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Moving From Poly (ADP-Ribose) Polymerase Inhibition to Targeting DNA Repair and DNA Damage Response in Cancer Therapy

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ABSTRACT

The DNA damage response (DDR) pathway coordinates the identification, signaling, and repair of DNA damage caused by endogenous or exogenous factors and regulates cell-cycle progression with DNA repair to minimize DNA damage being permanently passed through cell division. Severe DNA damage that cannot be repaired may trigger apoptosis; as such, the DDR pathway is of crucial importance as a cancer target. Poly (ADP-ribose) polymerase (PARP) is the best-known element of the DDR, and several PARP inhibitors have been licensed. However, there are approximately 450 proteins involved in DDR, and a number of these other targets are being investigated in the laboratory and clinic. We review the most recent evidence for the clinical effect of PARP inhibition in breast and ovarian cancer and explore expansion into the first-line setting and into other tumor types. We critique the evidence for patient selection techniques and summarize what is known about mechanisms of PARP inhibitor resistance. We then discuss what is known about the preclinical rationale for targeting other members of the DDR pathway and the associated tumor cell genetics that may confer sensitivity to these agents. Examples include DNA damage sensors (MLH1), damage signaling molecules (ataxia-telangiectasia mutated; ataxia-telangiectasia mutated–related and Rad3-related; CHK1/2; DNA-dependent protein kinase, catalytic subunit; WEE1; CDC7), or effector proteins for repair (POLQ [also referred to as POLθ], RAD51, poly [ADP-ribose] glycohydrolase). Early-phase clinical trials targeting some of these molecules, either as a single agent or in combination, are discussed. Finally, we outline the challenges that must be addressed to maximize the therapeutic opportunity that targeting DDR provides.

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INTRODUCTION

Genomic instability is a hallmark of cancer.[1] Oncogene-induced replication stress (DNA damage occurring during DNA replication) is a major cause of genomic instability in cancer cells. This can lead to additional mutagenesis, bypassing cell-cycle checkpoints that have evolved to protect DNA fidelity. This may directly or indirectly result in slowed or stalled replisome progression and subsequent uncoupling of DNA synthesis from the helicase that unwinds the DNA.

In addition to replication stress, DNA damage can be induced by endogenous (eg, spontaneous or enzymatic reactions, chemical modifications, replication errors) or exogenous (eg, ultraviolet radiation, ionizing radiation, genotoxic chemicals) factors. The DNA damage response (DDR) constitutes a network of proteins that sense, signal, and/or repair DNA damage. The DDR coordinates cell-cycle progression with DNA repair to minimize DNA damage being permanently passed to daughter cells.[2] Key proteins that signal DNA damage to cell-cycle checkpoints and DNA repair pathways include ataxia-telangiectasia mutated (ATM), ATM- and Rad3-related (ATR), and DNA-dependent protein kinase, catalytic subunit (DNA-PKcs) kinases (Fig 1).[3-7] The triggered response pathways may involve any of the repair mechanisms, including (1) base excision repair for single-strand breaks (SSBs), (2) nucleotide excision repair for repair of bulky adducts, (3) mismatch repair for mispaired bases, (4) homologous recombination repair (HRR) for double-strand breaks (DSBs) and intrastrand/interstrand crosslinks, (5) nonhomologous end joining (NHEJ) for DSB repair via direct religation of the ends, or (6) microhomology-mediated end joining (MMEJ) for repairing DSBs (Fig 1).[8] If the DNA damage is too severe or the lesion is irreparable, DDR checkpoints may trigger apoptosis. Abrogation or overwhelming of response pathways can also result in irreparable damage and cellular death. This has been exploited in the development of poly (ADP-ribose) polymerase (PARP) inhibitors for tumors with defective HRR. With greater understanding of the biology of DNA damage and repair, novel DDR-targeting molecules that exploit replication stress via DDR inhibition are being developed as new anticancer therapies.[9-11] The potential targets are numerous; there are approximately 450 genes coding for proteins involved in the DDR. We review the current role of PARP inhibition in the

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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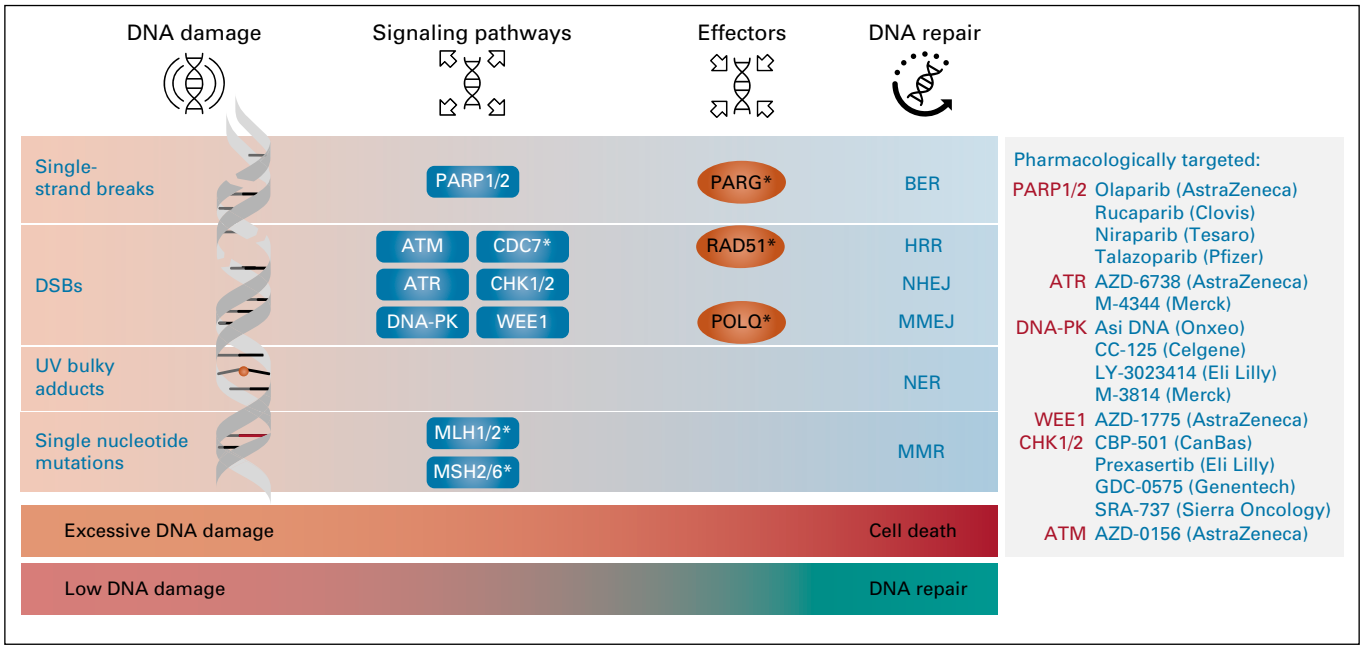

FIG 1. DNA damage response (DDR) signaling pathways and repair mechanisms. DNA damage may be caused by a number of exogenous and endogenous sources. The DDR comprises a network of proteins that are either DNA damage sensors or signaling molecules, or effector proteins that execute repair. Once DNA damage is detected, repair mechanisms can include base excision repair (BER) for single-strand breaks, nucleotide excision repair (NER) for repair of bulky adducts, mismatch repair (MMR) for mispaired bases, homologous recombination repair (HRR), nonhomologous end joining (NHEJ), and microhomology-mediated end joining (MMEJ) for double-strand break (DSB) repair. Cells with excessive or unrepairable DNA may enter cell-cycle arrest and/or trigger apoptosis. There are several hundred proteins implicated in the DDR; factors shown in the schematic are the subset of DDR proteins that are being targeted pharmacologically, including poly (ADP-ribose) polymerase (PARP)1/2 by PARP inhibitors. ATM, ataxia-telangiectasia mutated; ATR, ATM- and Rad3-related; DNA-PK, DNA-dependent protein kinase; UV, ultraviolet. (*) Inhibitors in preclinical development.

treatment of cancer and discuss the importance of DDR in cancer cells, as well as potential strategies for increasing the efficacy of DDR-targeted therapies, including new DDR targets and drugs.

THE CURRENT ROLE OF PARP INHIBITION IN THE TREATMENT OF CANCER

Since the discovery of PARP1/2, a family of 17 proteins with structural similarity to the PARP1 catalytic domain has been identified.[12] Several PARPs are involved in repairing SSBs through base excision repair and DSBs through HRR, NHEJ, and alt-NHEJ (also known as MMEJ; Appendix Fig A1, online only). Molecules that inhibit PARP function act not only by inhibiting enzymatic activity, but also by trapping PARP1 on DNA (Appendix Fig A1). On the basis of in vitro data, it is believed that the potency of the various PARP inhibitors is associated with their PARP-trapping efficiency, resulting in stalled replication forks and subsequent DSB formation.[13] In the clinic, there are no data that compare the efficacy of any PARP inhibitor versus another or rechallenging with a PARP inhibitor after progressing while receiving a prior PARP inhibitor. Four different PARP inhibitors have been approved to date for use in the treatment of ovarian and breast cancer in Europe and the United States, with similar but not completely identical labels (Appendix Table A1, online only). They are administered as a single agent during maintenance therapy after response to platinum-based chemotherapy or as monotherapy.

Clinical Activity in Ovarian Cancer

Up to 50% of high-grade serous ovarian cancers have genetic or epigenetic defects in HRR (which results in homologous recombination deficiency [HRD]).[14] The most commonly affected genes are *BRCA1* and *BRCA2*, with contributions from other homologous recombination genes, such as *RAD51C*, *RAD51D*, *ATM*, *BARD1*, *PALB2*, and *BRIP1*, responsible for approximately 10% of patients with HRD.[15] There is a strong association between HRD and ovarian cancer platinum sensitivity,[15] which likely explains why platinum sensitivity has been successfully used as a clinical tool for patient selection for PARP inhibitor therapy.[16]

Currently, three PARP inhibitors (olaparib, niraparib, and rucaparib) have been approved for ovarian cancer in the maintenance setting after platinum-sensitive relapse in patients with germline *BRCA* (*gBRCA*) mutations (Table 1).[17-20] In the pivotal phase III trials (SOLO-2, NOVA, ARIEL-3), median progression-free survival (PFS) was significantly longer for the patients receiving maintenance PARP inhibitor therapy than for those receiving placebo (PARP inhibitor PFS ranged from 16.6 to 21.0 months *v* 5.4

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TABLE 1. Key Efficacy Data That Supported the Approval of PARP Inhibitors in Ovarian Cancer

Clinical Endpoint/Patient Subgroup	Median, months (95% CI)
Maintenance Setting	
Olaparib (Study 19): Platinum Sensitive, Recurrent, High-Grade Serous[17,21]	
PFS *v* placebo–all patients	8.4 (7.4 to 11.5) *v* 4.8 (4.0 to 5.5); HR, 0.35 (95% CI, 0.25 to 0.49); $P < .001$
PFS *v* placebo–BRCA mutation	11.2 (8.3 to NC) *v* 4.3 (3.0 to 5.4); HR, 0.18 (95% CI, 0.10 to 0.31); $P < .001$
PFS *v* placebo–BRCA WT	7.4 (5.5 to 10.3) *v* 5.5 (3.7 to 5.6); HR, 0.54 (95% CI, 0.34 to 0.85); $P = .0075$
OS *v* placebo–all patients	29.8 (26.9 to 35.7) *v* 27.8 (24.9 to 33.7); HR, 0.73 (95% CI, 0.55 to 0.96); $P = .025$
OS *v* placebo–BRCA mutation	34.9 (29.2 to 54.6) *v* 30.2 (23.1 to 40.7); HR, 0.62 (95% CI, 0.41 to 0.94); $P = .025$
OS *v* placebo–BRCA WT	24.5 (19.8 to 35.0) *v* 26.6 (23.1 to 32.5); HR, 0.83 (95% CI, 0.55 to 1.24); $P = .37$
Olaparib (SOLO-2): Platinum Sensitive, Relapsed, gBRCA1/2 Mutations[18]	
PFS *v* placebo	19.1 (16.3 to 25.7) *v* 5.5 (5.2 to 5.8); HR, 0.30 (95% CI, 0.22 to 0.41); $P < .001$
TFST or death	27.9 (22.6 to NC) *v* 7.1 (6.3 to 8.3); HR, 0.28 (95% CI, 0.21 to 0.38); $P < .001$
TTSP or death	NR (24.1 to NC) *v* 18.4 (15.4 to 22.8); HR, 0.50 (95% CI, 0.34 to 0.72); $P < .001$
TSST or death	NR (NC) *v* 18.2 (15.0 to 20.5); HR, 0.37 (95% CI, 0.26 to 0.53); $P < .001$
Niraparib (NOVA): Platinum Sensitive, Recurrent[19]	
PFS *v* placebo–gBRCA	21.0 *v* 5.5; HR, 0.27 (95% CI, 0.17 to 0.41); $P < .001$
PFS *v* placebo–non-gBRCA	9.3 *v* 3.9; HR, 0.45 (95% CI, 0.34 to 0.61); $P < .001$
PFS *v* placebo–HRD plus non-gBRCA	12.9 *v* 3.8; HR, 0.38 (95% CI, 0.24 to 0.59); $P < .001$
TFST *v* placebo–gBRCA	21.0 (17.5 to NR) *v* 8.4 (6.6 to 10.6); HR, 0.31 (95% CI, 0.21 to 0.48); $P < .001$
TFST *v* placebo–non-gBRCA	11.8 (9.7 to 13.1) *v* 7.2 (5.7 to 8.5); HR, 0.55 (95% CI, 0.41 to 0.72); $P < .001$
PFS2 *v* placebo–gBRCA	25.8 (20.3 to NR) *v* 19.5 (13.3 to NR); HR, 0.48 (95% CI, 0.28 to 0.82); $P = .006$
PFS2 *v* placebo–non-gBRCA	18.6 (16.2 to 21.7) *v* 15.6 (13.2 to 20.9); HR, 0.69 (95% CI, 0.49 to 0.96); $P = .03$
Rucaparib (ARIEL-3): Platinum Sensitive, High Grade, Recurrent, After Two or More Lines of Previous Therapy[20]	
PFS *v* control–g/s BRCA mutation	16.6 (13.4 to 22.9) *v* 5.4 (3.4 to 6.7); HR, 0.23 (95% CI, 0.16 to 0.34); $P < .001$
PFS *v* control–HRD deficient	13.6 (10.9 to 16.2) *v* 5.4 (5.1 to 5.6); HR, 0.32, (95% CI, 0.24–0.42); $P < .001$
PFS *v* control–LOH high	9.7 (7.9 to 13.1) *v* 5.4 (4.1 to 5.7); HR, 0.44, (95% CI, 0.29 to 0.66); $P < .001$
PFS *v* control–LOH low	6.7 (5.4 to 9.1) *v* 5.4 (5.3 to 7.4); HR, 0.58 (95% CI, 0.40 to 0.85); $P = .0049$

(continued on following page)

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TABLE 1. Key Efficacy Data That Supported the Approval of PARP Inhibitors in Ovarian Cancer (continued)

Monotherapy Setting	
Olaparib (Study 42): g*BRCA*1/2 Mutations, Three or More Lines of Previous Therapy[22]	
PFS–all patients	6.7 (5.5 to 7.6)
PFS–platinum sensitive	9.4 (6.7 to 11.4)
PFS–platinum resistant	5.5 (4.2 to 6.7)
Rucaparib (ARIEL-2 and Study 10): s/g*BRCA*1/2 Mutations, High Grade, Three or More Lines of Previous Therapy[23]	
PFS–platinum sensitive	11.1 (7.3 to 12.8)
PFS–platinum resistant	5.3 (1.7 to NR)

NOTE. Data are months (95% CI) unless otherwise indicated.

Abbreviations: OS, overall survival; g/s, germline or somatic mutations; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; NC, noncalculable; NR, not reached; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival; PFS2, progression-free survival 2; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy; TTSP, time to second progression; WT, wild type.

to 5.5 months for placebo).[18-20] The SOLO-2 study[18] was restricted to patients with germline or somatic *BRCA* mutations, but NOVA[19] and ARIEL-3[20] (as well as Study 19[21] in the phase II setting) also recruited patients without *BRCA* mutations. Although the PFS benefit was greater in the context of germline or somatic *BRCA* mutations (hazard ratio [HR], 0.18 to 0.27 in the various studies), patients with *BRCA* wild-type tumors also consistently derived a significant benefit from PARP inhibition (HR, 0.38 to 0.58 in various molecular subgroups; Table 1). In the monotherapy setting, the efficacy in phase II was broadly comparable with other treatment options available in heavily pretreated, relapsed patients (Table 1).[18,20,22,24] Rucaparib has been approved by the Food and Drug Administration (FDA) for the treatment of patients with a somatic or germline *BRCA1/2* mutation who have received two or more prior chemotherapeutic agents, whereas olaparib has been approved for patients with a germline *BRCA1/2* mutation who have received three or more prior chemotherapeutic agents.

In the first-line setting, the SOLO-1 trial randomly assigned 391 patients with *BRCA*-mutated, newly diagnosed, stage III or IV high-grade serous or endometrioid ovarian cancer in a 2:1 ratio to olaparib or placebo after a complete or partial response to cytoreductive surgery and platinum-based chemotherapy.[25] Olaparib maintenance therapy resulted in a 3-year improvement in median PFS over placebo (HR, 0.30; 95% CI, 0.23 to 0.41; $P < .001$). After a minimum of 36 months of follow-up, the median PFS had not yet been reached in the olaparib arm (compared with 13.8 months in the placebo arm).

The main adverse events (AEs) associated with all three approved PARP inhibitors in ovarian cancer were nausea, fatigue, vomiting, and anemia.[18-20] Discontinuation rates ranged between 10% and 15%.[18-20] The incidence of myelodysplastic syndrome/acute myeloid leukemia, a potentially serious hematologic toxicity, was 1% to 2% in the PARP inhibitor and placebo arms of the pivotal trials.[18-20]

Clinical Activity in Breast Cancer

Olaparib was the first PARP inhibitor to demonstrate significant treatment benefit over standard treatment (investigator's choice of one of three standard chemotherapy regimens) in patients with germline *BRCA*-mutated, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer and has subsequently been approved for use in the United States (Appendix Table A1). This was on the basis of the phase III OlympiAD trial, which reported a median PFS for olaparib (300 mg twice a day) of 7.0 months compared with 4.2 months for standard of care (HR, 0.58; 95% CI, 0.43 to 0.80; $P < .001$).[26] Overall, there were fewer grade 3 and above AEs in the olaparib arm compared with the standard-therapy group (36.6% *v* 50.5%).

More recently, talazoparib was also approved by the FDA for the treatment of patients with *gBRCA* mutations, HER2-negative locally advanced, or metastatic breast cancer. In the phase III, randomized, open-label EMBRACA trial, talazoparib demonstrated benefit versus chemotherapy, with a median PFS of 8.6 months versus 5.6 months with physician's choice of therapy (HR, 0.54; 95% CI, 0.41 to 0.71; $P < .001$).[27] Grade 3 to 4 hematologic AEs occurred in 55% of talazoparib and 38% of standard-therapy patients; nonhematologic grade 3 events were 32% and 38%, respectively.[27]

The use of PARP inhibition is also being explored in patients with early-stage breast cancer and germline *BRCA* mutations, including in the neoadjuvant and adjuvant settings.[28-31] The randomized OlympiA phase III study will examine adjuvant use of olaparib in patients with high-risk HER2-negative breast cancer with *gBRCA* mutations and should reveal whether PARP inhibition can improve outcomes in breast cancer if given in an earlier setting.[31]

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THE FUTURE ROLE OF PARP INHIBITION IN CLINICAL PRACTICE

The therapeutic reach of PARP inhibitors is expanding to other cancer types, many of which are associated with *BRCA* mutations. Trials are ongoing in pancreatic, endometrial, prostate, urothelial, colorectal, small-cell and non–small-cell lung, and gastroesophageal cancers, as well as glioblastoma (Table 2). In 2016, olaparib received FDA breakthrough designation for the treatment of metastatic castration-resistant prostate cancer (mCRPC) with *BRCA1/2* and *ATM* mutations, followed by rucaparib in 2018. In the phase II TOPARP-A trial, olaparib showed an overall response rate (ORR) of 33% (16 of 49 patients) in patients with mCRPC who no longer responded to standard treatments, with 12 patients receiving olaparib for more than 6 months.[32] An analysis of tumor samples from TOPARP-A patients using next-generation sequencing to analyze DNA repair genes found 16 patients with somatic homozygous deletions of both *BRCA1* and *FANCA*, somatic frameshift mutations in *PALB2,* heterozygous *PALB2* deletions, and biallelic aberrations in *HDAC2;* of these 16 patients, 14 responded to olaparib.[32] Recently, the phase II TRITON2 study in patients with mCRPC associated with an identified HRR gene alteration reported an ORR of 44% for rucaparib in patients with a *BRCA* mutation, and two of eight patients with either *BRIP1* or *FANCA* mutations also responded, leading to an ORR of 25% in these patients.[33] Thus, for many of these indications, identifying suitable patients with impaired DDR systems seems key to improving treatment outcomes.

Selecting the Right Patients for PARP Inhibition Treatment

Patients whose tumors harbor *BRCA* mutations are likely to respond to PARP inhibition, and identifying these patients is now well established in hospitals. Genomic scars and mutational signatures associated with an HRD phenotype have been identified and can define a wider population that may benefit from DDR-targeting agents.[34-37] Molecular signature of HRD and accompanying computational analyses are yet to have a direct translation into clinical use. Companion diagnostics, such as the MyChoice HRD assay (Myriad, Salt Lake City, UT)[38] and the FoundationFocus CDx*BRCA* loss of heterozygosity test (Foundation Medicine, Cambridge, MA),[39] have some value in enriching for patients likely to respond to PARP inhibitors, but as yet are unable to identify patients who will not benefit.[19,20] In ovarian cancer, platinum sensitivity has been shown to function as a surrogate marker for HRD.[15] However, it is also known that platinum and PARP inhibitor responsiveness is not always overlapping, suggesting differences in the underlying DNA repair mechanism. Inherited mutations in *BRIP1*, *BARD1*, *CHEK2*, *RAD51C*, and *ATM* genes have all been postulated to confer an increased risk of tumor development, but the extent to which these HRR genes contribute to HRD remains unclear.[20,40-42] Another patient selection assay for PARP inhibitors identifies non-BRCA1/2 HRR proteins, such as nuclear RAD51 focus formation by immunofluorescence. RAD51 is essential for HRR, and RAD51 scores have been associated with HRD and therapeutic response to chemotherapy and PARP inhibitors.[43-45] Recently, this type of assay has been established in paraffin-embedded tissue blocks without the need for exogenous DNA damage, allowing its transfer to the clinic to predict the current status of HRD before therapeutic decision making. In terms of patient selection, understanding innate tumor genomics before treatment and combining this knowledge with information from functional analysis assessing sensitivity to PARP inhibition may be applied to generate patient-personalized treatment plans.

Understanding Resistance

Several mechanisms of acquired PARP inhibitor resistance have been described in preclinical settings. However, to date, only restoration of HRR and expression of hypomorphic forms of BRCA1 have been shown to be clinically relevant.[46,47] The re-expression of BRCA variants may occur via secondary reversion mutations that restore the open reading frame and, consequently, the function of BRCA1, BRCA2, PALB2, or RAD51C (also responsible for resistance to platinum).[46-49] Notably, documented patients with *BRCA1* reversion mutations exhibit an MMEJ signature, suggesting that POLQ (required for MMEJ) is a driver of resistance.[50] Hence, POLQ inhibitors, which are in preclinical development, may suppress acquired PARP inhibitor resistance, while conferring synthetic lethality (SL) in HRR- and NHEJ-deficient cancers. Epigenetic changes in HRR genes have also been shown to contribute to PARP inhibitor sensitivity and resistance, with methylation of genes such as *BRCA1* and *RAD51C* conferring PARP inhibitor sensitivity and their subsequent demethylation being associated with protein re-expression and development of resistance.[45,51,52]

It is likely that in other cancers, different mechanisms of resistance may emerge, likely depending on the germline or other mutational profile or other factors, such as origin of the disease or prior treatment. These mutations may include loss of PARP1 expression, compromised regulation of end-resection via loss of 53BP1, MAD2L2/Rev7, or the Shieldin complex, and activation of *trans*-lesion DNA synthesis through loss of CHD4, allowing less efficient HRR to proceed.[47,53,54] A clustered regularly interspersed palindromic repeats–Cas9 mutagenesis screen identified several clusters of mutations in *PARP1* that cause PARP inhibitor resistance.[55] Recently, the stabilization of stalled replication forks has also emerged as a novel PARP inhibitor resistance mechanism.[56] Loss of the MLL3/4 complex protein, PTIP, protected BRCA2-deficient cells from DNA damage by inhibiting the recruitment of the MRE11 nuclease and subsequent DNA degradation of stalled replication forks, which prevented PARP inhibitor-induced lethality.[56] In this sense, Yazinski et al[57] have further

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TABLE 2. PARP Inhibitors in Clinical Development in Tumor Types Other Than Ovarian Cancer

Compound	Trial ID	Trial Title	Phase
Niraparib	NCT01905592	A Phase III Trial of Niraparib Versus Physician's Choice in HER2 Negative, Germline BRCA Mutation-Positive Breast Cancer Patients (BRAVO)	III
	NCT03601923	Niraparib in Patients With Pancreatic Cancer	II
	NCT03553004	Niraparib in Metastatic Pancreatic Cancer After Previous Chemotherapy (NIRA-PANC): A Phase 2 Trial (NIRA-PANC)	II
	NCT03016338	Study of Niraparib in Recurrent Endometrial Cancer	II
	NCT03431350	A Study of Niraparib Combination Therapies for the Treatment of Metastatic Castration-Resistant Prostate Cancer (QUEST)	I/II
Olaparib	NCT02184195	Olaparib in gBRCA Mutated Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum-Based Chemotherapy (POLO)	III
	NCT01924533	Efficacy and Safety Study of Olaparib in Combination With Paclitaxel to Treat Advanced Gastric Cancer	III
	NCT02810743	Substantially Improving the Cure Rate of High-Risk BRCA1-Like Breast Cancer (SUBITO)	III
	NCT03286842	To Study Clinical Effectiveness and Safety of Olaparib Monotherapy in Metastatic Breast Cancer Patients	III
	NCT02987543	Study of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men With Metastatic Castration-Resistant Prostate Cancer (PROfound Study)	III
Rucaparib	NCT02975934	A Study of Rucaparib Versus Physician's Choice of Therapy in Patients With Metastatic Castration-Resistant Prostate Cancer and Homologous Recombination Gene Deficiency (TRITON3)	III
	NCT02042378	A Study of Rucaparib in Patients With Pancreatic Cancer and a Known Deleterious BRCA Mutation	II
	NCT02678182	Planning Treatment of Oesophago-Gastric Cancer: A Maintenance Therapy Trial (PLATFORM)	II
	NCT03533946	Rucaparib in Nonmetastatic Prostate With BRCAness (ROAR)	II
	NCT03397394	Rucaparib in Patients With Locally Advanced or Metastatic Urothelial Carcinoma (ATLAS)	II
	NCT03413995	Trial of Rucaparib in Patients With Metastatic Hormone-Sensitive Prostate Cancer Harboring Germline DNA Repair Gene Mutations (TRIUMPH)	II
	NCT02855944	A Study of Rucaparib Versus Chemotherapy BRCA Mutant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Patients (ARIEL4)	III
Talazoparib	NCT02282345	Neoadjuvant Talazoparib for Patients With a BRCA Deleterious Mutation	II
	NCT02401347	Talazoparib Beyond BRCA (TBB) Trial	II
	NCT03148795	A Study of Talazoparib in Patients With DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer	II
Veliparib	NCT02163694	A Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the PARP Inhibitor Veliparib (ABT-888) in HER2 Negative Metastatic or Locally Advanced Unresectable BRCA-Associated Breast Cancer	III
	NCT01149083	Veliparib With or Without Carboplatin in Treating Patients With Stage III or Stage IV Breast Cancer	II
	NCT01657799	Comparison of Veliparib and Whole Brain Radiation Therapy (WBRT) Versus Placebo and WBRT in Subjects With Brain Metastases From Non-Small Cell Lung Cancer (NSCLC)	II
	NCT02890355	FOLFIRI or Modified FOLFIRI and Veliparib as Second Line Therapy in Treating Patients With Metastatic Pancreatic Cancer	II
	NCT03044795	Response to PARP Inhibitor Predicted by the RAD51 Assay (REPAIR)	II
	NCT02106546	Randomized, Double-Blind, Multicenter, Study Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Placebo Plus Carboplatin and Paclitaxel in Previously Untreated Advanced or Metastatic Squamous Non-Small Cell Lung Cancer	III
	NCT01506609	The Study Evaluating Efficacy and Tolerability of Veliparib in Combination With Temozolomide or in Combination With Carboplatin and Paclitaxel Versus Placebo in Subjects With BRCA1 and BRCA2 Mutation and Metastatic Breast Cancer	II
	NCT02470585	Veliparib With Carboplatin and Paclitaxel and as Continuation Maintenance Therapy in Subjects With Newly Diagnosed Stage III or IV, High-Grade Serous, Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	III
	NCT02032277	A Study Evaluating Safety and Efficacy of the Addition of ABT-888 Plus Carboplatin Versus the Addition of Carboplatin to Standard Chemotherapy Versus Standard Chemotherapy in Subjects With Early-Stage Triple-Negative Breast Cancer	III

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demonstrated that PARP-inhibitor–resistant, BRCA1-deficient cells become dependent on ATR for survival. Another proposed mechanism of resistance is the upregulation of PgP transporter for drug efflux genes resulting in reduced availability of PARP inhibitor.[58] The PARP inhibitor AZD2461, designed as a next-generation olaparib with poor PgP affinity, may prove to overcome this mechanism of resistance.[59]

MOVING FROM PARP TO DDR INHIBITION IN THE CLINIC

Exploiting Synthetic Lethality

The concept of SL was first described in fruit flies, when two single genetic, loss-of-function events had no effect on viability alone, but when combined resulted in lethality.[60] The sensitivity of BRCA-deficient cancers to PARP inhibition[61,62] is not true SL, because loss-of-function mutations in both *BRCA* and *PARP1* genes do not result in lethality.[55] Instead, it is the trapping of PARP on DNA after its inhibition that confers lethality to HRD. Nevertheless, the potential of SL as an anticancer strategy still holds true, and screens for novel SL interactions have identified numerous opportunities within the DDR (Fig 2).[63-66] For example, POLQ required for MMEJ is upregulated and acts as a backup in cells lacking HRR. Consequently, POLQ inhibition in cancer cells lacking HRR (eg, in *BRCA*-mutated cells) results in SL via a mechanism distinct from PARP inhibition.[50,67] Loss of RNASEH2B in metastatic prostate cancer and chronic lymphocytic leukemia increases PARP-trapping DNA lesions, offering another therapeutic target on the basis of SL.[68]

Future DDR Treatment Strategies

The clinical validation of tumor killing induced by PARP inhibitors in BRCA-deficient cancers highlights the importance of investigating other DDR deficiencies to help overcome resistance to current therapies. DDR integrates the regulation of cell-cycle progression and DNA repair, allowing time for repair and preventing permanent DNA damage.[54] DDR inhibitors are being developed against two classes of molecules involved in DNA damage signaling and DNA repair (Fig 3). ATM, ATR, DNA-PKcs, CHK1, CHK2, and WEE1 are protein kinases that respond to different types of DNA damage and/or regulate specific cell-cycle transitions. ATM and DNA-PKs are recruited to DSBs and execute checkpoint signaling and DNA repair, respectively. ATR is activated by replication stress, where it facilitates fork stabilization and restart. CHK1 and CHK2 are effector kinases that function downstream of ATR and ATM, respectively. WEE1 is a classic checkpoint kinase that negatively regulates entry into mitosis. RAD51 and POLQ are directly involved in the DSB repair processes of homologous recombination and MMEJ, respectively. Poly (ADP-ribose) glycohydrolase (PARG) is an enzyme that catabolizes poly (ADP)ribose chains generated by the PARP family of enzymes. Compounds targeting some of these molecules are already in clinical development in settings of either HRD cancers or in combination with chemotherapies and targeted agents (Table 3). As monotherapy, the efficacy of DDR inhibitors will depend on selected genetic backgrounds for DDR dependency, such as ATR inhibition in ATM-deficient tumors, WEE1 inhibition in cyclin E or MYC-amplified tumors, or POLQ inhibitors in HRD or NHEJD tumors. Abrogation of the G2/M checkpoint by CHK1/2 and WEE1 inhibitors is currently being tested in clinical trials in combination with chemotherapy. As expected, efficacy as part of combination therapy will depend on identifying the timing and dosing regimen with the combination partner, limiting toxicities and maintaining a beneficial therapeutic index.

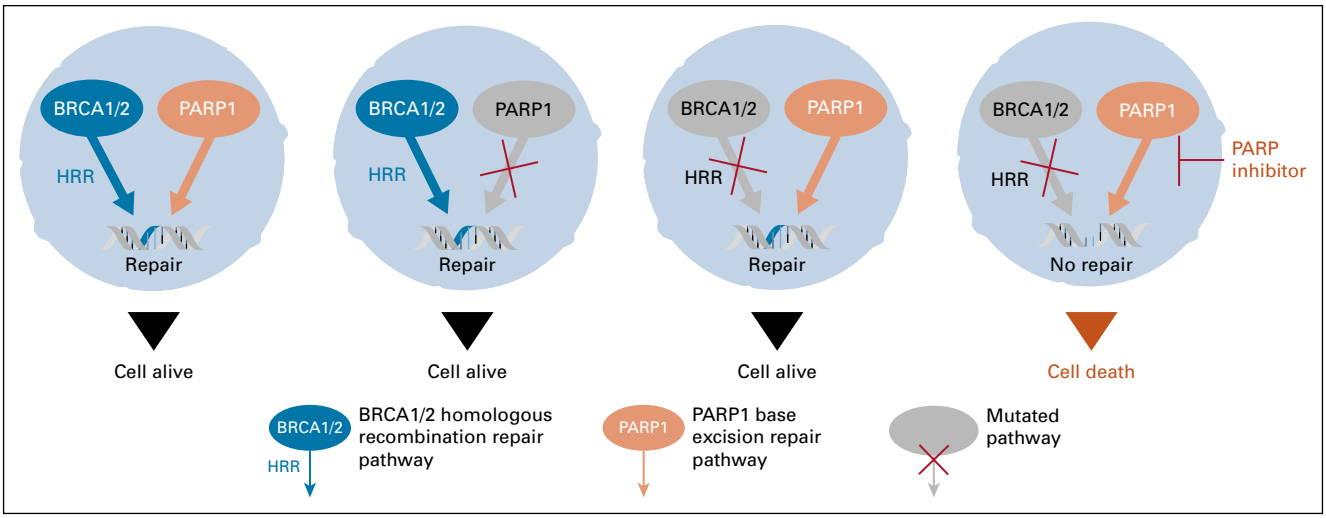

FIG 2. Induction of cell death in BRCA-deficient cancer cells. Trapping of poly (ADP-ribose) polymerase (PARP) on DNA after its inhibition confers lethality to homologous recombination repair (HRR)-deficient cells. This concept has been exploited in the clinic and can be applied to other molecules in the DNA damage response (DDR) pathway.

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TABLE 3. Compounds Targeting DDR in Clinical Development (other than PARP1/2 inhibitors)

DDR Target	Compound Name	Company Name	Highest Development Stage (phase)	Indication
CHK1/2	CBP-501	CanBas	II	Non–small-cell lung cancer
	Prexasertib	Eli Lilly	II	SCLC, ovarian cancer, triple-negative breast cancer, metastatic castrate-resistant prostate cancer
	GDC-0575	Genentech	I	Solid tumors
	SRA-737	Sierra Oncology	I	Solid tumors
WEE1	AZD-1775	AstraZeneca	II	SCLC, squamous cell lung cancer, ovarian cancer, triple-negative breast cancer, advanced acute myeloid leukemia or myelodysplastic syndrome, gastric cancer, head and neck cancer, pancreatic cancer
ATR	AZD-6738	AstraZeneca	I	Various solid malignancies
	M-4344	Merck KGaA	I	Various solid malignancies
	M6620 (VX-970)	Merck KGaA	II	Various solid malignances
DNA-PK	CC-115	Celgene	II	Glioblastoma
	LY-3023414	Eli Lilly	II	SCLC, endometrial cancer, prostate cancer, pancreatic cancer, lymphoma
	AsiDNA	Onxeo SA	I	Various solid malignancies
	M-3814	Merck KGaA	I	Various solid malignancies
ATM	AstraZeneca	AZD-0156	I	Various solid malignancies

Abbreviations: ATM, ataxia-telangiectasia mutated; ATR, ATM- and Rad3-related; DDR, DNA damage response; DNA-PK, DNA-dependent protein kinase; PARP, poly (ADP-ribose) polymerase; SCLC, small-cell lung cancer.

ATM inhibition sensitizes cells to ionizing radiation and to DSB-inducing agents.[69] The ATM inhibitor AZD0156 is being tested in a multiarm phase I trial as monotherapy and in combination with cytotoxic chemotherapies or PARP inhibitors (ClinicalTrials.gov identifier: NCT02588105). For ATR, a synthetically lethal interaction has been established with CHK1 inhibition, making ATR an attractive DDR target.[70] Multiple phase I studies are ongoing to investigate ATR inhibitors in the clinical setting for advanced cancers. CHK1 and CHK2 kinase inhibitors, which function downstream of ATM and ATR, seem to act synergistically with agents that generate replication stress.[71]

Inhibition of WEE1 potentiates the cytotoxic effects of numerous DNA-damaging drugs as a single agent.[72] In a phase I trial, AZD1775 in combination with chemotherapy showed superior response rates in *TP53* mutated (21%) compared with patients with *TP53* wild-type disease (12%).[73] Data from the phase II trial of AZD1775 in combination with carboplatin showed an ORR of 43% and a median PFS and OS of 5.3 months and 12.6 months, respectively, in patients with relapsed/refractory *TP53*-mutated ovarian cancer who had previously received first-line platinum plus paclitaxel-based therapy.[74] A separate randomized phase II trial of AZD1775 plus paclitaxel and carboplatin in patients with *TP53*-mutated ovarian cancer reported a significant increase in PFS by independent central review with AZD1775 plus paclitaxel-carboplatin versus paclitaxel alone, with a median PFS of 34.1 versus 31.9 weeks, respectively (HR, 0.63; 95% CI, 0.38 to 1.06).[75] Several clinical trials of AZD1775 are ongoing; these may better define the subpopulation of patients responding to AZD1775 monotherapy and combination regimens.

Effective repair by NHEJ relies on the activity of DNA-PKcs throughout all phases of the cell cycle. DNA-PK inhibition sensitizes cells to DSB-inducing agents, such as radiotherapy and topoisomerase II inhibitors.[76] A number of novel DNA-PK inhibitors have recently entered clinical development, as monotherapy, in combination with radiotherapy or liposomal doxorubicin, or using a dual inhibitor of DNA-PK and mammalian target of rapamycin.[77]

POLQ is required for MMEJ (alt-NHEJ), which is upregulated in many cancers promoting error-prone repair and potentially cancer evolution. POLQ-dependent MMEJ repair is particularly important in HRR-deficient cancers (eg, *BRCA1/2*-mutated tumors). Preclinical studies have shown that POLQ deficiency is synthetically lethal with BRCA, ATM, Ku, 53BP1, and FA pathway mutations, and that inhibitors may be effective as single agents, in combination with PARP inhibitors or platinum compounds.[78] POLQ deficiency also radiosensitizes tumors[78] and potentially offers an improved therapeutic index compared with DNA-PKcs or ATM inhibitors, because it is not expressed in normal cells.[79] POLQ small-molecule inhibitors are currently in preclinical development (Artios Pharma, Cambridge, UK; Repare Therapeutics, Boston, MA).

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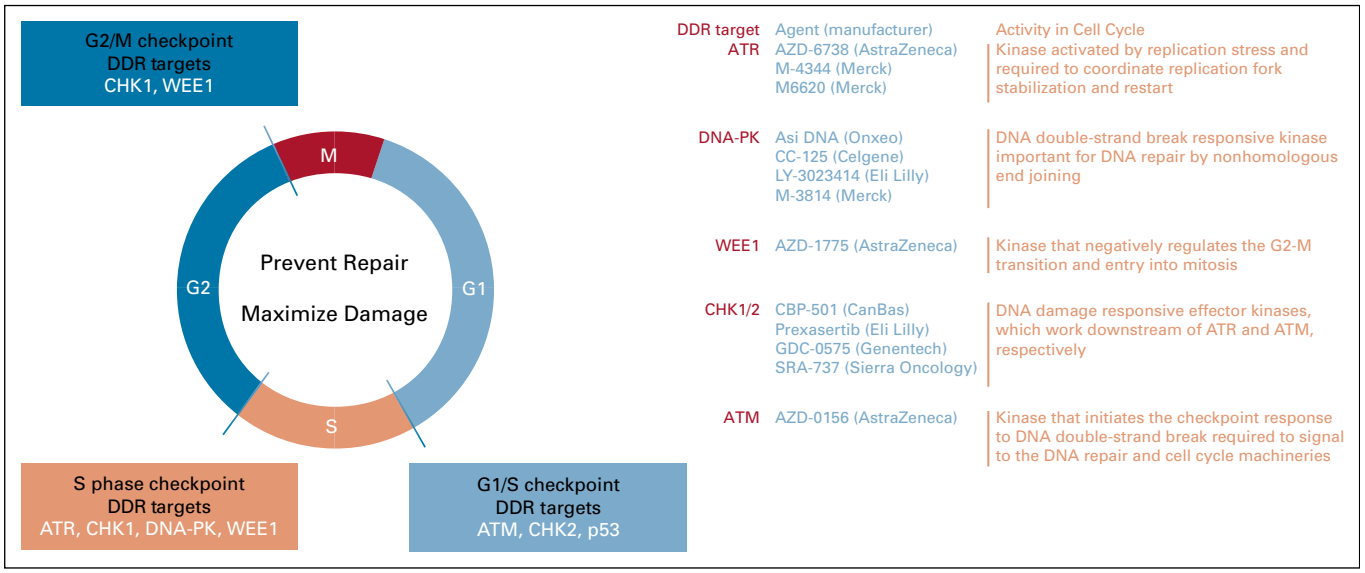

FIG 3. The cell-cycle and potential DNA damage repair (DDR) targets for use in cancer therapy. The three key cell-cycle checkpoints, G1/S-phase, S-phase, and G2/M, and associated proteins are being targeted by small-molecule inhibitors in clinical trials (top right list). Cancer cells have increased susceptibility to S-phase–induced DNA damage that in turn may lead to either replication catastrophe or apoptosis (unsustained levels of S-phase DNA damage) or mitotic catastrophe (double-strand breaks carried into mitosis). ATM, ataxia-telangiectasia mutated; ATR, ATM- and Rad3-related; DNA-PK, DNA-dependent protein kinase.

PARG catalyzes the hydrolysis of poly (ADP-ribose) and therefore reverses the effects of PARP, removing PAR chains. Inhibition of PARG, in a similar fashion to PARP inhibition, leads to DNA damage that depends on HRR for repair.[80] PARG inhibitors are in development (Ideaya BioSciences, San Francisco, CA), offering an additional clinical opportunity of SL with *XRCC1* mutations that compromise SSB repair.[81]

Inhibitors of RAD51 are also being developed (Cyteir Therapeutics, Lexington, MA) to exploit the SL of the activation-induced cytidine deaminase (AID)-RAD51 axis.[82] RAD51 inhibition has been shown in preclinical studies to potently activate AID-induced cytotoxicity and to selectively induce cell death in AID-expressing cancer cells.[83]

The increasing understanding of the DDR network is leading to many novel therapeutic opportunities. As a cautionary aspect, the knowledge of the therapeutic window and biomarkers of all mentioned inhibitors, including PARP inhibitors, remains limited.

Opportunities for Combination Therapy With DDR-Targeting Compounds

The multiple biologic functions of DDR-related molecules underscore the rationale for combination treatment with other therapies, including PARP inhibitors. The primary challenge is the development of overlapping toxicities versus the therapeutic index. In terms of combination therapy, an interesting concept to explore is sequential treatment with DDR inhibitors rather than a standard, parallel combination approach—first induce vulnerability and then prompt selective killing of the targeted tumor cells.

Combination therapy with other DDR-targeting agents possibly provides the most rational option. Several trials are already under way, including a phase II study of olaparib plus AZD6738 (ATR inhibitor; ClinicalTrials.gov identifier: NCT02264678), a phase Ib study of olaparib plus AZD1775 (WEE1 inhibitor; ClinicalTrials.gov identifier: NCT02511795), and a phase II study assessing either ATR or WEE1 in combination with olaparib versus olaparib monotherapy in triple-negative breast cancer (TNBC; VIOLETTE; ClinicalTrials.gov identifier: NCT03330847). Other approaches include combinations with angiogenesis inhibitors, although the rationale for synergy of such combinations is poorly understood. In a phase II study of cediranib, an inhibitor of vascular endothelial growth factor receptor tyrosine kinases, combined with olaparib versus olaparib alone in recurrent platinum-sensitive ovarian cancer, improved PFS in the combination arm, with a significant differential benefit in patients with *BRCA* wild-type disease relative to those with known deleterious *BRCA1/2* mutations.[84] Additional trials are ongoing in patients with relapsed platinum-sensitive ovarian cancer: niraparib plus bevacizumab (a monoclonal antibody against human vascular endothelial growth factor) in the phase I/II AVANOVA trial (ClinicalTrials.gov identifier: NCT02354131); olaparib plus cediranib in the maintenance setting in the phase III ICON9 (ClinicalTrials.gov identifier: NCT03278717) and NRG-GY004/005 (ClinicalTrials.gov identifier: NCT02446600) trials; and in the first-line setting (olaparib plus bevacizumab in the phase III PAOLA-1 study; ClinicalTrials.gov identifier: NCT02477644).

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Combining DDR inhibitors with immunotherapy offers another rational and timely combination approach. PARP inhibitors have been shown to upregulate programmed death-ligand 1 (PD-L1) expression and enhance tumor-associated immunosuppression.[85] Furthermore, *gBRCA1*-mutated tumors show increased levels of lymphocyte infiltrates and neo-antigen expression.[86] In the phase I/II MEDIOLA trial (ClinicalTrials.gov identifier: NCT02734004), in the patient cohort with relapsed, platinum-sensitive, *BRCA*-mutated ovarian cancer, the combination of olaparib with durvalumab (a monoclonal antibody directed against PD-L1) showed good tolerability, with an ORR of more than 70% (including six complete responses).[87] The recently launched DORA study (ClinicalTrials.gov identifier: NCT03167619) is a randomized phase II study of olaparib alone versus olaparib plus durvalumab as a maintenance strategy after response to four cycles of first- or second-line platinum therapy in metastatic TNBC.[88] Another trial (TOPACIO/KEYNOTE-162; ClinicalTrials.gov identifier: NCT02657889) of niraparib combined with pembrolizumab (a monoclonal antibody that blocks the programmed death-1 receptor) in patients with advanced TNBC or recurrent ovarian cancer reported an ORR of 25% in all evaluable patients and 45% in patients with t*BRCA* mutations.[89] In the first-line setting, phase III trials combining PARP inhibitor maintenance with immune checkpoint inhibitors include FIRST (niraparib plus TSR042 [an anti–programmed death-1 antibody]; ClinicalTrials.gov identifier: NCT03602859); DUO-O (olaparib plus durvalumab; ClinicalTrials.gov identifier: NCT03737643); ATHENA (rucaparib plus nivolumab; ClinicalTrials.gov identifier: NCT03522246); JAVELIN ovarian 100 PARP (talazoparib plus avelumab [an anti PD-L1 antibody]; ClinicalTrials.gov identifier: NCT03642132); and the MK-7339-001/ENGOT-ov43 trial (olaparib plus pembrolizumab; ClinicalTrials.gov identifier: NCT03740165).

OVERCOMING CHALLENGES IN DDR INHIBITION

The molecular heterogeneity among ovarian cancers associated with *BRCA* mutations is well established. In addition, higher mutational load and better response to platinum were reported in high-grade serous ovarian cancers with *BRCA2* mutations compared with *BRCA1* mutations.[90] Data from The Cancer Genome Atlas Research Network has shown that ovarian cancers with *BRCA1* promoter hypermethylation do not display the same platinum sensitivity as *BRCA1/2*-mutated ovarian cancers.[14] Understanding the differences between the mechanisms of action for different PARP inhibitors and the influence of specific *BRCA* mutations on their effectiveness will also be important to support the future development of DDR inhibitors.

Resistance mechanisms extend beyond PARP inhibitors and will remain a challenge for the development of novel DDR-inhibitor therapies. DDR deficiencies are common across multiple cancers, and targeting them has already been shown to be effective in the clinic, with a subset of patients experiencing long-term benefit after treatment with DDR inhibitors in clinical trials. Rational combinations will also be found for the treatment of patients with non–HRR-deficient disease, ultimately tailoring DDR-targeting agents for specific patient populations and for specific innate and acquired mechanisms of resistance.

Key questions for the near future include defining the genetic and epigenetic level of HRD, how to incorporate predictive biomarkers of HRD and PARP inhibitor sensitivity, such as functional assays or mutational HRD signatures, into clinically relevant platforms, and how the molecular heterogeneity within tumors affect treatment regimens and resistance mechanisms. Can these be captured in clinically relevant assays?

Finally, the optimal treatment sequence of DDR inhibitors with chemotherapy or other agents is still being determined. However, the recent positive results from the SOLO-1 trial, showing that in the first-line setting, maintenance therapy with olaparib after platinum-based chemotherapy provided a substantial PFS benefit compared with placebo, suggests that moving PARP inhibitors/DDR agents earlier in the treatment course may be appropriate for certain patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Moving From Poly (ADP-Ribose) Polymerase Inhibition to Targeting DNA Repair and DNA Damage Response in Cancer Therapy

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APPENDIX

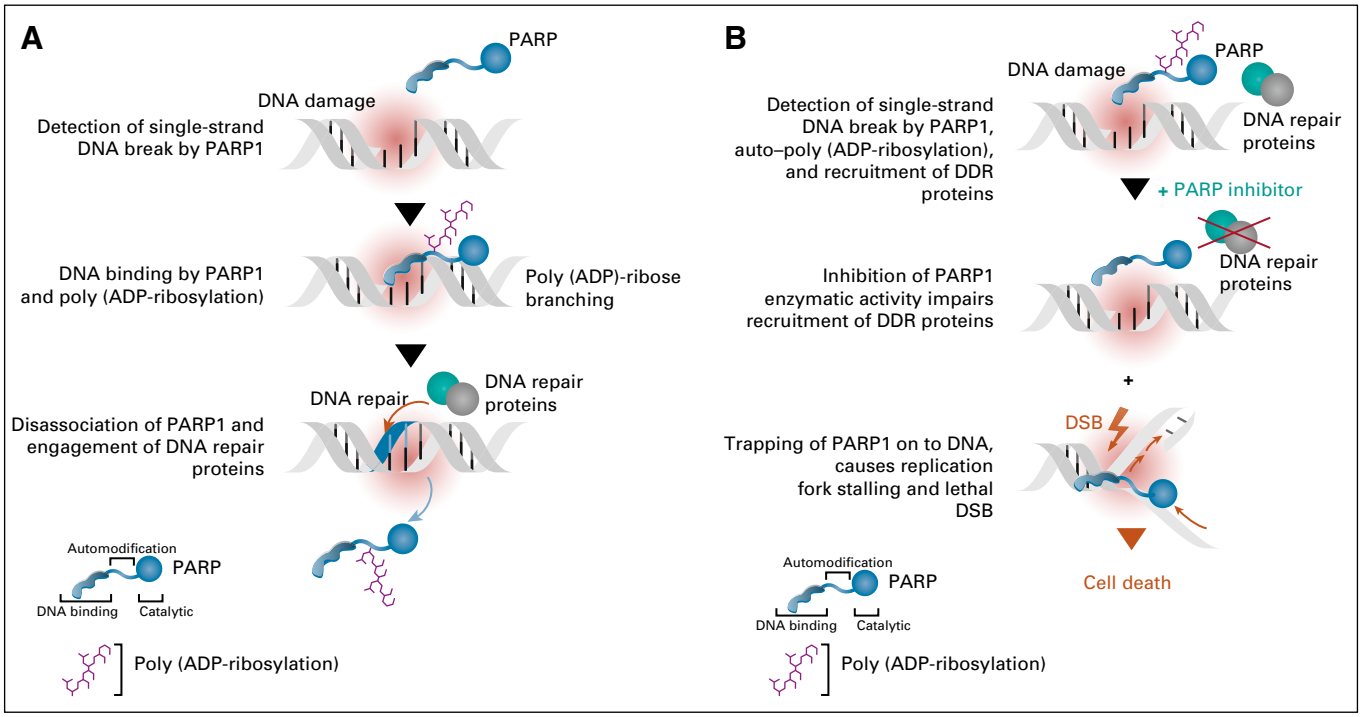

FIG A1. PARP function in DNA repair and mechanism of pharmacological PARP inhibition. (A) At the molecular level, DNA damage (break) is detected by PARP1 via its DNA binding domain, triggering its activation (formation of homodimer) and cleavage of nicotinamide adenine dinucleotide (NAD+) generating nicotinamide and ADP-ribose. Successive addition of ADP- ribose units leads to the formation of long and branched chains of poly (ADP-ribose) (PAR), covalently attached to acceptor proteins, including histones and other DNA repair proteins, resulting in PAR polymers adjacent to the DNA breaks. These highly negatively charged polymers form a scaffold that recruits critical proteins for DNA repair. (B) PARP inhibitors act not only by inhibiting the enzymatic activity but also by trapping PARP on DNA; the latter presenting a physical obstacle to the replication machinery. To resolve the PARP-DNA interaction Homologous Recombination Repair (HRR) is necessary. Therefore, in HRR-deficient cancer cells trapped PARP results in replication fork collapse and ultimately cell death. DDR, DNA damage response; DSB, double-strand break; PARP, poly (ADP-ribose) polymerase.

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TABLE A1. PARP Inhibitor Approvals and Their Ovarian and Breast Cancer Indications

Product	Approval Indication
Olaparib	EMA (Dec 2014): as monotherapy for maintenance treatment of patients with platinum-sensitive, relapsed, BRCA-mutated (germline and/or somatic), high-grade serous ovarian cancer who are in response (complete or partial) to platinum-based chemotherapy.
	FDA (Dec 2014): treatment of patients with germline BRCA1/2 mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy (capsule formulation).
	FDA (Aug 2017): maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy (tablet formulation).
	FDA (Jan 2018): adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.
Rucaparib	FDA (Dec 2016): treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated with advanced ovarian cancer who have been treated with two or more chemotherapies (patient selection using an FDA-approved companion diagnostic for rucaparib).
	FDA (Apr 2018): maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer for patients who are in a complete or partial response to platinum-based chemotherapy.
	EMA (May 2018): treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA-mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more prior lines of platinum-based chemotherapy and who are unable to tolerate additional platinum-based chemotherapy.
Niraparib	FDA (Mar 2017): maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, whose tumors have a complete or partial response to platinum-based chemotherapy.
	EMA (Nov 2017): maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.
Talazoparib	FDA (Oct 2018): treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative, locally advanced, or metastatic breast cancer (patient selection using an FDA-approved companion diagnostic for talazoparib).

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase.

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