform.[33] Taken together, these findings imply that nearly 1/3rd of patients have targetable HRR mutations which are better detected by cotesting on somatic as well as germline assays. Furthermore, BRCA2 mutations seem to be early oncogenic drivers of disease.

Germline predisposition in carcinoma prostate

Findings of the aforementioned studies indicate a significant impact of germline alterations on the risk and natural history of the disease. The heterogenous pace of progression is well documented in carcinoma prostate.[34] Furthermore, inherited susceptibility accounts for more than half of the relative risk of carcinoma prostate.[35] Studies have shown that patients with HRR gene mutations have a higher propensity for distant spread and recurrence.[36] Given these findings, germline HRR gene mutations may show enrichment in more aggressive diseases. This is supported by incremental rates of BRCA mutations in the normal population (<1%), patients with high risk localized carcinoma prostate (5.3%), and patients with metastatic disease at diagnosis (19%).[33,37,38]

Along these lines, a study evaluated 692 samples of patients with metastatic carcinoma prostate at diagnosis (unselected by family history) and reported the following findings. First, 11.8% of all carcinoma prostate cases had a germline alteration involving an HRR gene (Most common being BRCA2: 44% of all). Second, the prevalence of carcinoma prostate in a first-degree relative did not vary with germline mutation status. However, the presence of an underlying germline mutation was associated with a higher Gleason score, as well as a higher risk of other cancers in first-degree relatives (Breast, ovarian, pancreatic, endometrial, gastrointestinal, and leukemia).[39]

To summarize, advanced carcinoma prostate shows enrichment in targetable HRR gene mutations and cotesting through somatic and germline platforms are likely to maximize yield. This enrichment likely stems from a propensity to more aggressive disease rather than in response to prior lines of therapy. Finally, these mutations

are actionable, providing us with a novel therapeutic option different from the conventional choices of taxanes and androgen axis-based therapies.

PARP INHIBITOR MONOTHERAPY IN PROSTATE CANCER

Tables 1 and 2 detail the studies evaluating PARP inhibitor monotherapy in metastatic castration-resistant prostate cancer (CRPC). Although recent evidence is supportive of the earlier use of combined therapy with PARP inhibitors, monotherapy in second or subsequent line settings remains the most established method of using these agents. A meta-analysis of trials evaluating PARP inhibitor monotherapy reported significant improvement in progression-free survival (PFS) and overall survival (OS) with fixed effects but not random effects models, perhaps stemming from heterogenous patient populations (concerning included genetic lesions).[40]

Olaparib

The TOPARP-A study was the initial phase two study which enrolled all metastatic CRPC patients regardless of the underlying mutational profile. While the overall efficacy was unimpressive, patients with a positive biomarker (i.e., HRD mutation) showed impressive ORR and PFS despite being used in a heavily pre-treated population.[32] Given the likely futility of PARPi in non-HRD population, the subsequent TOPARP-B study compared 300 mg and 400 mg doses of Olaparib in phase two settings and documented no difference in efficacy (ORR, CR, PSA50, CTC reduction, and PFS). Notably, some non-BRCA HRD mutations showed slightly better responses at higher dates, but, further, data are needed before this is applied clinically.[41] Olaparib approval in HRD metastatic CRPC mainly stems from the PROfound study. Evaluating Olaparib versus physician's choice in phase three settings, this study documented superior ORR, CR, PFS, and OS with targeted agents in patients progressing on at least one prior AR-directed therapy (taxanes agnostic design) in patients with mutations in BRCA1, BRCA2, or ATM.[42] While these may suggest Olaparib as the preferred option in these settings, the following merit consideration. First, there is no basis for the inclusion of ATM mutated patients in the primary efficacy cohort (covered below). Second, options in the physician's choice arm were limited to abiraterone or enzalutamide, leading to a weak comparator arm given the sequential use of AR-directed therapy. A subsequent analysis of the trial reported improvement in PFS as well as OS in the primary efficacy arm.[43] Based on these findings, Olaparib therapy is recommended in patients with mutations in BRCA1, BRCA2, or ATM genes after the failure of enzalutamide or abiraterone therapy.

Rucaparib

The TRITON2 study evaluated rucaparib monotherapy at a dose of 600 mg BD in 28-day cycles in patients with metastatic CRPC and prior exposure to at least one AR directed, and a taxane. Patients needed to have somatic or germline mutations in any of the following HRD mutations: BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, or RAD54L. The BRCA cohort had an ORR of 33% (mostly partial responses). PSA response was reported in 63% of patients. Responses did not vary by germline versus somatic mutation status. Notably, BRCA1 mutants responded less well compared to BRCA2 mutants, and no benefit was documented in patients with hepatic metastasis, perhaps hinting at more aggressive disease biology.[44] Based on these findings, rucaparib is approved for patients with CRPC with germline/somatic mutations in BRCA 1 or 2 after the failure of one AR-directed and taxane based therapy. A subsequent phase three study TRITON3 is underway and builds on the lessons learned from the PROfound study in the form of inclusion of a taxane naïve subset with BRCA 1 or BRCA2 mutations only. Furthermore, docetaxel therapy was included in the standard of care arm, coming closer to real-world settings.[45]

Other PARP inhibitors tested in these settings

The TALAPRO-1 study reported similar efficacy with Talazoparib in patients with HRD (except CDK12 mutations) and prior chemotherapy, as well as AR-directed therapy.[46] The GALLAHAD study reported similar findings in these patients with niraparib therapy, except that all patients had biallelic/germline HRD mutations.[47]

Efficacy in non-BRCA HR gene mutations

While the efficacy in BRCA 1 and BRCA 2 mutants remains undisputed, the candidacy of other HRD genes remains controversial, especially ATM gene mutations. The TRITON2 study reported an ORR of 10.5%, 0%, 11%, and 28.6% in patients with ATM, CDK12, CHEK2, and other HRD genes, respectively. PSA responses and PFS outcomes mirrored the same, with no predictive capabilities of germline versus comatic status.[44] Similar poor responses were documented in the GALLAHAD and TALAPRO-1 trials as well.[46,47] However, since the overall cohort in the PROfound study reported a PFS benefit, Olaparib is approved in patients with PALB2, BRIP1, BARD1, RAD51, RAD54, ATM, CDK12, and CHEK2/1 mutations as well. However, subgroup analysis shows a lack of benefit with Olaparib therapy in patients with ATM, CDK12, and CHEK2 mutations.[42] Notably, the TALAPRO-1 study excluded patients with CDK12 mutations altogether given the lack of benefit in prior studies.[46]

Table 1: Primary outcomes in studies evaluating PARP inhibitor monotherapy in metastatic castration resistant prostate cancer.

Study	Therapy arms	Phase	Sample size	Disease status	Mandatory HRR status	HRD testing	Primary endpoints	Results
NCT01682772/ TOPARP-A	Olaparib	2	50	mCRPC after at least docetaxel	No	Tumor	Composite response rate	Unselected cohort: 33% HRD: 88%
NCT01682772/ TOPARP-B	Olaparib	2	98	mCRPC after at least docetaxel	Bi-allelic HRD	Tumor	Composite response rate Pre-planned secondary endpoint: ORR	*BRCA1/2*: 83%, ORR: 52.4% *PALB2*: 57%, ORR: 33.3% *ATM*: 37%, ORR: 8.3% *CDK12*: 25%, ORR: 0%
NCT02987543/ PROfound	Olaparib versus NHT	3	778	mCRPC after at least 1 NHT	Bi/ mono-allelic Somatic or germline HRD mutations	Tumor	Radiographic PFS Pre-planned secondary endpoint: OS	rPFS: *BRCA/ATM*: 7.4 months versus 3.6mo, HR=0.34 (95% CI 0.25–0.47) General HRD: 5.8 months versus 3.5 months, HR=0.49 (95% CI 0.38–0.63) OS: *BRCA/ATM*: 19.1 months versus 14.7 months HR=0.69 (CI 95% 0.5–0.97) No-*BRCA/ATM*: 14.1 months versus 11.5 months HR=0.96 (CI 95% 0.63–1.49)
NCT02854436/ GALAHAD	Niraparib	2	291	mCRPC after at least 1 chemotherapy and 1 NHT	Bi-allelic HRD or germline pathogenic BRCA1/2 alterations	Tumor or plasma	ORR	*BRCA*: 41% Non-*BRCA*: 9%
NCT02952534/ TRITON-2	Rucaparib	2	193	mCRPC after at least 1 chemotherapy and 1 NHT	Bi/ mono-allelic Somatic or germline Deleterious HRD mutations	Tumor or plasma	ORR and PSA response rate (PRR)	s*BRCA1/2*: 43.9%, PRR: 50.7% g*BRCA1/2*: 42.9%, PRR: 61.4% *ATM*: 10.5%, PRR: 4.1% *CDK12*: 0%, PRR: 6.7% *CHEK12:* 11.1%, PRR: 16.7%
NCT03148795/ TALAPRO-1	Talazoparib	2	100	mCRPC after at least 1 chemotherapy and 1 NHT	Mono- or bi-allelic HRD (*CDK12* excluded)	Tumor	ORR	*BRCA*: 50% *ATM*: 7% Other HRD: 0%

NHT: Novel hormonal therapy (Abiraterone/Enzalutamide), HRD: Homologous repair deficient, HRR: Homologous recombination repair, mCRPC: Metastatic castration resistant carcinoma prostate, ORR: Overall response rate, OS: Overall survival, PFS: Progression-free survival, and PRR: PSA response rate

Further, evidence for preferential therapy in BRCA mutants only comes from a meta-analysis by Wu *et al.* reporting a significant impact of PARPi monotherapy on ORR and PFS in HRD compared to non-HRD. Within the HRD subgroup,

Table 2: Key clinical details of subjects enrolled in clinical studies prospectively evaluating PARP inhibitor monotherapy in patients with castration resistant prostate cancer.

Study	Time from diagnosis	Metastatic (%)	Bone_only (%)	Visceral (%)	Gleason score 8 or more	Time_ CRPC	PS0	PS1	PS2	PS_Other	Prior therapies (N)	Abiraterone (%)	Enzalutamide (%)	Docetaxel (%)	Cabazitaxel (%)	Radium 223 (%)	Prostatectomy (%)
NCT01682772/ TOPARP-A	5 years	46	-	-	-	2.2	18	70	12	-	4 or more	96	28	100	58	2	50 (Prostatectomy/Radical radiotherapy)
NCT01682772/ TOPARP-B	300 mg group: 3.5 (2.4–6.4), 400 mg group: 5.2 (3.6–7.3)	300 mg group: 49, 400 mg group: 51	-	300 mg group: 30, 400 mg group: 32	300 mg group: 8 or more in 86, 400 mg group: 8 or more in 59	300 mg group: 2.4 (1.2–3.7), 400 mg group: 3.0 (1.8–4.0)	-	-	-	-	-	300 mg group: 49, 400 mg group: 45	300 mg group: 55, 400 mg group: 59	100	300 mg group: 31, 400 mg group: 45	300 mg group: 12, 400 mg group: 16	300 mg group: Prostatectomy in 14 and radical RT in 45, 400 mg group: Prostatectomy in 12 and radical RT in 43
NCT02987543/ PROfound	-	Olaparib: 26, Control: 19	Olaparib: 34, Control: 29	Olaparib: 27, Control: 34	Olaparib: 73, Control: 75	-	Olaparib: 51, Control: 42	Olaparib: 44, Control: 54	Olaparib: 5, Control: 3)	-	-	Olaparib: 59, Control: 59)	Olaparib: 61, Control: 59)	Olaparib: 45, Control: 44	Olaparib: 20, Control: 20	-	-
NCT02854436/ GALAHAD																	
NCT02952534/ TRITON-2	-	-	67.90	33	67	-	32.20	76	1.70	-	2 (Excluding Docetaxel for CSPC)	64.30	71.30	93.9 (14.8 in CSPC settings)	7	12.20	-
NCT03148795/ TALAPRO-1	-	45	Non-visceral: 68	32	61	-	41	50	9	-	-	62	63	99	48	-	-
NCI 9012	-	-	-	26.6 versus 17.6	-	-	63.3 versus 62.2	35.4 versus 37.8	1.3 versus 0	-	-	-	2.5 versus 2.7	30.3 versus 20.8	21.5 versus 14.9	-	-
Clark *et al*	Combination: 62 months (38–93), Monotherapy: 48 months (32–76)	-	46 in both arms	53 in both arms	-	-	Combination arm: 48, Monotherapy: 54	Combination: 51, Monotherapy: 42)	1 in each	-	-	-	-	100	Combination: 14, Monotherapy: 13	-	-

Study	ORR (%)	CRR (%)	CTC_Baseline	CTC conversion (%)	PSA_Baseline	PSA50 (%)	Median follow-up	mPFS	mOS	Median therapy duration	Discontinuation rates	Dose reduction rates (%)	Reduction_ Cause
NCT01682772/ TOPARP-A	19	Overall population: 33, HRD: 88	37 (14–110)	29	349.5 (153–806)	22	14.4 months	Radiographic PFS in biomarker positive: 9.8m, Biomarker negative: 2.7m (P<0.001)	Biomarker positive: 13.8m, Biomarker negative: 7.5m (P=0.05)	12 weeks (11–24)	6	26	Most common: Anaemia
NCT01682772/ TOPARP-B	20.0, 300 mg arm: 16.2, 400 mg arm: 24.2,	46.7, 300 mg group: 39.1 *v* 400 mg group: 54.3, P=0.14)	60 with baseline CTC >5/7.5ml	50.9, 300 mg group: 48.1, 400 mg group: 53.6	300 mg group: 151.5 (49.0–446.0), 400 mg group: 158.0 (45.5–472.0)	33.7, 300 mg group: 30.2, 400 mg group: 37	24.8 months	Radiographic PFS in 300 mg group: 5.5 months, 400 mg group: 5.6 months	300 mg group: 10.1 months, 400 mg group: 14.3 months	PENDING		300 mg group: 12, 400 mg group: 37	Most common: Anaemia
NCT02987543/ PROfound	Cohort A: 33, Cohort A and B: 22, Control: 4)	-	Baseline >5/7.5ml in cohort A: 60, Cohort A and B: 59.7, Control arm: 58.7	Cohort A: 30, Cohort A and B: 27, Control arm: 11	Olaparib arm: 68.2, Control arm: 106.5)	Cohort A: 43, Cohort A and B: 30, Control: 8	12.2 months	Cohort A: 7.4 months (p=0.034), Cohort A and B: 5.8 months (P<0.001), Control: 3.5 months	Cohort A: 18.5 months (HR=0.64, P=0.02), Cohort A and B: 17.5 months (HR: 0.67; 95 CI, 0.49–0.93)	7.4 months	Olaparib: 18 Control: 8	Olaparb: 22 Control: 4	Most common: Anaemia
NCT02952534/ TRITON-2	43.5 (95 CI, 31–63.4)	-	-	-	61.1	63	17.1 months	9.0 months (95 CI, 8.3–13.5 months)	73.0 at 12 months	6.5 months	7.80	63.5 had either dose reduction or interruption	-
NCT03148795/ TALAPRO-1	30	51	Median: 5/7.5 ml, 31.7 with baseline >5/7.5 ml	64	103.8 (24.0–303.1)	46	16.4 months	5.6 months	16.4 months	6.1 months	12	26	Only 3 from hematological
NCI 9012	Overall: 52.2 versus 45.0, DRD: 90.9 versus 80.0.DNA repair WT/Monoallelic alterations: 40.0 versus 36.8	-	-	-	36.4 (0.04–1,074) versus 32.7 (0.8–1,557)	Overall: 72.4 versus 63.9 (P=0.27), DRD: 92.3 versus 85.7 (P=1), DNA repair WT/ Monoallelic: 64.7 versus 46.2 (P=0.15)	-		32.3 versus 30.6 months	-			
Clark *et al*	Combination: 27, Monotherapy: 33	-	Measurable ar baseline in 50 patients of combination arm and 46 in monotherapy arm	Combination arm: 48, Monotherapy arm: 42	Combination arm: 86 (23–194), Monotherapy: 47 (32–76)	Combination: 48%, Monotherapy: 42	Combination arm: 15.9 months Monotherapy arm: 24.5 months	Overall population: 13.8 versus 8.2 months (p=0.034), HRD: 17.8 versus 6.5 months, HRR: 15.0 versus 9.7 months)	22.7 versus 20.9 months (HR 0.91, 95 CI 0.60–1.38, P=0.66)	Olaparib: 309 days (IQR: 145–457), Monotherapy: 253 days (IQR: 113–421)	-	-	-

NHT: Novel hormonal therapy (Abiraterone/Enzalutamide), HRD: Homologous repair deficient, HRR: Homologous recombination repair, mCRPC: Metastatic castration resistant carcinoma prostate, ORR: Overall response rate, OS: Overall survival, PFS: Progression-free survival, and PRR: PSA response rate

BRCA mutated patients had higher ORR and PFS compared to non-BRCA HRD mutated which was more than non-HRD patients.[48] Another meta-analysis by Arsalan *et al*. suggests that the benefit may be limited to BRCA 1/1 and PALB2 mutations.[49]

PARP inhibitors: Preferred agent selection

Given the presence of phase three evidence, Olaparib is the most commonly prescribed agent in patients with AR-directed therapy failure. Furthermore, it may be given in aforementioned non-BRCA HRD patients as well. However, lack of benefit on sub-group analysis and a weak comparator arm need to be kept in mind.[43] Furthermore, given the taxane agnostic nature of the PROfound study, rucaparib may be preferred in patients failing on docetaxel as well although Olaparib may also be used given the efficacy outcomes in the TOPARP-A and the TOPARP-B study.[32,41]

PARP INHIBITOR-BASED COMBINATIONS IN PROSTATE CANCER

Given the impressive efficacy of PARP inhibitor monotherapy in second/subsequent line settings, PARP inhibitor therapy in front-line settings becomes a natural research question.[43,44] Furthermore, co-targeting of AR signaling and PARP has a scientific rationale.

Basis behind combination therapy

Seminal conceptualization of AR-inhibition enhancing DNA-damage mediated killing stems from trials reporting enhanced efficacy of radiotherapy in patients receiving androgen deprivation therapy (ADT),[50,51] which reflects in biopsy specimen as well.[52] *In vitro* models also suggest enhanced killing with radiotherapy in presence of ADT.[53] Among multiple postulated mechanisms, AR-blockade-mediated impairment of DNA repair mechanisms has gained the most traction.[54] In this regard, a study reported an increase in the expression of DNA repair proteins in response to AR signaling.[55] PARP1 specifically modulates the transcriptional activity or AR and ETS activity and consequently can lead to ligand independent AR-signaling.[56] In addition, AR-signaling in CRPC is known to potentiate the expression of HRR genes and its inhibition may induce a state of "BRCAness."[57] *In vitro* studies have corroborated this through synthetic lethality assays as well.[58]

Current evidence behind combination therapy

Among the first studies evaluating PARP inhibitor, in addition to AR-directed therapy was the NCI-9012 study which evaluated the addition of veliparib to abiraterone therapy regardless of DRD status. Regardless of the treatment given, patients with an underlying HRD mutation fared better. However, veliparib addition did not lead to improved outcomes in the entire cohort, or in the ETS translocation subset. The impact of veliparib addition specifically in the HRD subset remains unknown.[59] Although a negative study, the NCI-9012 study informs us of the potential efficacy of AR-directed therapy in HRD subsets, the futility of universal PARP inhibitor prescription, and futility of ETS translocations as a potential biomarker. Given these findings, the BRCAAway study is currently evaluating HRD CRPC patients in terms of optimal combinations and sequencing.[60] A similar phase two study evaluating Olaparib addition to abiraterone therapy after docetaxel failure reported a higher PFS in all patients regardless of the HRR gene status. The findings of this study prompted the PROpel trial (discussed below).

Current phase three evidence for upfront combination therapy in CRPC is limited to the recently presented PROpel, and the MAGNITUDE study.[61,62] The PROpel study randomized patients with no prior therapy for CRPC (Docetaxel for CSPC allowed) to receive abiraterone with a placebo or Olaparib regardless of their HRD status. Less than 15% of patients had visceral disease and around a quarter of patients had an HRD mutation. The risk of progression was reduced by 34% in the entire cohort regardless of the HRD status, and without an increase with Grade 3 or higher ADRs or discontinuations. Notably, rates of thromboembolic events were higher (7.3% vs. 3.3%).[61] These findings seem to support the universal utility of Olaparib addition regardless of mutational status.

The MAGNITUDE trial, evaluating niraparib in almost equivalent settings (therapy naïve CRPC randomized to abiraterone with placebo vs. niraparib), gives us a clearer picture. This comes from a prudent difference in its schema, namely, stratification of patients with HRR status at baseline (*ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2,* and *PALB2*). Nearly, 40% of patients had BRCA2 mutations, and around a quarter of all patients had visceral metastasis at baseline. Similar to the PROpel study, nearly, 20% had already received docetaxel for prior CSPC. While PFS was prolonged in the HRD cohort (HR: 0.73; 95% CI: 0.56–0.96), it was more pronounced in the BRCA 1 or 2 mutated cohort (HR: 0.53; 95% CI: 0.36–0.79), and non-existent in the HRR cohort (at the pre-specified early futility analysis itself). In addition, niraparib was associated with more anemia, and thrombocytopenia leading to dose reductions and discontinuations. While these findings argue against combination therapy for all patients, doses of niraparib used here (200 mg) were lesser than in the initial monotherapy trials (300 mg).[62] Evidence from initial phase two studies on Olaparib seems to hint at a dose-effect curve in CRPC and whether these findings would remain antithetical

to the ones from PROpel study that had higher doses of niraparib been used remains an unanswered question.[32,41]

A similar dichotomy of findings is expected in the current ongoing combination therapy trials with the CASPAR trial administering rucaparib regardless of HRR status (without stratification), while the TALAPRO-2 study is evaluating Talazoparib in all patients but is stratified by HRR status. In addition, both studies are using enzalutamide as the AR-therapy backbone.[63-66] Of note, a recent pharmacovigilance meta-analysis has found an association between PARP inhibitors and subsequent risk of myelodysplastic syndromes/acute myeloid leukemia (Absolute risk: 0.73%).[67] While hardly any cases have been reported in the studies done in CRPC [Table 2], a longer follow-up is prudent. This is of paramount importance since most of the treatment-emergent myeloid neoplasms reported in ovarian cancer patients harbor a monosomal karyotype with TP53 mutations, a subset of AML with particularly dismal outcomes.[68,69] Whether baseline NGS-based testing for CHIP will allow for better, patient selection is currently unknown and the characteristics of myeloid neoplasms associated with prior PARPi use are beyond the scope of this review.

SUMMARY

While further evidence is awaited, the current evidence also lays out a dichotomy in terms of patient selection. In this regard, while the PROpel study provides a basis for the universal prescription of Olaparib and pre-clinical data seems to back the synergy with AR-directed therapy, one must remember that the subset specific efficacy from the PROpel study is not available. Furthermore, the HRR arm of the MAGNITUDE study provides us with prospective randomized evidence of futility, something that is backed by the NCI 9012 and the monotherapy studies (TOPARP-A) as well. Given that we are gradually moving in the era of personalization, universal PARP inhibitor use may not be prudent. Ongoing studies may change this outlook. Long-term safety and possible de-escalation of PARP inhibitors are additional questions of clinical importance.

GENETIC TESTING IN PROSTATE CANCER

Frequency and types of HRD mutations in carcinoma prostate have been covered above. This section details the current evidence behind genetic testing methods in carcinoma prostate to formulate a personalized testing strategy.

GERMLINE OR SOMATIC MUTATION TESTING?

Although germline and somatic mutation testing typically require different platforms and samples (Tumor tissue vs. peripheral blood/buccal swab), it is prudent to go for cotesting for the following reasons. First, diagnostic yield (in terms of finding a targetable lesion) is maximized.[39] Second, germline testing allows for early family member screening and counseling, which may be lifesaving.[70] Third, there is no difference in the responses and outcomes of patients with germline or somatic mutations when treated with PARP inhibitors [Table 2].[41] Of note, certain somatic mutation assays may hint at an underlying germline defect. If such an assay is being used, prior counseling and consent regarding germline testing are of paramount importance. In addition, given that many somatic mutations are truncal, retesting as per the clinical scenario remains prudent.

FINDING THE OPTIMAL TISSUE FOR TESTING

The bulk of evidence in this regard comes from the analysis of samples screened for the aforementioned PROfound trial. Consisting of 4858 samples from 4425 screened patients, the study makes the following observations regarding the success rate of testing through a targeted NGS platform. First, newly collected samples have a higher yield than archived samples (63.9% vs. 56.9%). Second, age of the sample has an impact (68.1% in age <1 year vs. 47.3% in age >10 years). Third, metastatic sites have a higher yield than primary (63.9% vs. 56.2%). Fourth, although the most common method, core biopsies have the least success rates by type of sample (52.4%). Finally, the biopsy site impacts success rates as mentioned here in decreasing order: Lymph nodes (74.7%), lungs (60.5%), liver (56.3%), prostate gland primary (56.2%), and bony metastasis (42.6%). The lowest yield from bone metastasis probably stems from the nucleic acid denaturation stemming from the decalcification process.[71] Another study reported similar findings with 746 biopsy/surgical samples. With an overall success rate of 68%, the highest success rates were for prostate tumor samples (core biopsy, palliative prostatectomy, or TURP). Among metastatic samples, lymph nodes and hepatic lesions had a success rate of >69%, while bone and lung samples were more challenging (42–52% success rate).[33]

These findings suggest that in the appropriate clinical setting, evaluation of a fresh sample (preferably lymph node biopsy) may maximize our chances to find a targetable mutation.

UTILITY OF LIQUID BIOPSY

Liquid biopsy may have two main utilities in CRPC: First, non-invasive detection of HRD mutations. The second, possible prognostic utility of circulating tumor cells. While the latter is a possible surrogate at best in the current scenario [Table 2], the former is already in mainstream clinical use.

An analysis of all paired samples collected in the TRITON 2/3 trials revealed a very high concordance rate. Three-fourth of all patients with BRCA mutations in tissue had a positive

liquid biopsy as well. While tumor tissue testing allows detection of copy number events (zygosity) and the tumor mutational burden as well (biomarker for immunotherapy usage), failure rates are typically lesser with liquid biopsy (3% vs. 30%).[72] A similar study reported 84% concordance with liquid biopsy.[73]

The following points merit consideration regarding the role of liquid biopsy in prostate cancer. A negative result should be considered in light of the disease status at the time of testing given that the yield of cfDNA NGS is enhanced in patients with progressive disease or PSA levels >10 ng/mL.[74] Second, clonal hematopoiesis of indeterminant potential (CHIP) may lead to false positive liquid biopsy results. In one case series, 10% of all cases with advanced CRPC had evidence of CHIP interference on liquid biopsy.[75] The aforementioned studies documenting high concordance rates with liquid biopsy have reported similar interference rates from underlying CHIP (most commonly with *ATM*, *BRCA2*, and *CHEK2*).[72,73]

SUMMARY OF GENETIC TESTING

While cotesting for somatic and germline abnormalities is of paramount importance for therapeutic decision making, a yield of somatic testing seems to be better with fresh samples in patients with more advanced diseases. Furthermore, if using liquid biopsy, progressive disease with rising PSA levels allows optimization of NGS performance. Given these findings, it may be prudent to order germline testing in all patients as per clinical guidelines and then subsequently procure tissue or liquid biopsy for somatic tissue testing as the need arises.

HUNTING FOR ADDITIONAL BIOMARKERS

Given the response rates ranging typically around 50%, better patient selection is possible for targeted therapy. At present, no functional assays exist for the assessment of HRD status. While intraductal variant and neuroendocrine differentiation are suggestive of an underlying HRD mutation, they have no predictive capacity over or independent of genomic testing.[76-80] While the usage of platinum sensitivity as a marker of BRCAness is established in serous ovarian carcinoma, extrapolation of the same to carcinoma prostate is challenging since platinum-based chemotherapy is not a standard frontline option. However, two series have reported impressive outcomes in carcinoma prostate HRD patients when treated with platinum-based therapy.[81,82] PTEN deficiency shows enrichment in advanced prostate cancer with *in vitro* evidence of PARPi efficacy.[83,84] Clinical studies have not confirmed this association. Evidence suggests against usage of EWS-translocation as a predictive biomarker as well.[59]

RESISTANCE TO PARP INHIBITORS

Mechanisms of PARP inhibitor resistance: A primer

Four major mechanisms which may contribute to clinical resistance to PARPi are altered drug availability, alterations in PARylation enzymes, PARP independent restoration of HR, and restoration of replication fork stability.[85] Tracing the steps involved in HRR allows us to elucidate the various alterations which may lead to resistance.

HRR: Basic steps

In response to a double stranded DNA break (DSB), cells activate HRR and NHEJ mechanisms simultaneously and the phase of the cell cycle decides the dominant mechanism.[86] The following sequence simplifies the usual steps for HRR, the details of which are beyond the scope of this review:

1. Depending on the phase of the cell cycle the cell is in, appropriate CDK activates the effector proteins (CtIP and ATM by CDK18).[87-89]
2. ATM and ATR kinases phosphorylate the variant H2A histone leading to its expansion and trapping of TP53 binding protein 1 (53BP1) (promotes NHEJ, negates HRR), as well as BRCA1 (part of HRR machinery)[90]
3. Resection of the ends of the DSB lesion (done by MRN, CtIP, and various nucleases) is the first step in committing toward HRR[91]
4. These resected ends and then coated by hyperphosphorylated replication protein A[92]
5. The PALB2 protein allows interaction between BRCA1 and BRCA2, responsible for the unloading of the RAD51 protein on the lesion[93]
6. The RAD51 protein is responsible for finding and invasion of the homologous sequence (formation of the D-loop structure). It also protects the single stranded DNA formed in the interim.[94]

The NHEJ machinery, mainly the 53BP1 and the RIF1 protein, inhibits BRCA1.[95] The 53BP1, specifically, also protects the DSB ends from resection through nucleosome barrier formation,[96] as well as recruitment of the SHIELDIN complex.[97] Of note, the ATM is needed for 53BP1 and RIF1 activation, implying that ATM plays a role in both HRR and NHEJ.[98]

Potential mechanisms of resistance *(In vitro)*

Increased RAD51 activity, either through downregulation of inhibitors such as EMI1/DDB2 or through upregulation of the TOPβ1 activator, allows HRR to bypass BRCA1 or 2 functions and leads to resistance.[99,100] Notably, bromodomain protein 4 overactivity leads to a similar rise in RAD51 activity which may be negated by using bromodomain inhibitors.[101,102]

Another common mechanism of PARP inhibitor resistance observed in *in vitro* studies is reversion mutations.[2]

A separate method of the resistance stems from replication fork stabilization downregulation of EZH2.[103] PTIP/CHD4/MELL 3- or 4-mediated reduction of MRE11 activity,[104] FANCD2-mediated MRE11 suppression,[21,105] SMARCAL1 deletion,[106] or RADX deletion[107] all lead to PARPi resistance in *in vitro* models through replication fork stabilization. While epigenetic mechanisms of PARPi resistance exist, they are yet to be targeted clinically.[2]

CLINICAL APPROACH TO SUSPECTED PARP INHIBITOR RESISTANCE

Testing for possible mechanisms

Detection of three possible alterations may guide us regarding the possible mechanism of resistance to PARP inhibitors: Mutations, expression patterns, and functional assays.[108] The most common mutations are reversion mutations in BRCA 1 or 2.[2] These mutations may cause resistance to both PARPi, as well as platinum agents.[109,110] Compared to other BRCA deficient malignancies, reversion mutations seem, especially common in CRPC (40% in one study).[111] Liquid biopsy may detect.[112] Mutations in 53BP1/REV7 are found in up to 20% of PARPi resistant cases.[113,114] Some PARP mutations may confer resistance through reduced trapping (R591C mutations).[115] Assessment of expression of the PTIP/EZH2 proteins as well as the PARG moieties may also define mechanisms of resistance.[104,116] In this regard, quantitative assessment of RAD51 foci on the genome may allow a functional assessment of HRR activity in a cell.[114]

Overcoming PARP inhibitor resistance

Therapeutic interventions reversing the likely resistance mechanism are being actively investigated. In addition, certain resistance mechanisms may be targetable, a phenomenon known as collateral sensitivity.[117] Among many others, radiotherapy is an accessible and proven modality for this purpose. PARP inhibitors sensitize cancer cells to radiation through impairment of DNA repair.[118] Along these lines, studies are evaluating a combination of PARPi with radiotherapy in clinical settings and some have reported encouraging outcomes.[119] Conversely, radiotherapy can overcome PARPi resistance resulting from a multitude of mechanisms. Concerning reversion mutations leading to the resumption of HRR, HRR requires nuclear localization of BRCA1 protein, while radiotherapy causes cytoplasmic extrusion of the same.[120-122] Functional p53 is required for this phenomenon.[118] On the other hand, tumors dependent on 53BP1 over-expression for PARPi resistance are exquisitely sensitive to radiotherapy. This probably stems from impairment in NHEJ. While PARPi is lethal in the G2/M phase of the cell cycle when HRR predominates, radiotherapy is cell cycle non-specific and NHEJ is the only mechanism of DSB repair in the G1 and early S-phase.[123] Although at least six clinical trials are evaluating the utility of radiotherapy in overcoming PARPi resistance, none are enrolling patients with CRPC (since radiotherapy is not the standard of care).[2] However, a phase one study (LuPARP) is evaluating Olaparib in addition to 177Lu-PSMA therapy.[124]

An additionally acquired vulnerability in PARPi resistant cancers stems from a reliance on ATM and ATR kinases. The PALB2/BRCA2 proteins, indispensable to the restoration of HRR, are dependent on ATR-kinase for activation. The RAD51 protein is another ATR-kinase-dependent protein mediating resistance through fork stabilization.[125] A similar relationship exists between TP53 binding protein 1 (TP53BP1)/DNA polymerase zeta processivity subunit 7 (REV7) proteins and the ATM-kinase.[126] Consequently, studies are evaluating a combination of PARPi with pharmacological inhibitors of ATM or ATR-kinases in various malignancies,[2] including CRPC.[127]

PARPi and immune checkpoint inhibitors also demonstrate *in vitro* synergy, mainly through PARPi-mediated upregulation of PD-L1 expression (through GSK3β).[128] STING-mediated inflammation in the tumor microenvironment is another potential mechanism of this synergy.[129] While a multitude of trials is evaluating this combination, none are focused on CRPC.[2] Another strategy is combining oncolytic herpes simplex viruses (oHSV) therapy with PARPi. Specifically, the MG18L oHSV knocks out RAD51 enhancing efficacy and overcoming resistance.[130] Clinical studies evaluating this combination are eagerly awaited. Finally, pharmacological inhibition of CDKs, leading to preferential utilization of HRR, is another option with strong pre-clinical data.[131]

CONCLUSION

The therapeutic landscape of carcinoma prostate may change in the personalized medicine era with a multitude of options for patients with HRD. PARP inhibitor monotherapy in the appropriate patients has a strong rationale and ongoing studies may shift clinical practices toward earlier use of PARP inhibitors in combination with AR-directed therapy. Long-term consequences of PARP inhibitor therapy, especially in terms of myeloid malignancies, need further clarification. Resistance to PARP inhibitors is multifactorial and may open an additional avenue for personalized medicine.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Withrow D, Pilleron S, Nikita N, Ferlay J, Sharma S, Nicholson B, *et al.* Current and projected number of years of life lost due to prostate cancer: A global study. Prostate 2022;82:1088-97.
2. Li LY, Guan YD, Chen XS, Yang JM, Cheng Y. DNA repair pathways in cancer therapy and resistance. Front Pharmacol 2021;11:629266.
3. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell 2011;144:646-74.
4. Pearl LH, Schierz AC, Ward SE, Al-Lazikani B, Pearl FM. Therapeutic opportunities within the DNA damage response. Nat Rev Cancer 2015;15:166-80.
5. Krokan HE, Bjørås M. Base excision repair. Cold Spring Harb Perspect Biol 2013;5:a012583.
6. Lindahl T. Instability and decay of the primary structure of DNA. Nature 1993;362:709-15.
7. Lindahl T. An N-glycosidase from *Escherichia coli* that releases free uracil from DNA containing deaminated cytosine residues. Proc Natl Acad Sci U S A 1974;71:3649-53.
8. Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature 2001;411:366-74.
9. Friedberg EC, Aguilera A, Gellert M, Hanawalt PC, Hays JB, Lehmann AR, *et al.* DNA repair: From molecular mechanism to human disease. DNA Repair (Amst) 2006;5:986-96.
10. Helleday T. Pathways for mitotic homologous recombination in mammalian cells. Mutat Res 2003;532:103-15.
11. Rose M, Burgess JT, O'Byrne K, Richard DJ, Bolderson E. PARP inhibitors: Clinical relevance, mechanisms of action and tumor resistance. Front Cell Dev Biol 2020;8:564601.
12. Dantzer F, Schreiber V, Niedergang C, Trucco C, Flatter E, De La Rubia G, *et al.* Involvement of poly(ADP-ribose) polymerase in base excision repair. Biochimie 1999;81:69-75.
13. Ali AA, Timinszky G, Arribas-Bosacoma R, Kozlowski M, Hassa PO, Hassler M, *et al.* The zinc-finger domains of PARP1 cooperate to recognize DNA strand breaks. Nat Struct Mol Biol 2012;19:685-92.
14. Bian C, Zhang C, Luo T, Vyas A, Chen SH, Liu C, *et al.* $NADP^+$ is an endogenous PARP inhibitor in DNA damage response and tumor suppression. Nat Commun 2019;10:693.
15. Ray Chaudhuri A, Nussenzweig A. The multifaceted roles of PARP1 in DNA repair and chromatin remodelling. Nat Rev Mol Cell Biol 2017;18:610-21.
16. Liu L, Kong M, Gassman NR, Freudenthal BD, Prasad R, Zhen S, *et al.* PARP1 changes from three-dimensional DNA damage searching to one-dimensional diffusion after auto-PARylation or in the presence of APE1. Nucleic Acids Res 2017;45:12834-47.
17. Kaelin WG Jr. The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Cancer 2005;5:689-98.
18. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, *et al.* Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005;434:913-7.
19. Gottipati P, Vischioni B, Schultz N, Solomons J, Bryant HE, Djureinovic T, *et al.* Poly(ADP-ribose) polymerase is hyperactivated in homologous recombination-defective cells. Cancer Res 2010;70:5389-98.
20. Patel AG, Sarkaria JN, Kaufmann SH. Nonhomologous end joining drives poly(ADP-ribose) polymerase (PARP) inhibitor lethality in homologous recombination-deficient cells. Proc Natl Acad Sci 2011;108:3406-11.
21. Liao H, Ji F, Helleday T, Ying S. Mechanisms for stalled replication fork stabilization: New targets for synthetic lethality strategies in cancer treatments. EMBO Rep 2018;19:e46263.
22. Murai J, Huang SY, Renaud A, Zhang Y, Ji J, Takeda S, *et al.* Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol Cancer Ther 2014;13:433-43.
23. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, *et al.* Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215-28.
24. Cooper CS, Eeles R, Wedge DC, Van Loo P, Gundem G, Alexandrov LB, *et al.* Analysis of the genetic phylogeny of multifocal prostate cancer identifies multiple independent clonal expansions in neoplastic and morphologically normal prostate tissue. Nat Genet 2015;47:367-72.
25. Hieronymus H, Schultz N, Gopalan A, Carver BS, Chang MT, Xiao Y, *et al.* Copy number alteration burden predicts prostate cancer relapse. Proc Natl Acad Sci U S A 2014;111:11139-44.
26. Lalonde E, Ishkanian AS, Sykes J, Fraser M, Ross-Adams H, Erho N, *et al.* Tumour genomic and microenvironmental heterogeneity for integrated prediction of 5-year biochemical recurrence of prostate cancer: A retrospective cohort study. Lancet Oncol 2014;15:1521-32.
27. Mehra R, Kumar-Sinha C, Shankar S, Lonigro RJ, Jing X, Philips NE, *et al.* Characterization of bone metastases from rapid autopsies of prostate cancer patients. Clin Cancer Res 2011;17:3924-32.
28. Van Allen EM, Foye A, Wagle N, Kim W, Carter SL, McKenna A, *et al.* Successful whole-exome sequencing from a prostate cancer bone metastasis biopsy. Prostate Cancer Prostatic Dis 2014;17:23-7.
29. Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, *et al.* Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. N Engl J Med 1995;332:1393-8.
30. Beltran H, Yelensky R, Frampton GM, Park K, Downing SR, MacDonald TY, *et al.* Targeted next-generation sequencing of advanced prostate cancer identifies potential therapeutic targets and disease heterogeneity. Eur Urol 2013;63:920-6.
31. Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 2016;69:992-5.
32. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, *et al.* DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697-708.

33. Abida W, Armenia J, Gopalan A, Brennan R, Walsh M, Barron D, *et al.* Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 2017;2017:00029.
34. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005;293:2095-101.
35. Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, *et al.* Familial risk and heritability of cancer among twins in nordic countries. JAMA 2016;315:68-76.
36. Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, *et al.* Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748-57.
37. Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. Cell 2015;163:1011-25.
38. Maxwell KN, Domchek SM, Nathanson KL, Robson ME. Population frequency of germline BRCA1/2 mutations. J Clin Oncol 2016;34:4183-5.
39. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, *et al.* Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443-53.
40. Niazi M, Jahangir A, Sahra S, Sattar S, Asti D, Bershadskiy A. Efficacy of PARP inhibitors as maintenance therapy for metastatic castration-resistant prostate cancer: A meta-analysis of randomized controlled trials. Oncology (Williston Park) 2021;35:708-15.
41. Mateo J, Porta N, Bianchini D, McGovern U, Elliott T, Jones R, *et al.* 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 2020;21:162-74.
42. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, *et al.* Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382:2091-102.
43. Hussain M, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, *et al.* Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 2020;383:2345-57.
44. Abida W, Patnaik A, Campbell D, Shapiro J, Bryce AH, McDermott R, *et al.* Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. J Clin Oncol 2020;38:3763-72.
45. Ryan CJ, Watkins SP, Despain D, Karlovich CA, Simmons A, Golsorkhi AA, *et al.* Trial of rucaparib in prostate indications 3 (TRITON3): An international, multicenter, randomized, open-label phase 3 study of rucaparib vs physician's choice of therapy for patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination deficiency (HRD). J Clin Oncol 2017;35 Suppl 15:TPS5087.
46. de Bono JS, Mehra N, Scagliotti GV, Castro E, Dorff T, Stirling A, *et al.* Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): An open-label, phase 2 trial. Lancet Oncol 2021;22:1250-64.
47. Smith MR, Scher HI, Sandhu S, Efstathiou E, Lara PN, Yu EY, *et al.* Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): A multicentre, open-label, phase 2 trial. Lancet Oncol 2022;23:362-73.
48. Wu K, Liang J, Shao Y, Xiong S, Feng S, Li X. Evaluation of the efficacy of PARP inhibitors in metastatic castration-resistant prostate cancer: A systematic review and meta-analysis. Front Pharmacol 2021;12:777663.
49. Naqvi SA, Bin Zafar MD, Islam M, Ikram W, Raina A, Singh P, *et al.* Differential efficacy of PARP inhibitors in metastatic castration-resistant prostate cancer with DNA repair defects: A systematic review and meta-analysis. J Clin Oncol 2022;40 Suppl 6:134-4.
50. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, *et al.* Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295-300.
51. Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW, *et al.* Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011;365:107-18.
52. Zelefsky MJ, Reuter VE, Fuks Z, Scardino P, Shippy A. Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer. J Urol 2008;179:1368-73.
53. Wo JY, Zietman AL. Why does androgen deprivation enhance the results of radiation therapy? Urol Oncol 2008;26:522-9.
54. Al-Ubaidi FL, Schultz N, Loseva O, Egevad L, Granfors T, Helleday T. Editor's note: Castration therapy results in decreased Ku70 levels in prostate cancer. Clin Cancer Res 2021;27:6066.
55. Polkinghorn WR, Parker JS, Lee MX, Kass EM, Spratt DE, Iaquinta PJ, *et al.* Androgen receptor signaling regulates DNA repair in prostate cancers. Cancer Discov 2013;3:1245-53.
56. Schiewer MJ, Goodwin JF, Han S, Brenner JC, Augello MA, Dean JL, *et al.* Dual roles of PARP-1 promote cancer growth and progression. Cancer Discov 2012;2:1134-49.
57. Li L, Karanika S, Yang G, Wang J, Park S, Broom BM, *et al.* Androgen receptor inhibitor-induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. Sci Signal 2017;10:eaam7479.
58. Asim M, Tarish F, Zecchini HI, Sanjiv K, Gelali E, Massie CE, *et al.* Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. Nat Commun 2017;8:374.
59. Hussain M, Daignault-Newton S, Twardowski PW, Albany C, Stein MN, Kunju LP, *et al.* Targeting androgen receptor and DNA repair in metastatic castration-resistant prostate cancer: Results from NCI 9012. J Clin Oncol 2018;36:991-9.
60. Hussain M. BRCAAway: A Randomized Phase II Trial of Abiraterone, Olaparib, or Abiraterone + Olaparib in Patients with Metastatic Castration-Resistant Prostate Cancer with DNA Repair Defects; 2021. Report No. NCT03012321. Available from: https://clinicaltrials.gov/ct2/show/NCT03012321 [Last accessed on 2022 May 01].
61. Saad F, Armstrong AJ, Thiery-Vuillemin A, Oya M, Loredo E, Procopio G, *et al.* 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). J Clin Oncol 2022;40 Suppl 6:11.

62. Chi KN, Rathkopf DE, Smith MR, Efstathiou E, Attard G, Olmos D, *et al*. 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. J Clin Oncol 2022;40 Suppl 6:12.
63. Alliance for Clinical Trials in Oncology. CASPAR A Phase III Trial of Enzalutamide and Rucaparib as a Novel Therapy in First-Line Metastatic Castration-Resistant Prostate Cancer. Alliance for Clinical Trials in Oncology; 2022. Report No. NCT04455750. Available from: https://clinicaltrials.gov/ct2/show/NCT04455750 [Last accessed on 2022 May 01].
64. Rao A, Ryan CJ, VanderWeele DJ, Heller G, Lewis LD, Watt C, *et al.* 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). J Clin Oncol 2021;39 Suppl 6:TPS181.
65. Agarwal N, Azad A, Shore ND, Carles J, Fay AP, Dunshee C, *et al*. TALAPRO-2: A phase 3 randomized study of enzalutamide (ENZA) plus talazoparib (TALA) versus placebo in patients with new metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2021;39 Suppl 15:TPS5089.
66. Pfizer. TALAPRO-3: A PHASE 3, Randomized, Double-blind, Study of Talazoparib with Enzalutamide Versus Placebo with Enzalutamide in men with Ddr Gene Mutated Metastatic Castration-Sensitive Prostate Cancer; 2022. Report No. NCT04821622. Available from: https://clinicaltrials.gov/ct2/show/NCT04821622 [Last accessed on 2022 May 01].
67. Morice PM, Leary A, Dolladille C, Chrétien B, Poulain L, González-Martín A, *et al.* Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: A safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database. Lancet Haematol 2021;8:e122-34.
68. Oliveira JL, Greipp PT, Rangan A, Jatoi A, Nguyen PL. Myeloid malignancies in cancer patients treated with poly(ADP-ribose) polymerase (PARP) inhibitors: A case series. Blood Cancer J 2022;12:11.
69. Csizmar CM, Saliba AN, Swisher EM, Kaufmann SH. PARP inhibitors and myeloid neoplasms: A double-edged sword. Cancers (Basel) 2021;13:6385.
70. Daly MB. NCCN Guidelines Index Table of Contents Genetic; 2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf [Last accessed on 2022 Apr 06].
71. Hussain M, Corcoran C, Sibilla C, Fizazi K, Saad F, Shore N, *et al.* Tumor genomic testing for >4,000 men with metastatic castration-resistant prostate cancer in the phase III trial PROfound (Olaparib). Clin Cancer Res 2022;28:1518-30.
72. Germline Genetic Testing in Advanced Prostate Cancer Practices and Barriers: Survey Results from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium; 2022.
73. Schweizer MT, Sivakumar S, Tukachinsky H, Coleman I, De Sarkar N, Yu EY, *et al.* Concordance of DNA repair gene mutations in paired primary prostate cancer samples and metastatic tissue or cell-free DNA. JAMA Oncol 2021;7:1-5.
74. Schweizer MT, Gulati R, Beightol M, Konnick EQ, Cheng HH, Klemfuss N, *et al.* Clinical determinants for successful circulating tumor DNA analysis in prostate cancer. Prostate 2019;79:701-8.
75. Jensen K, Konnick EQ, Schweizer MT, Sokolova AO, Grivas P, Cheng HH, *et al.* Association of clonal hematopoiesis in DNA repair genes with prostate cancer plasma cell-free DNA testing interference. JAMA Oncol 2021;7:107-10.
76. Schweizer MT, Antonarakis ES, Bismar TA, Guedes LB, Cheng HH, Tretiakova MS, *et al*. Genomic characterization of prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. JCO Precis Oncol 2019;3:PO.18.00327.
77. Pantazopoulos H, Diop MK, Grosset AA, Rouleau-Gagné F, Al-Saleh A, Boblea T, *et al.* Intraductal carcinoma of the prostate as a cause of prostate cancer metastasis: A molecular portrait. Cancers (Basel) 2022;14:820.
78. Gupta K, Gupta S. Neuroendocrine differentiation in prostate cancer: Key epigenetic players. Transl Cancer Res 2017;6:S104-8.
79. Rodriguez-Calero A, Gallon J, Akhoundova D, Maletti S, Ferguson A, Cyrta J, *et al.* Alterations in homologous recombination repair genes in prostate cancer brain metastases. Nat Commun 2022;13:2400.
80. Bhagirath D, Liston M, Akoto T, Lui B, Bensing BA, Sharma A, *et al.* Novel, non-invasive markers for detecting therapy induced neuroendocrine differentiation in castration-resistant prostate cancer patients. Sci Rep 2021;11:8279.
81. Schmid S, Omlin A, Higano C, Sweeney C, Martinez Chanza N, Mehra N, *et al.* Activity of platinum-based chemotherapy in patients with advanced prostate cancer with and without DNA repair gene aberrations. JAMA Netw Open 2020;3:e2021692.
82. Mota JM, Barnett E, Nauseef JT, Nguyen B, Stopsack KH, Wibmer A, *et al.* Platinum-based chemotherapy in metastatic prostate cancer with DNA repair gene alterations. JCO Precis Oncol 2020;4:PO.19.00346.
83. Jamaspishvili T, Berman DM, Ross AE, Scher HI, De Marzo AM, Squire JA, *et al.* Clinical implications of PTEN loss in prostate cancer. Nat Rev Urol 2018;15:222-34.
84. Turnham DJ, Bullock N, Dass MS, Staffurth JN, Pearson HB. The PTEN conundrum: How to target PTEN-deficient prostate cancer. Cells 2020;9:E2342.
85. Noordermeer SM, van Attikum H. PARP inhibitor resistance: A tug-of-war in BRCA-mutated cells. Trends Cell Biol 2019;29:820-34.
86. Karanam K, Kafri R, Loewer A, Lahav G. Quantitative live cell imaging reveals a gradual shift between DNA repair mechanisms and a maximal use of HR in mid S phase. Mol Cell 2012;47:320-9.
87. Yun MH, Hiom K. CtIP-BRCA1 modulates the choice of DNA double-strand-break repair pathway throughout the cell cycle. Nature 2009;459:460-3.
88. Tomimatsu N, Mukherjee B, Hardebeck MC, Ilcheva M, Camacho CV, Harris JL, *et al.* Phosphorylation of EXO1 by CDKs 1 and 2 regulates DNA end resection and repair pathway choice. Nat Commun 2014;5:3561.
89. Ning JF, Stanciu M, Humphrey MR, Gorham J, Wakimoto H,

Nishihara R, *et al.* Myc targeted CDK18 promotes ATR and homologous recombination to mediate PARP inhibitor resistance in glioblastoma. Nat Commun 2019;10:2910.
90. Polo SE, Jackson SP. Dynamics of DNA damage response proteins at DNA breaks: A focus on protein modifications. Genes Dev 2011;25:409-33.
91. Cejka P. DNA end resection: Nucleases team up with the right partners to initiate homologous recombination. J Biol Chem 2015;290:22931-8.
92. Liu VF, Weaver DT. The ionizing radiation-induced replication protein A phosphorylation response differs between ataxia telangiectasia and normal human cells. Mol Cell Biol 1993;13:7222-31.
93. Sy SM, Huen MS, Chen J. PALB2 is an integral component of the BRCA complex required for homologous recombination repair. Proc Natl Acad Sci U S A 2009;106:7155-60.
94. Godin SK, Sullivan MR, Bernstein KA. Novel insights into RAD51 activity and regulation during homologous recombination and DNA replication. Biochem Cell Biol 2016;94:407-18.
95. Symington LS, Gautier J. Double-strand break end resection and repair pathway choice. Annu Rev Genet 2011;45:247-71.
96. Fradet-Turcotte A, Canny MD, Escribano-Díaz C, Orthwein A, Leung CC, Huang H, *et al.* 53BP1 is a reader of the DNA-damage-induced H2A Lys 15 ubiquitin mark. Nature 2013;499:50-4.
97. Noordermeer SM, Adam S, Setiaputra D, Barazas M, Pettitt SJ, Ling AK, *et al.* The shieldin complex mediates 53BP1-dependent DNA repair. Nature 2018;560:117-21.
98. Di Virgilio M, Callen E, Yamane A, Zhang W, Jankovic M, Gitlin AD, *et al.* Rif1 prevents resection of DNA breaks and promotes immunoglobulin class switching. Science 2013;339:711-5.
99. Zhao L, Si CS, Yu Y, Lu JW, Zhuang Y. Depletion of DNA damage binding protein 2 sensitizes triple-negative breast cancer cells to poly ADP-ribose polymerase inhibition by destabilizing Rad51. Cancer Sci 2019;110:3543-52.
100. Moudry P, Watanabe K, Wolanin KM, Bartkova J, Wassing IE, Watanabe S, *et al.* TOPBP1 regulates RAD51 phosphorylation and chromatin loading and determines PARP inhibitor sensitivity. J Cell Biol 2016;212:281-8.
101. Bowry A, Piberger AL, Rojas P, Saponaro M, Petermann E. BET inhibition induces HEXIM1 and RAD51-dependent conflicts between transcription and replication. Cell Rep 2018;25:2061-9.e4.
102. Wilson AJ, Stubbs M, Liu P, Ruggeri B, Khabele D. The BET inhibitor INCB054329 reduces homologous recombination efficiency and augments PARP inhibitor activity in ovarian cancer. Gynecol Oncol 2018;149:575-84.
103. Rondinelli B, Gogola E, Yücel H, Duarte AA, van de Ven M, van der Sluijs R, *et al.* EZH2 promotes degradation of stalled replication forks by recruiting MUS81 through histone H3 trimethylation. Nat Cell Biol 2017;19:1371-8.
104. Chaudhuri AR, Callen E, Ding X, Gogola E, Duarte AA, Lee JE, *et al.* Replication fork stability confers chemoresistance in BRCA-deficient cells. Nature 2016;535:382-7.
105. Michl J, Zimmer J, Buffa FM, McDermott U, Tarsounas M. FANCD2 limits replication stress and genome instability in cells lacking BRCA2. Nat Struct Mol Biol 2016;23:755-7.
106. Taglialatela A, Alvarez S, Leuzzi G, Sannino V, Ranjha L, Huang JW, *et al.* Restoration of replication fork stability in BRCA1- and BRCA2-deficient cells by inactivation of SNF2-family fork remodelers. Mol Cell 2017;68:414-30.e8.
107. Dungrawala H, Bhat KP, Le Meur R, Chazin WJ, Ding X, Sharan SK, *et al.* RADX promotes genome stability and modulates chemosensitivity by regulating RAD51 at replication forks. Mol Cell 2017;67:374-86.e5.
108. Shimelis H, Mesman RL, Von Nicolai C, Ehlen A, Guidugli L, Martin C, *et al.* BRCA2 hypomorphic missense variants confer moderate risks of breast cancer. Cancer Res 2017;77:2789-99.
109. Edwards SL, Brough R, Lord CJ, Natrajan R, Vatcheva R, Levine DA, *et al.* Resistance to therapy caused by intragenic deletion in BRCA2. Nature 2008;451:1111-5.
110. Sakai W, Swisher EM, Karlan BY, Agarwal MK, Higgins J, Friedman C, *et al.* Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature 2008;451:1116-20.
111. Carneiro BA, Collier KA, Nagy RJ, Pamarthy S, Sagar V, Fairclough S, *et al.* Acquired resistance to poly (ADP-ribose) polymerase inhibitor olaparib in BRCA2-associated prostate cancer resulting from biallelic BRCA2 reversion mutations restores both germline and somatic loss-of-function mutations. JCO Precis Oncol 2018;2:PO.17.00176.
112. Gornstein EL, Sandefur S, Chung JH, Gay LM, Holmes O, Erlich RL, *et al.* BRCA2 reversion mutation associated with acquired resistance to olaparib in estrogen receptor-positive breast cancer detected by genomic profiling of tissue and liquid biopsy. Clin Breast Cancer 2018;18:184-8.
113. Bruna A, Rueda OM, Greenwood W, Batra AS, Callari M, Batra RN, *et al.* A biobank of breast cancer explants with preserved intra-tumor heterogeneity to screen anticancer compounds. Cell 2016;167:260-74.e22.
114. Cruz C, Castroviejo-Bermejo M, Gutiérrez-Enríquez S, Llop-Guevara A, Ibrahim YH, Gris-Oliver A, *et al.* RAD51 foci as a functional biomarker of homologous recombination repair and PARP inhibitor resistance in germline BRCA-mutated breast cancer. Ann Oncol 2018;29:1203-10.
115. Pettitt SJ, Krastev DB, Brandsma I, Dréan A, Song F, Aleksandrov R, *et al.* Genome-wide and high-density CRISPR-Cas9 screens identify point mutations in PARP1 causing PARP inhibitor resistance. Nat Commun 2018;9:1849.
116. Gogola E, Duarte AA, de Ruiter JR, Wiegant WW, Schmid JA, de Bruijn R, *et al.* Selective loss of PARG restores PARylation and counteracts PARP inhibitor-mediated synthetic lethality. Cancer Cell 2018;33:1078-93.e12.
117. Hutchison DJ. Cross resistance and collateral sensitivity studies in cancer chemotherapy. Adv Cancer Res 1963;7:235-50.
118. Chalmers A, Johnston P, Woodcock M, Joiner M, Marples B. PARP-1, PARP-2, and the cellular response to low doses of ionizing radiation. Int J Radiat Oncol Biol Phys 2004;58:410-9.
119. Mehta MP, Wang D, Wang F, Kleinberg L, Brade A, Robins HI, *et al.* Veliparib in combination with whole brain radiation therapy in patients with brain metastases: Results of a phase 1 study. J Neurooncol 2015;122:409-17.
120. Wang H, Yang ES, Jiang J, Nowsheen S, Xia F. DNA damage-induced cytotoxicity is dissociated from BRCA1's DNA repair

function but is dependent on its cytosolic accumulation. Cancer Res 2010;70:6258-67.
121. Jiang J, Yang ES, Jiang G, Nowsheen S, Wang H, Wang T, *et al.* p53-dependent BRCA1 nuclear export controls cellular susceptibility to DNA damage. Cancer Res 2011;71:5546-57.
122. Yang ES, Nowsheen S, Rahman MA, Cook RS, Xia F. Targeting BRCA1 localization to augment breast tumor sensitivity to poly(ADP-Ribose) polymerase inhibition. Cancer Res 2012;72:5547-55.
123. Barazas M, Gasparini A, Huang Y, Küçükosmanoğlu A, Annunziato S, Bouwman P, *et al.* Radiosensitivity is an acquired vulnerability of PARPi-resistant BRCA1-deficient tumors. Cancer Res 2019;79:452-60.
124. Peter MacCallum Cancer Centre, Australia. 177Lu-PSMA-617 Therapy and Olaparib in Patients with Metastatic Castration Resistant Prostate Cancer. Australia: Peter MacCallum Cancer Centre; 2020. Report No. NCT03874884. Available from: https://clinicaltrials.gov/ct2/show/NCT03874884 [Last accessed on 2022 May 16].
125. Yazinski SA, Comaills V, Buisson R, Genois MM, Nguyen HD, Ho CK, *et al.* ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells. Genes Dev 2017;31:318-32.
126. Bunting SF, Callén E, Wong N, Chen HT, Polato F, Gunn A, *et al.* 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks. Cell 2010;141:243-54.
127. University of Michigan Rogel Cancer Center. Multi-Center Phase II Study Testing the Activity of Olaparib and AZD6738 (ATR Inhibitor) in Metastatic Castration-Resistant Prostate Cancer; 2022. Report No. NCT03787680. Available from: https://clinicaltrials.gov/ct2/show/NCT03787680 [Last accessed on 2022 May 12].
128. Jiao S, Xia W, Yamaguchi H, Wei Y, Chen MK, Hsu JM, *et al.* PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res 2017;23:3711-20.
129. Shen J, Zhao W, Ju Z, Wang L, Peng Y, Labrie M, *et al.* PARPi triggers the STING-dependent immune response and enhances the therapeutic efficacy of immune checkpoint blockade independent of BRCAness. Cancer Res 2019;79:311-9.
130. Ning J, Wakimoto H, Peters C, Martuza RL, Rabkin SD. Rad51 degradation: Role in oncolytic virus-poly(ADP-Ribose) polymerase inhibitor combination therapy in glioblastoma. J Natl Cancer Inst 2017;109:1-13.
131. Johnson SF, Cruz C, Greifenberg AK, Dust S, Stover DG, Chi D, *et al.* CDK12 inhibition reverses *de novo* and acquired PARP inhibitor resistance in BRCA wild-type and mutated models of triple-negative breast cancer. Cell Rep 2016;17:2367-81.

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