Targeting DNA repair for cancer treatment: Lessons from PARP inhibitor trials

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Abstract: Ionizing radiation is frequently used to treat solid tumors, as it causes DNA damage and kill cancer cells. However, damaged DNA is repaired involving poly-(ADP-ribose) polymerase-1 (PARP-1) causing resistance to radiation therapy. Thus, PARP-1 represents an important target in multiple cancer types, including prostate cancer. PARP is a nuclear enzyme essential for single-strand DNA breaks repair. Inhibiting PARP-1 is lethal in a wide range of cancer cells that lack the homologous recombination repair (HR) pathway. This article provides a concise and simplified overview of the development of PARP inhibitors in the laboratory and their clinical applications. We focused on the use of PARP inhibitors in various cancers, including prostate cancer. We also discussed some of the underlying principles and challenges that may affect the clinical efficacy of PARP inhibitors.

Introduction

DNA repair pathways in normal cells ensure error-free replication and maintain genomic integrity. However, it is known that DNA repair genes are frequently mutated in cancer which contributes significantly to cancer development and progression [1]. DNA repair dysfunction is an ideal ally for the cancer cells to acquire an aggressive phenotype and therapeutic resistance [2,3]. Our cells utilize multiple different mechanisms of DNA repair based on the kind of lesion-induced. These include direct repair, mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), and double-strand break (DSB) recombinational repair, which encompasses both non-homologous end-joining (NHEJ) and homologous recombinational repair (HR). This remarkable redundancy in the DNA repair pathway is in place to ensure precision in the process of DNA replication. This also guarantees that the cells have a second chance to survive, even if one of these pathways fails.

During cancer development, the cells continue to acquire different mutations, not only due to defects in DNA repair/ genomic instability but also due to poor redox balance in these cells. The poorly functioning redox regulation causes these cells to have higher oxidative stress. The sustained oxidative stress leads to significant oxidative DNA damage, which further contributes to genomic instability and higher mutational burden [4]. In this context, the same backup repair pathways assist them to remain viable and repair the damage caused by chemotherapeutic or other genotoxic agents used for treatment. Given that the cancers with defective DNA repair genes rely on alternative pathways, it was correctly hypothesized that further blocking of the other DNA repair pathways would be lethal for these cells. The concept of "synthetic lethality" [5], which describes a situation "where a defect in one gene is compatible with cell viability but results in cell death when combined with a defect in another gene", has thus formed the basis of newer targeted therapies especially focusing the DNA repair pathways in cancers [6].

Exploiting Synthetic Lethality Approach for Cancer Treatment

Though synthetic lethality was established decades earlier, the potential of this approach for drug targeting in cancer was only harnessed in recent years, due to a lack of robust and systematic tools for identifying the synthetic lethal genetic combinations. Recently, genome-wide drug-sensitization screening using short hairpin RNA (shRNA) and small

interfering RNA (siRNA)–as well as small-molecule inhibitors have led to the identification of many novel drug candidates (reviewed in McLoran et al.) [7]. The synthetic lethality approach is specifically useful in cancer, as it facilitates the development of cancer-specific cytotoxic agents, which would not affect the "non-mutated" normal cells with a robust repair system. One example of this approach, which has been very successful in the clinic, is the use of PARP (Poly-ADP-ribose polymerase) inhibitors for BRCA mutant cancers.

The Promise of PARP Inhibitors

The PARP family of proteins comprised of 17 members which were identified on the basis of their homology in the catalytic domain. PARP1, a nuclear enzyme, is the most prominent member of the family as it accounts for 85% of total PARP activity [8]. PARP enzyme catalyzes the transfer of the first ADP-ribose from nicotinamide adenine dinucleotide (NAD^+) to the amino acid residues on target proteins and generates a poly-ADP-ribose unit chain (PAR). This process of "PARylation" on proteins as well as on the PARP enzyme itself (self-PARylation) creates a negative charge which reworks the protein structure and function, helping with the binding of multiple proteins (Fig. 1). The PARylation at DNA breaks helps in the recruitment of DNA repair
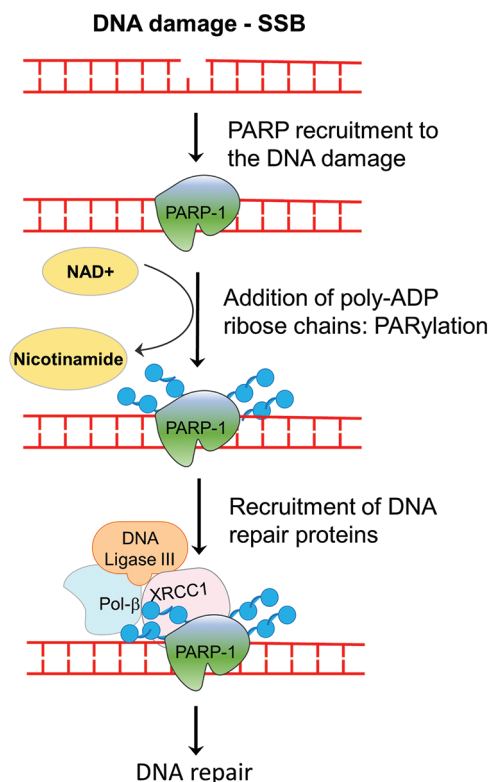
proteins like DNA ligase 3, XRCC1, DNA polymerase β as well as the MRE11-Rad50-NBS1 (MRN) complex [9,10]. Therefore, the PARP enzyme function is crucial not only for BER but also in the HR and NHEJ mechanisms. Since, the PARP function is specifically crucial for single-strand break (SSB) repair, inhibiting PARP will lead to persistent SSBs that, when encountered by the replication fork, are converted into double-stranded breaks (DSBs). The repair of DSB would require a functional HR repair pathway. Therefore, cancers with HR repair deficiencies would be highly sensitive to PARP inhibition, as the lesions will remain unrepaired and eventually cause cell death (Fig. 2). This hypothesis was verified by mouse models, where deletion of PARP-1 increased sensitivity to DNA-damaging agents that induce DNA SSBs, without being embryonic lethal [11,12]. Multiple studies using PARP inhibitors in various tumor models found that PARP inhibitors could sensitize tumor cells to cytotoxic therapies such as temozolomide, topoisomerase I inhibitors, platinum-based chemotherapeutics, and radiation treatment [13–15].

With a better understanding of SSB repair and homologous recombination (HR) repair-mediated DSB repair, two seminal studies applied the approach of synthetic lethality with promising results, as they demonstrated the potential of poly-(ADP-ribose) polymerase (PARP1) inhibition in treating BRCA-mutant tumors [16,17]. BRCA1 and BRCA2 play a crucial role in the repair of double-stranded breaks (DSBs) by homologous recombination (HR) [18]. Heterozygous germline mutation in the BRCA1 gene confers a 60% lifetime risk of breast or ovarian cancer, whereas BRCA2 mutations are associated with a risk of breast or ovarian cancer of 55% and 15%, respectively [19]. Reasonably, tumors with malfunctioning

FIGURE 1. Role of PARP enzyme in DNA repair. In the event of a single-stranded break in cells, PARP enzymes are recruited to the strand break, where it catalyzes the addition of PAR chains on itself or on the other target proteins. PARylation-mediated changes in the chromatin assembly help in the recruitment of repair enzymes, which ultimately repair the break. SSB, single-strand break; NAD^+, nicotinamide adenine dinucleotide; Pol beta, DNA polymerase beta; PAR, poly-ADP ribose.
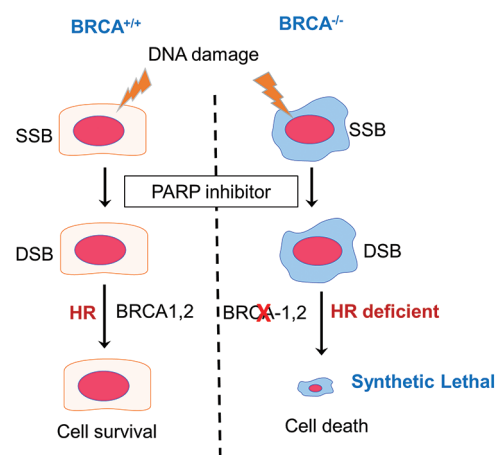

FIGURE 2. The concept of synthetic lethality in the context of BRCA mutation carriers treated with PARP inhibitors. In the event of DNA damage caused by oxidative base damage, ionizing radiation, and other chemical agents, single-strand breaks (SSBs) are generated. PARP inhibitors block the repair of SSBs, which when left unrepaired are converted to double-strand breaks (DSBs) following replication. In cells with functional BRCA genes, these DSB lesions are repaired by homologous recombination (HR) and the cells remain viable. However, in cells that are HR deficient, such as BRCA mutant tumor cells, the DSBs cannot be repaired, leading to cell death. PARP inhibition, therefore, is synthetic lethal in HR-deficient cells.

BRCA genes are deficient in the HR repair pathway. Based on these preclinical studies which showed that cells with dysfunctional BRCA1 or BRCA2 are dramatically more sensitive to PARP inhibitors, multiple PARP inhibitors were tested in *in silico*, *in vitro*, and *in vivo* studies and in clinical trials which are summarized in Tables 1 and 2, respectively and in Fig. 3.

PARP Inhibitors in Breast and Ovarian Cancers

Olaparib became the first PARP inhibitor to be approved in the clinic (Table 3). Olaparib is being developed for BRCA mutation-positive ovarian cancer [86]. The subsequent phase II studies of Olaparib, in patients with high-grade ovarian cancer revealed a highly statistically significant improvement in progression-free survival (PFS) (median 8.4 months *vs.* 4.8 months; HR, 0.35; $p < 0.001$) [87]. Most interestingly, the patients with a documented germline BRCA mutation showed a significantly higher survival rate (median 11.2 months *vs.* 4.3 months; HR, 0.18; $p < 0.001$) [88]. Subsequent trials established the safety of Olaparib as a single agent, and good responses were witnessed in patients with *BRCA*-mutated breast, ovarian, or prostate tumors [89,90]. Owing to their specificity in targeting cancer cells, only mild side effects have been reported from PARP inhibitor treatment as evident from these trials. Another randomized, double-blind, placebo-controlled phase 3 trial of Olaparib, as a maintenance therapy for BRCA mutated ovarian cancer, SOLO 1 (NCT01844986), led to its approval by the United States Food and Drug Administration (FDA) in 2018. The median progression-free survival was better in the Olaparib treated group (median 49.9 months *vs.* 13.8 months; HR, 0.31; $p < 0.0001$) [91]. The risk of disease progression or death was 70% lower in the Olaparib treated group than the placebo group.

It is also important to note that BRCA defective cells are much more sensitive to PARP inhibitors than to the knockdown of PARP using a siRNA approach [16]. The study suggested that trapping PARP on specific DNA lesions, may be important for the effective killing of HR-defective cells (Fig. 3). Trapping of PARP leads to stalled replication forks which causes the conversion of single-strand breaks (SSBs) to double-strand breaks (DSBs). These DSBs are repaired by HR-efficient cells, however, in cells deficient in HR, it leads to cell killing. Most PARP inhibitors have almost similar efficacy in inhibiting the catalytic activity of PARP, however, they differ in their ability to trap PARP on the lesions [92]. These studies cemented the foundation for testing of other PARP inhibitors including Rucaparib, Veliparib, and Niraparib in clinical trials for the treatment of breast and ovarian cancer [93–95] (Table 2). The positive findings from subsequent trials in ovarian and breast cancer patients, led FDA to approve two more PARP inhibitors for clinical use in patients with BRCA-mutant ovarian cancer: Rucaparib [96] and Niraparib [97] (Table 3). Along with these, currently, phase 3 trials of Veliparib and Talazoparib are ongoing (NCT02163694 and NCT01945775).

The FDA has also approved two PARP inhibitors for BRCA mutated HER 2 negative breast cancer: Olaparib and talazoparib (BC). Olaparib approval for BRCA mutated HER2 negative metastatic and early breast cancer was based

TABLE 1

PARP inhibitors in *in silico*, *in vitro*, and *in vivo* studies for prostate cancer, breast cancer, and ovarian cancer

S. No.	PARP inhibitor	Cancer	Study type	Cell line	Target	References
1	5F02	Prostate cancer	*In vitro* and *in vivo*	PC-3 xenograft	Non-NAD-like PARP-1 inhibitor	[20]
2	Simmiparib	Breast cancer	*In vitro* and *in vivo*	Xenografts, CDX and PDX	PARP-1, PARP-2	[21]
3	DDHCB		*In vitro* and *in vivo*	HCC-1937 cell line xenografts	PARP-1	[22]
4	BTH-8		*In vivo* and *in vitro*, using BRCA-deficient cancer cells	HCC-1937 cell line xenograft	PARP-1	[23]
5	YHP-836		*In vitro* and *in vivo*	MDA-MD-436 cell line xenograft	PARP-1, PARP-2	[24]
6	ZC-22		*In vitro* and *in vivo*	MDA-MD-231 cell line xenograft	PARP and CDK4/6	[25]
7	Mefuparib hydrochloride (MPH)		*In vitro* and *in vivo*	MDA-MB-436 cell line xenograft	PARP-1, PARP-2	[26]
8	1,2,4-triazoles		*In silico* and *in vitro*	MCF-7 cell line	PARP-1	[27]
9	Mortaparib	Ovarian cancer	*In vitro* and *in vivo*	SKOV3 ovarian cancer cells xenograft	PARP-1 and mortalin	[28]
10	ZC-22		*In vitro* and *in vivo*	OVCAR5 Ovarian cancer cells xenograft	PARP and CDK4/6	[25,29]

TABLE 2

PARP inhibitors as monotherapy in various phases of clinical trials, for metastatic castration-resistant prostate cancer (mCRPC), breast cancer, and ovarian cancer

S. No.	PARP inhibitor	Cancer	Main trial	Status	Cohort	Target	References
1	Niraparib	Prostate Cancer	GALAHAD NCT02854436	Under phase 2 trial Trial start: 31 Aug. 2016 Estimated completion: 31 Oct. 2022 Status: active	mCRPC with alternation in DNA repair	PARP-1, PARP-2	[30,31]
2	Talazoparib		TALAPRO-1 NCT03148795	Under phase 2 trial Trial start: 4 Jul. 2017 Estimated completion: 31 Oct. 2024	mCRPC with alterations in DDR-HRR who have received both AR-directed therapy and taxane-based chemotherapy	PARP-1, PARP-2, PARP-16	[32,33]
3	Pamiparib		NCT05327621	Under phase 2 trial Trial start: 01 May 2022 Estimated completion: 20 Mar. 2025	mCRCP with homologous recombination deficiency or BRCA 1 or 2 somatic/germline mutation.	PARP-1 PARP-2	[34]
4	Veliparib (With or without Abiraterone Acetate and Prednisone)		NCT01576172	Phase 2 trial completed on 23 Apr. 2020	mCRPC	PARP-1, PARP-2	[35]
5	Fluzoparib (Alone or with Apatinib)	Breast Cancer	FZPL-III-303 NCT04296370	Under phase 3 trial Trial start: 13 Jul. 2020 Estimated completion: 30 Jun. 2025	BRCA mutated HER-2 negative metastatic breast cancer	PARP-1, PARP-2	[36]
6	Niraparib		BRAVO NCT01905592	Phase 3 trial completed 26 Oct. 2021	BRCA mutated HER-2 negative metastatic breast cancer	PARP-1, PARP-2	[37,38]
			NCT05232006	Under phase 2 trial Trial start: May 2022 Estimated completion: May 2030	Advanced metastatic breast cancer in germline PALB2 mutations carriers		
7	2X-121		NCT03562832	Under phase 2 trial Trial start: 20 Jun. 2018 Estimated completion: Oct. 2022 Status: active	Metastatic breast cancer	PARP-1, PARP-2 and Tankyrase 1/2	[39]
8	Rucaparib		NCT02505048	Phase 2 trial completed on Dec. 2019	Metastatic breast cancer with BRCAness genomic signature	PARP-1, PARP-2, PARP-3	[40]
9	NMS-03305293		NCT04182516	Under phase 1 trial Trial start: 25 Nov. 2019 Estimated completion: 30 Dec. 2023	Patients with advanced solid tumors (including breast cancer)	PARP	[41]
10	AZD5305 (Alone or in combination with anti-cancer agents)		NCT04644068	Under phase 1/2 trial Trial start: 12 Nov. 2020 Estimated completion: 29 Jul. 2025	Patients with advanced solid malignancy (including breast cancer)	PARP-1	[42,43]
11	RP12146		NCT05002868	Under phase 1 trial Trial start: 05 Oct. 2021 Estimated completion: Aug. 2023	Patients with locally advanced or metastatic solid tumors (including locally advanced/	PARP	[44]

(Continued)

Table 2 (continued)

S. No.	PARP inhibitor	Cancer	Main trial	Status	Cohort	Target	References
					metastatic breast cancer)		
12	AZD9574 (alone or in combination with anti-cancer agents)		NCT05417594	Under phase 1/2 trial Trial start: 24 Jun. 2022 Estimated completion: 30 Jun. 2025	Advanced cancer that has recurred/ progressed (including breast cancer)	PARP	[45]
13	E7449 (Alone or in combination with Temozolomide (TMZ) or with Carboplatin and Paclitaxel		NCT01618136	Phase 1/2 trial completed in Jul. 2015	Patients with advanced solid tumors (including triple-negative breast cancer)	PARP-1, PARP-2 and tankyrase 1/2	[46,47]
14	AMXI-5001		ATLAS-101 NCT04503265	Under phase 1/2 trial Trial start: 12 Aug. 2020 Estimated completion: Jan. 2023	Advanced malignant neoplasm (including breast cancer) who have failed other therapies	PARP and microtubule polymerization inhibitor	[48]
15	Pamiparib		NCT03333915	Under phase 2 trial Trial start: 21 Dec. 2016 Estimated completion: Nov. 2021 Status: active	Chinese patients with triple negative breast cancer	PARP-1, PARP-2	[49]
16	Simmiparib		NCT02993913	Under phase 1 trial for malignant solid tumors Trial start: Dec. 2016 Estimated primary completion: Dec. 2018 Status: unknown	Malignant tumors	PARP-1, PARP-2	[50,51]
17	Veliparib	Ovarian Cancer	VELIA NCT02470585	Under phase 3 trial Trial start: 29 Jun. 2015 Estimated completion: 08 Dec. 2026	With Carboplatin and Paclitaxel and as continuation maintenance therapy in advanced ovarian cancer	PARP-1, PARP-2	[52]
18	IMP4297		NCT04169997	Under phase 3 trial Trial start: 24 Dec. 2019 Estimated completion: 30 Dec. 2022	Advanced ovarian cancer	PARP	[53]
19	Talazoparib		NCT04598321	Under phase 1 trial Trial start: 29 Mar. 2021 Estimated completion: Jan. 2027	BRCA mutated ovarian cancer	PARP-1, PARP-2, PARP-16	[54]
20	E7449 (Alone or in Combination with Temozolomide (TMZ) or with Carboplatin and Paclitaxel		NCT01618136	Phase 1/2 trial completed in Jul. 2015	Patients with advanced solid tumors (including ovarian cancer)	PARP-1, PARP-2 and tankyrase 1/2	[46,47]
21	Pamiparib		NCT05489926	Under phase 2 trial Trial start: 16 Aug. 2022 Estimated completion: Dec. 2023	Epithelial Ovarian Cancer EOC with prior exposure to a PARP inhibitor	PARP-1, PARP-2	[55]
22	Fluzoparib		NCT03509636	Phase 1 trial completed on 23 Jul. 2020	BRCA mutated ovarian cancer	PARP-1, PARP-2	[56,57]
23	AZD5305		NCT04644068	Under phase 1/2 trial Trial start: 12 Nov. 2020 Estimated completion: 29 Jul. 2025	Patients with advanced solid malignancy (including ovarian cancer)	PARP-1	[42,43]

(Continued)

Table 2 (continued)

| S. No.	PARP inhibitor	Cancer	Main trial	Status	Cohort	Target	References
24	RP12146		NCT05002868	Under phase 1 trial Trial start: 05 Oct. 2021 Estimated completion: Aug. 2023	Patients with Locally Advanced or Metastatic Solid Tumors (including platinum sensitive ovarian cancer)	PARP	[44]
25	AZD9574 (Alone or in combination with anti-cancer agents)		NCT05417594	Under phase 1/2 trial Trial start: 24 Jun. 2022 Estimated completion: 30 Jun. 2025	Advanced cancer that has recurred/ progressed (including ovarian cancer)	PARP	[45]
26	E7449 (Alone or in Combination with Temozolomide (TMZ) or with Carboplatin and Paclitaxel		NCT01618136	Phase 1/2 trial completed in Jul. 2015	Patients with advanced solid tumors (including ovarian cancer)	PARP-1, PARP-2 and tankyrase 1/2	[46,47]
27	NMS-03305293		NCT04182516	Under phase 1 trial Trial start: 25 Nov. 2019 Estimated completion: 30 Dec. 2023	Patients with advanced solid tumors (including ovarian cancer)	PARP	[41]
28	AMXI-5001		ATLAS-101 NCT04503265	Under phase 1/2 trial Trial start: 12 Aug. 2020 Estimated completion: Jan. 2023	Advanced malignant neoplasm (including ovarian cancer) who have failed other therapies	PARP and microtubule polymerization inhibitor	[48]
29	[18F] FluorThanatrace (FTT)		Pilot study	Pilot study	Patients with ovarian carcinoma	PARP-1	[58]
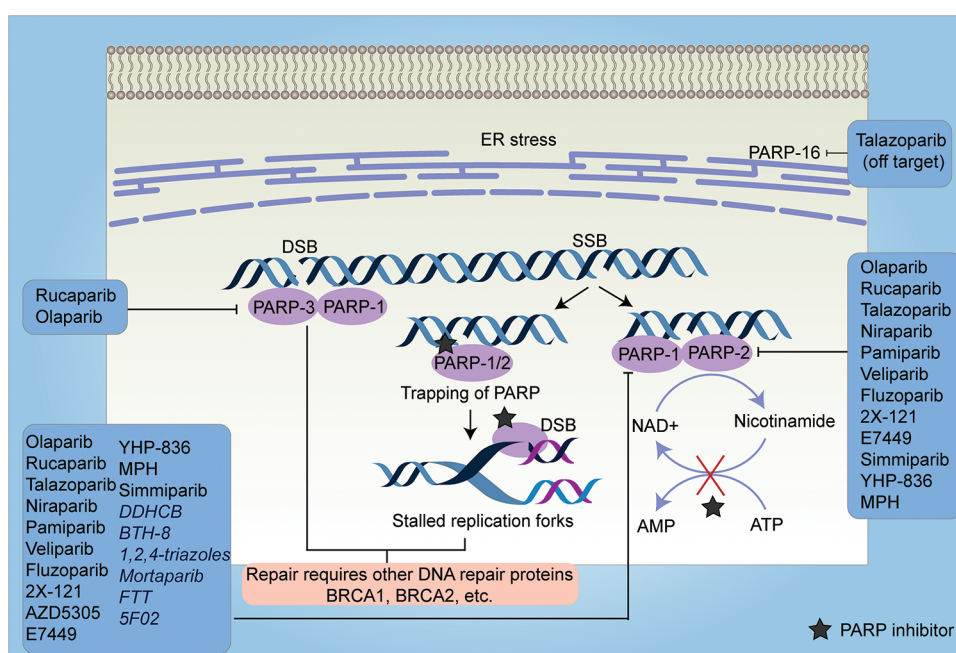
FIGURE 3. A schematic representation of the mechanism of action of PARP inhibitors and their targets. PARP inhibitors work either by inhibiting the PARylation reaction (except 5F02 which is a non-NAD-like PARP inhibitor) or by trapping the PARP enzyme at the DNA lesions. Trapping of PARP at single-strand breaks (SSBs) causes stalled replication forks which in turn leads to the production of double-strand breaks (DSBs). In HR-efficient cells, these lesions are repaired, however, in HR-deficient cells, it leads to cell death. Most of the PARP inhibitors target either PARP-1, 2, and 3 (inhibition of PARP-16 is off-target effect of Talazoparib) or PARP-1 and PARP-2 or only PARP-1. The inhibitors which exclusively target PARP-1 are depicted in italics. SSB-Single Strand Breaks, DSB-Double Strand Breaks, ER-Endoplasmic Reticulum, FTT-[18F]FluorThanatrace, MPH-(Mefuparib Hydrochloride).

TABLE 3

PARP inhibitors clinically approved by United States FDA (Food and Drug Administration) for metastatic castration-resistant prostate cancer (mCRPC), breast cancer, and ovarian cancer

S. No.	PARP inhibitor	Cancer	Main trial	Status	Cohort	Target	References
1	Rucaparib	Prostate cancer	TRITON2 NCT02952534	Clinically approved, 15 May 2020 (Accelerated approval)	mCRPC with a deleterious BRCA alteration who have received both AR-directed therapy and taxane-based chemotherapy	PARP-1, PARP-2, PARP-3	[59,60]
2	Olaparib		PROfound NCT02987543	Clinically approved, 19 May 2020	mCRPC associated with a deleterious alteration in an HRR gene who received AR- directed therapy	PARP-1, PARP-2, PARP-3	[61–63]
3	Olaparib	Breast cancer	OlympiAD NCT02000622	Clinically approved, 12 Jan. 2018	BRCA mutated HER-2 negative metastatic breast cancer who have received chemotherapy either in neoadjuvant, adjuvant or metastatic setting	PARP-1, PARP-2, PARP-3	[64–68]
			OlympiA NCT02032823	Clinically approved, 11 Mar. 2022	For adjuvant treatment of BRCA mutated HER-2 negative early breast cancer who have received local treatment and neoadjuvant or adjuvant chemotherapy		
4	Talazoparib		EMBRACA NCT01945775	Clinically approved, 16 Oct. 2018	BRCA mutated HER-2 negative locally advanced/ metastatic breast cancer	PARP-1, PARP-2, PARP-16	[64–71]
5	Olaparib	Ovarian cancer	NCT01078662	Clinically approved 19 Dec. 2014	BRCA mutated ovarian cancer who have received 3 or more prior lines of chemotherapy	PARP-1, PARP-2, PARP-3	[72–78]
			SOLO-1 NCT01844986	Clinically approved, 19 Dec. 2018	As first-line maintenance treatment of BRCA-mutated advanced ovarian cancer		
			PAOLA-1 NCT02477644	Clinically approved, 08 May 2020	In combination with bevacizumab for first-line maintenance treatment of homologous recombination deficient (HRD)–positive advanced ovarian cancer		
6	Niraparib		NOVA NCT01847274	Clinically approved, 27 Mar. 2017	Maintenance treatment for platinum sensitive ovarian cancer	PARP-1, PARP-2	[79–83]
			QUADRA NCT02354586	Clinically approved, 23 Oct. 2019	HRD-positive advanced ovarian cancer patients treated with three or more prior chemotherapy regimens		
			PRIMA NCT02655016	Clinically approved, 29 Apr. 2020	Maintenance treatment in patients with advanced Ovarian cancer following complete or partial response to front line platinum-based chemotherapy		
7	Rucaparib		ARIEL3 NCT01968213	Clinically approved, 6 Apr. 2018	Maintenance treatment of recurrent epithelial ovarian, cancer who are sensitive to platinum-based chemotherapy	PARP-1, PARP-2, PARP-3	[84,85]

on OlympiAD and OlympiA trials, respectively. OlympiAD was a randomized, open-label, phase 3 trial that compared Olaparib with standard treatment in metastatic breast cancer patients with BRCA mutated HER-2 negative breast cancer [98]. Olaparib treated group showed significantly longer median progression-free survival than the standard therapy group (7.0 months *vs.* 4.2 months; HR, 0.58; $p < 0.001$) and 42% lower risk of disease progression or death than the standard therapy group. Early this year, Olaparib was approved for adjuvant treatment of BRCA-mutated HER-2 negative early breast cancer patients who have received local treatment and neoadjuvant or adjuvant chemotherapy. This approval was based on OlympiA, a randomized double-blind, phase 3 trial. 3-year invasive disease-free survival was better in the Olaparib group (85.9% *vs.* 77.1%; HR, 0.58; $p < 0.001$) and 3-year distant disease-free survival was longer in the Olaparib treated group (87.5% *vs.* 80.4%; HR, 0.57; $p < 0.001$) [65].

Talazoparib was FDA approved for BRCA mutated HER-2 negative locally advanced/metastatic breast cancer based on EMBRACA trial [69,70].

A recent study profiled the crystal structure of the 10 most potent PARP inhibitors by either binding to PARP1 and PARP2 and revealed that veliparib and niraparib are selective inhibitors of PARP1 and PARP2; Olaparib, Rucaparib, and Talazoparib are more potent inhibitors of the PARP1 but are less selective [99] (Fig. 3). Going forward these studies would help improve efficacy and minimize toxicities from PARP inhibitors. Most PARP inhibitors compete with NAD at the active site of PARP-1 enzyme. Since NAD-like PARP inhibitors are less selective as NAD is ubiquitous and NAD competitors could lead to off-target effects, non-NAD-like PARP inhibitors are a novel class of drugs that target histone-dependent activation of PARP-1, a mechanism that is unique to PARP-1. One such inhibitor is 5F02 which showed superior anti-tumor activity in *in vitro* and *in vivo* models of prostate cancer [20].

PARP Inhibitors-the New Phase of Treatment for Metastatic Prostate Cancer?

The promising outcomes from the clinical trials involving PARP inhibitors for breast and ovarian cancer patients have resulted in a series of studies from research groups across the world to try to broaden the patient cohort which could be benefitted from their use. It is now known that these BRCA mutations also increase the risk of other cancers such as colon (reviewed by Oh et al., [100], melanoma [101], pancreatic, gastric cancers, and prostate cancers (reviewed by Cavanagh et al., [102]). BRCA1 and BRCA2 mutations have shown a pivotal role in DNA repair dysfunction in prostate cancers. Germline BRCA2 carriers have a 5.0 to 8.6-fold increased risk of developing prostate carcinoma [103,104]. Also, the prevalence of germline HR mutations among men with metastatic prostate cancer ranges from 8%–14%, indicative of a large proportion of men with advanced disease may benefit from these agents. In addition, PARP inhibition also showed selective lethality in tumor cells with *TMPRSS2-ERG* gene fusions [105], which are identified in more than 50% of prostate tumors, especially in hormone-insensitive metastatic prostate cancer. Given these findings, as well as the lack of effective treatments for castration-resistant metastatic prostate cancer (mCRPC), PARP inhibitors were tested for efficacy in this patient subset. The phase II open-label, single-arm, two-stage, TOPARP-A trial was conducted to test Olaparib efficacy in tested metastatic-castration resistant prostate cancer (mCRPC) has shown promising results [106]. The study found that 14 out of 16 patients who responded to Olaparib treatment had aberrations in DNA repair-related genes. Further classifying the response based on the mutation showed that all patients with a BRCA2 alteration responded to treatment with Olaparib and defects in ATM were also indicative of response to Olaparib, excluding 1 patient with ATM alteration, who did not respond to therapy. In the rest of 28% patients without DNA repair defects, Olaparib was not observed to be effective [106]. These impressive results

led the FDA to grant a breakthrough designation for the use of Olaparib in mCRPC patients with BRCA1/2 or ATM alterations.

The second part of the TOPARP study (TOPARP-B) aimed to validate the role of Olaparib in BRCA2 or ATM carriers and to provide added efficacy data in presence of less common mutations in other DNA repair-related genes, which have been previously linked to PARP inhibitors sensitivity, such as RAD51, FANC, ATR, CDK12, MRE11, CHEK1, CHEK2, and ETS gene fusions. The study confirmed that Olaparib has antitumor activity against heavily pre-treated mCRPC with DDR gene defects, with BRCA1/2 aberrant tumors being the most sensitive but with confirmed responses in patients with other DDR alterations (PALB2 57% (4/7; mPFS 5.3mo); ATM 37% (7/19; mPFS 6.1mo); CDK12 25% (5/20; mPFS 2.9mo)). Another phase 2 trial is also underway to compare abiraterone *vs.* Olaparib as a single agent *vs.* the combination of the two drugs in metastatic CRPC patients with germline or somatic HR mutations.

A phase III PROFOUND trial, in which patients with abiraterone and/or enzalutamide-pretreated CRPC were screened for somatic HR deficiency mutations and then randomized to either AR-targeted therapy or Olaparib. In the Olaparib group, the progression-free survival was significantly longer than the control group (median 7.4 *vs.* 3.6; HR, 0.34; $p < 0.001$). As compared to either enzalutamide or abiraterone, Olaparib was associated with better measures of response. This led to its approval by FDA in May 2020 for mCRPC associated with a deleterious alteration in HRR genes who received AR-directed therapy [61,62].

TRITON 2, a phase 2 trial, led to accelerated approval of rucaparib in May 2020, for mCRPC patients with a deleterious BRCA alteration who have received both AR-directed therapy and taxane-based chemotherapy [59,60]. Another phase 3 trial named TRITON3 is underway to study the efficacy of rucaparib, a potent PARP1, PARP2, and PARP3 inhibitor, in patients with mCRPC associated with HR deficiency (*BRCA1/2* or *ATM* gene mutations) in comparison to *vs.* treatment with physician's choice of abiraterone acetate, enzalutamide, or docetaxel.

It will be important to see if these trials would validate the use of PARP inhibitors in prostate cancer patients. An integrated genomic analysis of advanced prostate cancer revealed that aberrations of BRCA2, BRCA1, and ATM were observed at substantially higher frequencies (19.3% overall) compared to those in primary prostate cancers [107], which reinforces the testing of PARP inhibitors in mCRPC. Also, considering that most metastatic CRPC patient survival is less than 10 months, PARP inhibitors do open new avenues for mCRPC patients with HR repair deficiency.

Therapeutic Potential of the Combination of PARP Inhibitors and Immune Checkpoint Inhibitors (ICI)

In the last decade, Immunotherapy has dramatically improved treatment outcomes for cancer patients across multiple tumor types, including lung, melanoma, ovarian, genitourinary, and,

more recently, breast cancer, with long-lasting responses. Despite promising results, immunotherapy only benefits a subset of patients due to low overall response rates. There is currently a lot of interest in either in patient selection through biomarkers or finding combinatorial approaches to build synergy with immunotherapy. DNA-damaging agents, in particular, have the potential to improve immunotherapy response by promoting neoantigen release, increasing tumor mutational burden, and increasing PD-L1 expression. The rationale behind using combination of PARP inhibitors in DDR-defective cancer cells is that these prevent single-strand DNA repair, which increases DNA damage, enhancing the load of tumor mutations, thus making the tumors more immunologically "hot" [108]. In DDR-defective cells, trapping of PARP at the lesions was shown to result in stalled replication forks and unrepaired lesions, which increased micronuclei formation. These micronuclei are detected by the cytoplasmic DNA sensor, cGAS, which leads to activation of STING/pTBK1 and type 1 Interferon (IFN) gene signaling that in turn is crucial in mounting robust anti-tumor immune response [108–110]. Several ongoing clinical trials are exploring the benefit of the combination of immunotherapy and PARP inhibition,

summarized in Table 4. One such trial, NCT02484404, was carried out for mCRPC, in which the combination of Durvalumab (anti-PDL-1 antibody) and Olaparib was shown to induce PSA responses (reduction ≥ 50%) in 8 out of 17 patients (47%) [110,111]. Progression-free survival was longer in patients with known DDR mutations than the DDR-proficient ones. However, interestingly, the durvalumab and Olaparib combination demonstrated clinical activity in platinum-resistant recurrent ovarian cancer independent of BRCA status. While the data now available indicate that combining PARP inhibitors with ICI could overcome immunological insufficiency, additional data from ongoing trials will be necessary to shed further light on this.

The Road Ahead for PAPR Inhibitors: Promises and Challenges

The clinical trials done with PARP inhibitors so far are highly encouraging and substantiate the fact that these inhibitors could offer better responses not just in breast and ovarian cancer, but in other "PARP-dependent tumors" as well.

TABLE 4

PARP inhibitors in combination with immunotherapy in various phases of clinical trials for prostate cancer, breast cancer, and ovarian cancer

S. No.	PARP inhibitor	Immunotherapy	Cancer	Main trial	Status	Cohort	References
1	Olaparib	Pembrolizumab (anti-PD-1 antibody)	Prostate cancer	KEYLYNK-010 NCT03834519	Under phase 3 trial Trial start: 02 May 2019 Estimated completion: 29 Sept. 2023	mCRPC	[111–114]
		Durvalumab (anti-PD-L1 antibody) and Cediranib (VEGFR)		NCT04336943	Under phase 2 trial Trial start: 13 Apr. 2021 Estimated completion: 30 Apr. 2025	Prostate cancer with high neoantigen load	
		Durvalumab (anti-PD-L1 antibody)		NCT02484404	Under phase 1/2 trial Trial start: 29 Jun. 2015 Estimated completion: 30 Dec. 2024	Prostate cancer	
		Pembrolizumab (anti-PD-1 antibody)		KEYNOTE-365 NCT02861573	Under phase 1/2 trial Trial start: 17 Nov. 2016 Estimated completion: 30 May 2025	mCRPC	
2	Talazoparib	Avelumab (anti-PD-L1 antibody)		NCT03330405	Under phase 2 trial Trial start: 19 Oct. 2017 Estimated completion: 03 Jan. 2023	castration resistant prostate cancer	[115]
3	Rucaparib	Nivolumab (anti-PD-1 antibody)		CheckMate 9KD NCT03338790	Under phase 2 trial Trial start: 19 Dec. 2017 Estimated completion: 15 Jul. 2023	mCRPC	[116]
4	Pamiparib	BGB-A317 (tislelizumab) (PD-1)		NCT02660034	Phase 1 trial completed on 09 Sep. 2020	mCRPC	[117]

(Continued)

Table 4 (continued)

S. No.	PARP inhibitor	Immunotherapy	Cancer	Main trial	Status	Cohort	References
5	Olaparib	Durvalumab (anti-PD-L1 antibody)	Breast cancer	DORA NCT03167619	Phase 2 trial completed on 30 Jun. 2022	Platinum treated triple negative breast cancer	[111,118–122]
		Pembrolizumab (anti-PD-1 antibody)		NCT03025035	Under phase 2 trial Trial start: 10 Sep. 2017 Estimated completion: Nov. 2025	BRCA mutated/HRD-defect breast cancer	
		Durvalumab (anti-PD-L1 antibody)		NCT02484404	Under phase 1/2 trial Trial start: 29 Jun. 2015 Estimated completion: 30 Dec. 2024	Triple negative breast cancer	
		Atezolizumab (anti-PD-1 antibody)		NCT02849496	Under phase 2 trial Trial start: 15 Nov. 2016 Estimated completion: 31 Aug. 2023	BRCA mutated Non-HER2 positive breast cancer	
		Durvalumab (anti-PD-L1 antibody)		OlympiaN NCT05498155	Under phase 2 trial Trial start: 21 Oct. 2022 Estimated completion: 20 Nov. 2026	BRCA mutated HER2 negative breast cancer	
		Durvalumab (anti-PD-L1 antibody)		NCT03544125	Phase 1 trial completed in 18 Nov. 2020	Metastatic triple negative breast cancer	
6	Talazoparib	Avelumab (anti-PD-L1 antibody)		NCT03330405	Under phase 2 trial Trial start: 19 Oct. 2017 Estimated completion: 03 Jan. 2023	Triple negative breast cancer	[115]
7	Niraparib	Dostarlimab (PD-1) plus radiation therapy		NADiR NCT04837209	Under phase 2 trial Trial start: 21 Jul. 2021 Estimated completion: 01 Dec. 2029	Metastatic triple negative breast cancer	[123–125]
		Pembrolizumab (anti-PD-1 antibody)		TOPACIO NCT02657889	Phase 1 trial completed on 17 Sep. 2021	Triple negative breast cancer	
		TSR-042 (Dostarlimab)		NCT04673448	Under phase 1 trial Trial start: 18 Oct. 2021 Estimated completion: 30 Mar. 2026	Metastatic breast cancer	
8	Pamiparib	BGB-A317 (tislelizumab) (anti-PD-1 antibody)		NCT02660034	Phase 1 trial completed on 09 Sep. 2020	Triple negative breast cancer	[117]
9	Rucaparib	Atezolizumab (anti-PD-1 antibody)		NCT03101280	Phase 1 trial completed on 11 Aug. 2020	Triple negative breast cancer	[126]
10	Olaparib	Durvalumab (anti-PD-L1) and Cediranib (VEGFR)	Ovarian cancer	NCT02484404	Under phase 1/2 trial Trial start: 29 Jun. 2015 Estimated completion: 30 Dec. 2024	Advanced/recurrent ovarian cancer	[111,127–129]
		Tremelimumab (anti-CTLA-4 antibody)		NCT04034927	Under phase 2 trial Trial start: 11 Oct. 2019 Estimated completion: 31 Dec. 2022	Platinum sensitive recurrent ovarian cancer	
		Tremelimumab (anti-CTLA-4 antibody)		NCT02571725	Under phase 1/2 trial Trial start: 23 Feb. 2016 Estimated completion: 15 Jul. 2027	Recurrent BRCA mutated ovarian cancer	

Table 4 (continued)

S. No.	PARP inhibitor	Immunotherapy	Cancer	Main trial	Status	Cohort	References
		Durvalumab and tremelimumab		NCT02953457	Under phase 2 trial Trial start: 29 Jun. 2017 Estimated completion: 15 Dec. 2022	BRCA-mutated ovarian cancer	
11	Niraparib	Atezolizumab (anti PD-L1 antibody)		ANITA NCT03598270	Under phase 3 trial Trial start: 21 Nov. 2018 Estimated completion: Jan. 2025	Recurrent ovarian carcinoma	[124,125,130,131]
		Dostarlimab (PD-1)		MOONSTONE NCT03955471	Phase 2 trial completed on 12 Jan. 2022	Platinum resistant ovarian cancer	
		TSR-042 (Dostarlimab)		NCT04673448	Under phase 1 trial Trial start: 18 Oct. 2021 Estimated completion: 30 Mar. 2026	BRCA mutated ovarian cancer	
		Pembrolizumab (anti PD-1 antibody)		NCT02657889	Phase 1 trial completed on 17 Sep. 2021	Recurrent Ovarian cancer	
12	Talazoparib	Avelumab (anti-PD-L1 antibody)		NCT03330405	Under phase 2 trial Trial start: 19 Oct. 2017 Estimated completion: 03 Jan. 2023	recurrent platinum sensitive ovarian cancer	[115]
13	Rucaparib	Atezolizumab (anti-PD-L1 antibody)		NCT03101280	Phase 1 trial completed on 11 Aug. 2020	Advanced ovarian cancer	[126]

Data from these clinical trials also argue for the need to change our conventions of treating cancer mainly based on anatomical sites and rather create a "molecular stratification" which may improve treatment response, especially in advanced-stage tumors with limited treatment alternatives. In line with this theory, increasing evidence suggests that BRCA may be inactivated by multiple mechanisms in a large proportion of breast cancers, despite possessing a functional gene structure, a trait now called "BRCAness". It would be interesting to see whether the use of PARP inhibitors could be extended to these cases as well. On a cautious note, it is also important to draw our attention to breast cancer cases with confirmed BRCA mutations, which do not respond well to PARP inhibitors.

The study 42, which examined Olaparib monotherapy in germline BRCA mutation carriers, found an objective response rate of 34% only [132]. Also, there were cases of ovarian cancers, with no apparent BRCA defect, which responded well to PARP inhibitor therapy. Even though the number of these cases has been marginal, it is important to understand the reason for the failure to improve the predictivity of treatment response. Also, while the distinction in sensitivity between BRCA1 and BRCA2-associated ovarian cancers remains unclear in the clinical setting, emerging *in vitro* data does indicate that all *BRCA* mutations are not equal in their functionality. This suggests that the location of *BRCA1* mutation may influence the efficacy of PARP inhibitors, which should be considered in future studies.

Another important area of active research in the field is identifying accurate biomarkers of response to PARP inhibitors apart from *BRCA* mutation status. Measurement of PARylation levels of peripheral blood mononuclear cells was explored in a study [133]. The homologous recombination deficiency score which has been used to identify patients with defective DNA repair mechanisms (including tumors without *BRCA* mutations) was shown to be associated with increased response rates in neoadjuvant settings [134]. Studies are also undergoing to find methods for evaluation of HR proficiency through the formation of nuclear RAD51 foci [135] as well as the evaluation of BRCA promoter hypermethylation or the levels of 53BP1 expression [136]. However, these results need to be validated in independent large cohorts.

As with other chemotherapeutic drugs, the development of resistance to PARP inhibitors also needs to be addressed. Studies have demonstrated that using PARP inhibitors in cancer cells carrying mutations in *BRCA1* or *BRCA2* could develop resistance by acquiring secondary mutations in the *BRCA* genes that, interestingly, reverse the effect of the original mutation, restoring the levels of functional BRCA proteins [137,138]. Upregulation of genes that encode P-glycoprotein efflux pumps, a known culprit for drug resistance could also hamper the effectiveness of PARP inhibitors [139]. Alterations in signaling pathways have also emerged as mechanisms of PARP1 inhibitor resistance. One example involves the role of microRNAs (miR-622), in modulating the balance of the DNA repair pathway [140].

Another study revealed that phosphorylation of PARP1 at Y907 by c-Met leads to PARP inhibitor resistance and identified c-Met as an important regulator of PAPR inhibitor response [141]. Current approaches to PARP inhibitor resistance are centered on combining PARP inhibition with other DNA damage response inhibitors, immune-checkpoint inhibition, or targeted therapies. To further improve therapeutic outcomes, it is important to improve our understanding of HR-deficient cancers and find agents that target the acquired vulnerabilities of PARP inhibitor-resistant tumors, delay the onset of resistance, or selectively kill unresponsive cells.

Conclusions

With the advent of techniques like next-generation sequencing, liquid biopsies, and circulating tumor DNA analyses, the possibility of utilizing a personalized therapeutic approach seems highly possible. On the clinical end, ongoing PARP trials would offer significant information on optimal agent selection, scheduling, and dosing either alone or in combination, which will be important for the rationalized use of PARP inhibitors in multiple cancer types. However, overcoming mechanisms of resistance and the identification of reliable predictive biomarkers of response would need to be first addressed using *in vitro* and pre-clinical model systems. With the success of immunotherapy in multiple cancer types, it will also be important to answer if PARP inhibition and immunotherapy could work synergistically and improve overall survival in cancer patients.

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