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REVIEW

Trial watch – inhibiting PARP enzymes for anticancer therapy

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ABSTRACT

Poly(ADP-ribose) polymerases (PARPs) are a members of family of enzymes that catalyze poly(ADP-ribosyl)ation (PARylation) and/or mono(ADP-ribosyl)ation (MARylation), two post-translational protein modifications involved in crucial cellular processes including (but not limited to) the DNA damage response (DDR). PARP1, the most abundant family member, is a nuclear protein that is activated upon sensing distinct types of DNA damage and contributes to their resolution by PARylating multiple DDR players. Recent evidence suggests that, along with DDR, activated PARP1 mediates a series of prosurvival and proapoptotic processes aimed at preserving genomic stability. Despite this potential oncosuppressive role, upregulation and/or overactivation of PARP1 or other PARP enzymes has been reported in a variety of human neoplasms. Over the last few decades, several pharmacologic inhibitors of PARP1 and PARP2 have been assessed in preclinical and clinical studies showing potent antineoplastic activity, particularly against homologous recombination (HR)-deficient ovarian and breast cancers. In this Trial Watch, we describe the impact of PARP enzymes and PARylation in cancer, discuss the mechanism of cancer cell killing by PARP1 inactivation, and summarize the results of recent clinical studies aimed at evaluating the safety and therapeutic profile of PARP inhibitors in cancer patients.

Abbreviations: ATM, ataxia telangiectasia mutated; BER, base excision repair; BRCA1, breast cancer 1 early onset; BRCA2, breast cancer 2 early onset; DDR, DNA damage response; DSBs, double-strand breaks; FDA, Food and Drug Administration; GI, gastrointestinal; HER, human epidermal growth factor receptor; HR, homologous recombination; MAR, mono(ADP-ribose); NAD^+, nicotinamide adenine dinucleotide; NER, nucleotide excision repair; NHEJ, non-homologous end joining; ORR, overall response rate; PAR, poly(ADP-ribose); PARG, poly(ADP-ribose) glycohydrolase; PARP, poly(ADP-ribose) polymerase; PARylation, poly(ADP-ribosyl)ation; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; Polθ, polymerase (DNA directed) theta SSB, single-strand break; TNBC, triple negative breast carcinoma; VEGF, vascular endothelial growth factor; WGR, tryptophan (W) glycin (G) and arginine (R) domain; Zn, zinc finger domain

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Introduction

Poly(ADP-ribosyl)ation (PARylation) is a post-translational protein modification that is catalyzed by members of the poly(ADP-ribose) polymerase (PARP) enzyme family (i.e., PARP1, PARP2, tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase [TNKS] and TNKS2) and has crucial functions in multiple physiologic and pathologic processes.[1,2] This modification involves the covalent addition of a linear or multibranched polymer of ADP-ribose units from the respiratory co-enzyme nicotinamide adenine dinucleotide (NAD^+) to DNA or multiple acceptor proteins involved in cellular processes as diverse as DNA damage, DNA replication, DNA transcription, differentiation, gene regulation, protein degradation, and mitotic spindle maintenance.[3-5] However, most members of the PARP family, which includes 17 identified enzymes to date, catalyze the covalent attachment of ADP-ribose onto acceptor proteins as a monomer (mono(ADP-ribose), MAR) instead of a polymer (PAR) (reviewed in ref. 6).[6] This prompted some authors to suggest the use of ADP-ribosyltransferase (ARTD) as an official unifying name for this family.[7] A complete overview of functions of the PARP family can be found in several reviews.[1,2,8-16]

PARylation is considered to be a key step in the DNA damage response (DDR), a complex signal transduction pathway that is triggered in response to DNA lesions and is fundamental for the preservation of genomic stability.[17-21] To date, PARP1, PARP2, and PARP3 are the only family members that have been shown to contribute to DDR by promptly detecting and repairing DNA damage,[7,10,15,22] with PARP1 being responsible for the resolution of up to 90% of the lesions.[3,4,23] PARP1, the most abundant isoform of the PARP enzyme family, is a nuclear protein that acts as a sensor of both single-strand breaks (SSBs) and double-strand breaks (DSBs),[24,25] and thereby participates in a variety of DNA damage repair pathways, including base excision repair (BER),[26-31] nucleotide excision repair (NER),[32,33] non-homologous end joining (NHEJ),[29,34,35] and homologous recombination (HR).[36-39]

PARP1 contains 6 functional domains: 3 amino (N)-terminal homologous zinc finger (Zn) domains, 2 of which (Zn1 and Zn2)

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are responsible for DNA damage detection whereas the third (Zn3) couples DNA binding and catalytic activity; 2 central domains, the breast cancer 1, early onset (BRCA1) C-terminal (BRCT) region and the tryptophan, glycine, and arginine (WGR) module, both of which are involved in protein-protein interactions; and carboxy (C)-terminal catalytic domain, which sequentially transfers ADP-ribose subunits from the donor NAD^+ to acceptor proteins.[5,24,40]

Soon after the appearance of DNA lesions, such as SSBs, DSBs, DNA crosslinks, and stalled replication forks, PARP1 engages at the site of damage.[8,15,41] The currently accepted model postulates that the binding of PARP1 to damaged DNA via the 3 N-terminal Zn domains induces a conformational rearrangement in the WGR domain, which in turn leads to activation of the catalytic domain.[8,40,42] Of note, the catalytic activity of PARP is allosterically enhanced 10- to 500-fold within 15 to 30 s of DNA binding. The activation of PARP results in massive synthesis and covalent conjugation of long linear and branched PAR chains (PAR polymers) on several proteins surrounding the DNA lesions, including nucleosomal/linker histones, topoisomerase I, and PARP1 itself.[3,43-45]

PARylation contributes to DNA damage repair at multiple levels. First, the increased amount of negative charge carried by PAR polymers induces extensive chromatin relaxation at the damaged site.[46,47] Second, once formed, PAR polymers are recognized by a panoply of proteins (PAR-binding proteins) via one of the 4 PAR-binding domains identified so far (reviewed in ref. 6).[6] This PAR-mediated recruitment contributes to chromatin remodeling and sets the stage for DNA repair.[27,28,48-54] Third, the formation of PAR polymers diminishes the affinity of PARP1 and histones for DNA, providing a mechanism for removing PARP1 from damaged DNA and restoring chromatin compaction.[55-57] Furthermore, polymer growth is also antagonized by 2 enzymes that hydrolyze PAR, poly(ADP-ribose) glycohydrolase (PARG) and ADP-ribosylhydrolase like 2 (ADPRHL2, best known as ARH3).[58,59] Of note, O-acyl-ADP-ribose deacylase 1 (OARD1, best known as TARG1) is believed to be responsible for removal of the terminal ADP-ribose monomer.[60] The concerted action of these enzymes removes PAR polymers from PARP1, restoring its ability to recognize DNA strand breaks and initiate a new round of damage signaling.

Recent evidence indicates that PARylation by this arsenal of enzymatic tools not only contributes to the repair of potentially deleterious alterations in the structure of DNA but also drives cell fate decisions in response to a variety of extrinsic and intrinsic perturbations.[14] Indeed, the roles of PARP1 in the cell span from maintaining life to inducing metabolic death (termed parthanatos).[61-64] Moreover, PARP hyperactivation (for instance during DDR) may deplete intracellular stores of NAD^+ thus undermining NAD^+-dependent processes, including (but not limited to) glucose metabolism,[3,41] and/or leading to bioenergetic catastrophe and cell death.[3,41,65,66]

Given their contribution to DDR, PARP enzymes, and in particular PARP1, have been extensively evaluated as targets for anticancer therapy. The large wave of preclinical and clinical studies launched during the last decade has highlighted the therapeutic benefit of PARP1/2 inhibitors, especially in cancers bearing mutations in components of DNA damage repair pathways, including (but not limited to) the HR players *BRCA1* and *BRCA2*. On the basis of these observations, the US Food and Drug Administration (FDA) approved for the first time the PARP inhibitor olaparib for patients with *BRCA*-mutated ovarian cancers who have had at least 3 lines of therapy (http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm427598.htm) and granted the designation of breakthrough therapy to the PARP inhibitor rucaparib for the treatment of women with BRCA-mutated advanced ovarian cancer who have received at least 2 prior lines of platinum-based chemotherapy (http://www.fda.gov/).

As part of our Trial Watch series,[67,68] here we describe the contribution of PARP to cancer and discuss preclinical and clinical investigations assessing the therapeutic use of PARP inhibitors for cancer therapy.

PARP activity and cancer

The precise effect of PARP enzymes and PARylation on tumorigenesis is complex and not yet fully elucidated. Some observations, including the high rate of spontaneous genomic instability of *Parp-1*$^{-/-}$ and *Parp-2*$^{-/-}$ cells,[69-72] seem to suggest an oncosuppressive role of PARP1 and PARP2. Nevertheless, *Parp-1*$^{-/-}$ and *Parp-2*$^{-/-}$ mice demonstrate, respectively, a modest incidence/long latency[73,74] or the absence[71,72] of spontaneous tumor development, suggesting the existence of compensatory mechanisms acting in the absence of one of these enzymes.[75] In both knockout models, however, the absence of PARP1 or PARP2 rendered mice sensitive to DNA damaging agents, including alkylating compounds and ionizing radiation.[72] Moreover, the simultaneous deletion of transformation related protein 53 (*Tp53*) in *Parp1*$^{-/-}$ and *Parp2*$^{-/-}$ mice[69,71,73] or of protein kinase, DNA activated, catalytic polypeptide (*Prkdc*, best known as *DNAPk*) in *Parp1*$^{-/-}$ mice[76] promoted or accelerated spontaneous tumor development. Of note, *Parp1*$^{-/-}$ mice displayed accelerated aging and an shortened life span[77] as well as an altered hypoxic response,[78] whereas mice with double knockout of *Parp1* and *Parp2*,[72,79] *Parp1* and ataxia telangiectasia mutated (*Atm*),[80] *Parp1* and X-ray repair complementing defective repair in Chinese hamster cells 5 (*Xrcc5*, best known as *Ku80*),[74] or *Parp2* and *Atm*[81] presented early embryonic lethality. Also, despite some contrasting observations,[82,83] a large body of evidence suggests an increased susceptibility to mutation and/or carcinogen-induced tumorigenesis in mice carrying a homozygous deletion of the gene encoding PARP1[74,77,84-90] or PARP4.[91] A similar effect was also found in *Parg*$^{-/-}$ mice (lacking poly (ADP-ribose) glycohydrolase) treated with diethylnitrosamine[92] suggesting the importance of a balanced level of PAR for maintaining genomic stability.

Along with its role in suppressing tumorigenesis, PARP1 activity also seems to be required for cancer cell survival. Mutations of *PARP1* are in fact quite rare in cancer, even though single-nucleotide polymorphisms of the gene encoding *PARP1*, including V762A, have been associated with an increased risk of human cancers.[93-100] On the contrary, upregulation of the expression of *PARP1* and/or an increased level of PAR has been found in multiple cancer cell lines as well as in samples from patients affected by tumors of different origins, including the blood,[101,102] breast,[103-106] cervix,[107] colon,[108-112] endometrium,[103,113] liver,[114] lung,[103,115] ovary,[101,103,116-118]

prostate,[119-121] and skin.[122,123] Overexpression or overactivation of PARP enzyme has also been observed in Ewing sarcoma,[124,125] glioblastoma,[126,127] meningiomas of higher grade,[128] and laryngeal cancer.[129] Importantly, in some of these settings PARP deregulation has been linked to malignant transformation,[103,105,110,112,119,121,123] tumor aggressiveness,[9,116,122,128,130] and poor survival or resistance to therapy.[105,116,117,130]

Taken together, these findings indicate that PARP activity has a dual role in cancer, acting as a barrier against tumorigenesis (presumably by contributing to the preservation of genome stability) and promoting survival once the tumors have established.

PARP1 in cancer therapy

The idea of employing PARP1 inhibitors as antineoplastic agents stems from the early 1980s, and seminal work by Sydney Shall's group.[4] Since then, multiple companies have begun to invest in the strategic development of specific PARP1 inhibitors. On theoretical grounds PARP1 may be indirectly inhibited by depleting NAD^+, the substrate of PARylation.[131] Nonetheless, the use of pharmacologic inhibitors of the catalytic activity of PARP1 and PARP2 (hereafter referred to as PARP inhibitors for the sake of simplicity), including olaparib (also known as AZD2281),[132] rucaparib (also known as AG-014699),[133] veliparib (also known as ABT-888),[134] niraparib (also known as MK-4827),[135] iniparib (also known as BSI-201),[136-138] CEP-9722 (the pro-drug of CEP-8983),[139] E7016 (also known as GPI21016),[140] and INO-1001,[141] has been the most widely explored approach in the context of cancer therapy.[6,12,16,75,142-147]

Over the last 40 years, 2 major antineoplastic strategies have been pursued, both based on the role of PARP1 in repairing DNA lesions. In the first approach, PARP inhibitors are given in combinatorial regimens to sensitize tumor cells to conventional DNA damaging therapy. A wide range of preclinical studies showing the activity of PARP inhibitors in boosting the tumor killing effects of alkylating agents, topoisomerase I poisons, and ionizing radiation, either *in vitro* in tumor cell lines or *in vivo* in human tumor xenografts, support the validity of this approach (reviewed in ref. 146, 148, 149),[146,148,149]) even though the off-target and toxic effects of some of these combinations are slowing their further progression into clinical use (see below). In the second approach, the abrogation of PARP enzymatic activity is used to target tumor cells with a specific and pre-existing genomic defect in the mechanism of DNA repair. The rationale of this strategy, which is based on synthetic lethality (a concept first described by Dobzhansky in 1946[150] that was at the time a novelty in cancer therapy), is that cell killing occurs only if 2 conditions (e.g., the simultaneous inhibition or ablation of 2 cellular pathways) are combined whereas neither by itself is sufficient to affect viability. Evidence of the feasibility and efficacy of this synthetic lethality approach was first provided in 2005, when 2 seminal articles that were simultaneously published provided strong evidence that PARP inhibitor monotherapy efficiently depleted cancer cells with dysfunctional *BRCA1* and *BRCA2*.[151,152] In these settings, PARP inhibitors as a standalone therapeutic intervention for tumors with specific mutations in HR also displayed limited off-target toxicity and potential tumor specificity. Besides killing BRCA-mutant cancers, PARP inhibitors have also been shown to be synthetically lethal with a variety of other HR dysfunctions, thus extending the potential patient population that may benefit from these agents.[23,153-163] This phenomenon, named "BRCAness," includes deficiency in DDR players such as *ATM* in T-cell pro-lymphocytic leukemia, B-cell chronic lymphocytic leukemia, mantle cell lymphoma, and breast cancer;[156,157,159,164,165] in checkpoint kinase 2 (*CHEK2*, best known as *CHK2)* in sarcoma, breast cancer, ovarian cancer, and brain tumors;[166] in phosphatase and tensin homolog (*PTEN*) in glioblastoma as well as prostate, lung, and endometrial cancers;[167-171] and in meiotic recombination 11 homolog A (*MRE11A*) in colorectal cancer and myeloid malignancies.[172-174] Of relevance in the context of cancer therapy, basal-like triple negative breast cancers (TNBCs), an aggressive subtype of breast cancer frequently associated with poor prognosis,[175] are believed to have a BRCAness phenotype and thus might be targeted by PARP inhibitors.[176-181] Recent evidence suggests a predictive role of polymerase (DNA directed) theta (Polθ, also known as POLQ); a DNA polymerase involved in the error-prone alternative non–homologous end joining [alt-NHEJ] DNA repair) in the response of HR-deficient tumors to PARP inhibitors.[182] In particular, it has been reported that HR-deficient ovarian tumors overexpress POLQ and rely on POLQ-mediated repair for their survival.[182] In this study, depletion of POLQ enhanced the killing effect of PARP inhibitors in HR-deficient cells.[182] This result together with evidence that PARP1 recruits POLQ to DSBs,[183] highlight a role of PARP activity in alt-NHEJ. Further supporting the use of PARP inhibitors in HR-impaired tumors, inhibition of phosphatidylinositol 3-kinases (PI3K) or cyclin-dependent kinase 1 (CDK1) has been reported to sensitize BRCA-proficient cancer to PARP inactivation by affecting BRCA1/2 expression[184-186] or function,[187] respectively. Moreover, recent observations in BRCA1-deficient mice seem to suggest a cancer chemopreventive effect of PARP inhibitors,[188] although clinical confirmation is required. Also, high PAR levels are reported to predict the response to PARP inhibitors.[189-191]

An intense wave of investigations is underway to elucidate the precise mechanism underlying the synthetic lethality of PARP inhibitors in HR-defective tumor cells. Two non-mutually exclusive models postulate that inhibition of the catalytic activity of PARP results in abrogation of BER and the consequent accumulation of SSBs, which, once converted to DSBs during S-phase or upon replication fork collapse, are either left not repaired because of HR impairment[151,152,192] or are managed by the error-prone DSB repair pathway of NHEJ.[193,194] A third model suggests that PARP inhibitors trap PARP1 and PARP2 at the DNA lesion site thereby preventing access of other DDR players and provoking obstruction of the replicative fork.[195,196] In support of this latter model, recent evidence suggests that PARP inhibitors exert killing effects and synergize with the DNA-damaging agent temozolomide primarily by trapping PARP-DNA complexes rather than by inhibiting the catalytic activity of PARP.[197-199]

Taken together, these results indicate that inhibition of PARP activity may be an effective therapeutic strategy for the treatment of a variety of tumors bearing deficiencies in the HR pathway or displaying BRCAness properties.

Clinical investigation of PARP inhibitors

Completed clinical studies

When this Trial Watch was being redacted (March 2015), more than 40 studies had been published aimed at evaluating PARP inhibitors as standalone agents or combined with other chemotherapeutic agents in patients with cancers often harboring *BRCA* mutations or displaying BRCAness (Table 1), sources http://www.ncbi.nlm.nih.gov/pubmed). Of these studies, 24 involved olaparib, 9 veliparib, 2 rucaparib, 1 CEP-9722, 1 INO-1001, and 1 niraparib. In this section we will not discuss results of the studies using iniparib[200-204] because this compound has recently been reported to non-selectively modify cysteine-containing proteins in tumor cells and is therefore probably not a *bona fide* PARP inhibitor.[136,137]

PARP inhibitors as monotherapeutic or maintenance agents

With one single exception, in which serious adverse effects were reported for more than 50% of individuals,[205] in the vast majority of cases olaparib as a single agent was generally well tolerated in cancer patients.[206-216] In these studies, the adverse effects were predominantly low grade and included mild gastrointestinal (GI) symptoms, fatigue, and anemia. Similar low-grade toxic effects were also found for niraparib monotherapy at the maximum tolerated dose of 300 mg/day,[217] whereas some adverse effects, in particular GI symptoms, are reported for veliparib as a single agent.[218]

Preliminary evidence of antitumor activity of olaparib was reported in some phase I trials performed in patients with neoplasms, including ovarian cancer.[206-209] In line with preclinical studies, olaparib monotherapy was particularly effective in cancers harboring *BRCA1* or *BRCA2* mutations;[206,209] an overall clinical benefit rate of 46% was observed in *BRCA1/2*-mutated ovarian cancer, associated with platinum sensitivity.[209] Moreover, in a phase I dose escalation study enrolling 100 patients, niraparib displayed antineoplastic activity in ovarian and breast cancer from *BRCA1* or *BRCA2* mutation carriers as well as in sporadic high-grade serous ovarian, non-small cell lung cancer, and prostate cancer[217] (Table 1).

Table 1. Completed clinical trials testing the therapeutic profile of PARP inhibitors in cancer patients.

Agent	Indication(s)	Phase	Notes	Ref.
CEP-9722	Advanced solid tumors	I	As single agent or combined with temozolomide	264
Iniparib	Brain metastases	II	Combined with irinotecan and paclitaxel	200
	Breast cancer	II	Combined with carboplatin and gemcitabine	203
		III	Combined with carboplatin and gemcitabine	204
	Non-small cell lung cancer	II	Combined with cisplatin and gemcitabine	202
	Uterine cancer	II	Combined with carboplatin and paclitaxel	201
INO-1001	Melanoma	I	Combined with temozolomide	234
Niraparib	Advanced solid tumors	I	As single agent	217
Olaparib	Advanced solid tumors	I	As single agent	206
			As single agent	207
			As single agent	208
			Combined with bevacizumab	249
			Combined with cisplatin and gemcitabine	228
			Combined with dacarbazine	221
			Combined with topotecan	230
		II	As single agent	205
	Breast cancer	I	As single agent	210
			Combined with paclitaxel	255
		II	As single agent	211
	Breast or ovarian cancer	I	Combined with carboplatin	242
			Combined with cediranib	250
		II	As single agent	214
	Ewing sarcoma	II	As single agent	216
	Ovarian cancer	I	As single agent	209
		II	As single agent	212
			As single agent	213
			As single agent	215
			As single agent	219
			Combined with carboplatin and paclitaxel	256
			Combined with cediranib	251
	Pancreatic cancer	I	Combined with gemcitabine	329
	Solid tumors	I	Combined with cisplatin	238
Rucaparib	Advanced solid tumors	I	Combined with temozolomide	265
	Melanoma	II	Combined with temozolomide	237
Veliparib	Advanced solid tumors	I	Combined with low-dose fractionated whole abdominal radiation	262
	Advanced solid tumors or lymphomas	0	As single agent	330
		I	Combined with cyclophosphamide	261
			Combined with topotecan	231
	Brain metastases	I	Combined with whole brain radiation therapy	263
	CNS tumors	I	Combined with temozolomide	233
	Ovarian, fallopian tube or peritoneal cancer	I	Combined with cyclophosphamide	266
		II	As single agent	218
	Prostate cancer	Pilot study	Combined with temozolomide	260
	Uterine cancer	I/II	Combined with filgrastim and topotecan or pegfilgrastim	232

*sources: http://www.ncbi.nlm.nih.gov/pubmed, searching with the following terms: "PARP AND cancer AND patient" or "PARP1 AND cancer AND patient" or "NAME OF THE COMPOUND (e.g., olaparib) AND cancer AND patient".

The clinical efficacy of olaparib against BRCA-deficient tumors has been confirmed in subsequent phase II interventional studies, including one trial enrolling individuals with a panel of advanced solid tumors (tumor response rate of 26.2% overall and 31.1%, 12.9%, 21.7%, and 50.0% in ovarian, breast, pancreatic, and prostate cancers, respectively).[205] Along similar lines, olaparib was effective in BRCA-deficient patients with breast or ovarian cancers, with an overall response rate (ORR) of 41% and 22% in breast cancers[211] and 33% and 13% in ovarian cancer[213] in cohorts assigned to 400 mg and 100 mg twice daily, respectively. A similar antineoplastic effect of olaparib monotherapy was observed in 2 phase II studies performed in *BRCA1- or BRCA2*-mutated ovarian cancer patients.[212,214] Nevertheless, in the former study no statistically significant differences in progression-free survival (PFS) were found between olaparib *versus* pegylated liposomal doxorubicin,[212] and in the latter no objective responses were reported in subjects with breast cancer.[214] Of note, in one of these trials, olaparib was also effective in subjects with non-mutated *BRCA1* or *BRCA2* (ORR 24%),[214] whereas no significant responses or durable disease control were observed in a phase II study aimed at assessing the therapeutic potential of olaparib in individuals with metastatic Ewing sarcoma.[216] Finally, in an open-label phase II clinical trial veliparib was active in women with *BRCA*-mutationed recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer with an ORR of 26% (20% and 35% for platinum-resistant and platinum-sensitive patients, respectively)[218] (Table 1).

When given as maintenance treatment, olaparib significantly improved PFS among patients who had received 2 or more platinum-based regimens and who had a partial or complete response to their most recent platinum-based regimen (median PFS of 8.4 mo compared with 4.8 mo for placebo conditions).[215] Moreover, when considering *BRCA* mutation status, median PFS (but not overall survival) was significantly different in the olaparib *versus* placebo groups (11.2 mo *vs.* 4.3 mo)[219] (Table 1).

Driven by this evidence, the FDA recently granted accelerated approval to the PARP inhibitor olaparib for patients with advanced ovarian cancer who carry inherited mutations of *BRCA* and have previously received at least 3 lines of therapy (http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm427598.htm) and breakthrough therapy designation to the PARP inhibitor rucaparib as monotherapy for patients with advanced ovarian cancer who have received at least 2 lines of prior platinum-containing therapy, with *BRCA*-mutated tumors, inclusive of both germline and somatic *BRCA* mutations.

PARP inhibitors as radio- or chemosensitizing agents

In contrast to olaparib monotherapy, dose-limiting toxicities, including neutropenia and thrombocytopenia, were reported for combinations of olaparib with various therapeutic agents, including dacarbazine (an alkylating agent approved by the FDA for the treatment of patients with Hodgkin lymphoma and melanoma[220]);[221] cisplatin and gemcitabine (a platinum derivative compound and an antimetabolite nucleoside, respectively, that are currently used for the treatment of several solid neoplasms[222-227]);[228] and topotecan (a topoisomerase I inhibitor approved by the FDA for use alone or with other drugs to treat several type of solid neoplasms, including cervical, ovarian, and small cell lung cancer[229]).[230] Moreover, olaparib in combination with cisplatin and gemcitabine was associated with myelosuppression, even at relatively low doses.[228] In line with this observation, significant and/or dose limiting myelosuppression was observed for veliparib combined with topotecan with or without filgrastim/pegfilgrastim neutrophil support[231,232] as well as for veliparib,[233] INO-1001,[234] or rucaparib[237] administered together with temozolomide (an alkylating agent currently used to treat patients with brain tumors, including anaplastic astrocytoma and glioblastoma multiforme[190,235,236]). It is important to note that the use of an intermittent schedule improved the tolerability of olaparib plus cisplatin regimen,[238] but not that of olaparib plus carboplatin (a platinum derivative approved by the FDA for the treatment of solid tumors, including ovarian and non-small cell lung cancer[239-241]) regimen.[242] Contrasting data have been reported on the tolerability of olaparib and agents blocking vascular endothelial growth factor (VEGF) signaling, including bevacizumab (a VEGF-targeting recombinant humanized monoclonal antibody currently approved for the treatment of several solid tumors[243-245]) and cediranib (a tyrosine kinase inhibitor of vascular endothelial growth factor receptor [VEGFR-1, -2, -3] that exhibits preclinical and clinical antitumoral activity[246-248]).[249-251] Finally, the combinations of olaparib and paclitaxel (a microtubular poison of the taxane family approved by the FDA for use alone or with other drugs for the treatment of breast, non-small cell lung, and ovarian cancer[252-254]),[255] paclitaxel and carboplatin followed by olaparib maintenance monotherapy,[256] veliparib and low-dose cyclophosphamide (an alkylating agent with immunogenic properties currently approved for the treatment of multiple neoplasms[257-259]),[260,261] veliparib and low-dose fractionated whole abdominal radiation,[262] veliparib and whole-brain radiation therapy,[263] CEP-9722 and temozolomide,[264] and rucaparib and temozolomide[265] were all well tolerated and/or had a generally manageable and acceptable toxicity profile.

Regarding the efficacy of PARP inhibitor-based regimens, the results reported so far are contrasting (Table 1).

On the one hand, limited or no objective response was observed when (1) olaparib was administered together with dacarbazine[221] or with cisplatin plus gemcitabine[228] in patients with advanced solid tumors; (2) rucaparib was used together with temozolomide in individuals with melanoma (response rate of 17.4%, median time to progression 3.5 mo, median overall survival 9.9 mo);[237] (3) veliparib was combined with temozolomide in children with recurrent central nervous system tumors[233] or patients with metastatic castration-resistant prostate cancer;[260] (4) veliparib was employed in combination with low-dose fractionated whole abdominal radiation;[262] (5) veliparib was co-administered with topotecan and filgrastim/pegfilgrastim neutrophil support in women with persistent or recurrent uterine cervix cancer;[232] (6) CEP-9722 was given with temozolomide to patients with advanced solid tumors;[264] and (7) INO-1001 was combined with temozolomide in subjects with melanoma.[234] Also, the addition of veliparib to a low-dose cyclophosphamide regimen did not improve the response rate or the median PFS in patients with pretreated

primary peritoneal, fallopian tube, or high-grade serous ovarian cancers[266] (Table 1).

On the other hand, promising evidence of antineoplastic activity was reported for (1) olaparib combined with cisplatin in breast or ovarian cancer patients with germline *BRCA1/2* mutations (ORR of 43% and 71%, respectively);[238] (2) olaparib in combination with paclitaxel for first- or second-line treatment of patients with metastatic TNBC (37% of patients with a confirmed partial response);[255] (3) olaparib together with cediranib in ovarian (but not breast) cancer patients (ORR of 44%; median PFS of 17.7 and 9.0 mo for the women treated with cediranib plus olaparib and those administered with olaparib alone, respectively);[250,251] (4) olaparib combined with carboplatin in *BRCA1*- or *BRCA2*-mutated breast or ovarian cancer (~50% of patients with complete or partial responses);[242] (5) olaparib together with paclitaxel and carboplatin followed by olaparib maintenance monotherapy in patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer (PFS 12.2 mo *vs* 9.6 mo for olaparib plus chemotherapy group *versus* chemotherapy alone group, with the greatest clinical benefit reported for patients with *BRCA* mutations);[256] (6) veliparib in combination with cyclophosphamide in a subset of *BRCA*-mutated patients (7 patients with partial responses and 6 patients with disease stabilization among 35 patients enrolled in the study);[261] and (7) veliparib combined with whole-brain radiation therapy (median survival time of 10 mo and 7.7 mo for the non-small cell lung cancer and the breast cancer subgroups, respectively, compared to nomogram model-predicted values of 3.5 mo and 4.9 mo)[263] (Table 1). These latter results (and in particular the impressive efficacy of the combination of olaparib and cediranib in patients with BRCA-mutated and BRCA-WT ovarian tumors) support the further development of PARP-based regimens.

Ongoing clinical trials

At the time of writing this Trial Watch (March 2015), official sources listed 84 ongoing (not terminated, withdrawn, suspended, or completed) clinical trials launched after January 1 2012 with the aim of testing the safety and therapeutic potential of PARP inhibitors in cancer patients as single agents, in maintenance monotherapy, or in combination with other chemotherapeutic agents (source: http://www.clinicaltrials.gov/) (Table 2). Of these trials, 35 involve olaparib, 25 veliparib, 13 talazoparib, 5 niraparib, 3 rucaparib, 1 BGB-290, and 1 E7016. As mentioned above, clinical trials employing iniparib will not be discussed in this section.

The clinical profile of olaparib as a monotherapeutic agent (in some cases following conventional [mostly platinum-based] chemotherapy regimens) is being assessed (1) in 7 phase III trials performed in patients with BRCA1/2 (or other HR player)-mutated breast cancer (NCT02000622 and NCT02032823; the second is an adjuvant study), ovarian cancer (NCT01844986, NCT01874353, NCT02282020, and NCT02392676), or pancreatic cancer (NCT02184195); (2) in 3 phase II trials conducted in individuals with recurrent/metastatic Ewing sarcoma (NCT01583543), advanced non-small cell lung cancer (NCT01788332), or advanced castration-resistant prostate cancer (NCT01682772); and (3) in 5 phase I studies performed in patients with advanced solid tumors (NCT01851265, NCT01894243, NCT01894256, NCT01921140, and NCT02324998) (Table 2). The clinical study NCT01661868 (evaluating the safety and efficacy of olaparib in patients with recurrent BRCA-deficient ovarian cancer) has been withdrawn prior to enrollment due to lack of availability of the drug, whereas results of NCT01583543, which is currently listed as ongoing, but not recruiting participants, are reported in reference 216.[216]

In addition to olaparib, 3 other PARP inhibitors are being employed in phase III interventional studies as single agents or maintenance monotherapy: niraparib, whose efficacy is being investigated in 2 studies performed in patients with platinum-sensitive ovarian cancer (NCT01847274) or in individuals with human epidermal growth factor 2 (HER2)-negative, *BRCA*-mutated breast cancer (NCT01905592); rucaparib, whose therapeutic profile is being evaluated in 1 trial conducted in subjects with ovarian, fallopian tube, or peritoneal cancer who have received platinum-based chemotherapy (NCT01968213); and talazoparib, whose safety and efficacy is being compared to treatment of the physician's choice (e.g., capecitabine [an antimetabolite currently used for the treatment of human neoplasms, including breast and colorectal cancers[267]], the nucleoside analog gemcitabine, or eribulin or vinorelbine [2 antimitotic agents, the first of which was approved by the FDA for use alone or with cisplatin to treat non-small cell lung cancer patients[268,269]]) in subjects with *BRCA*-mutated advanced breast cancer (EMBRACA) (NCT01945775)[270] (Table 2).

Among the other PARP inhibitors given as stand-alone therapeutic regimens in phase I and/or II clinical trials, (1) BGB-290 is being used in patients with advanced solid tumors (NCT02361723); (2) niraparib is being administered to individuals with ovarian cancer who have received at least 3 previous chemotherapy regimens (NCT02354586); (3) rucaparib is being used in patients with platinum-sensitive ovarian, fallopian tube, or peritoneal cancer (NCT01891344) or BRCA-mutated pancreatic cancer (NCT02042378); (4) talazoparib is being used in subjects with advanced solid tumors (NCT01989546 and NCT02286687), *BRCA*-mutated breast cancer (NCT02034916 and NCT02282345; the latter is a neoadjuvant study), endometrial cancer (NCT02127151), or *BRCA1/2* mutation-associated ovarian cancer (NCT02326844); and (5) veliparib is being used in patients with advanced solid tumors (NCT02210663), ovarian, fallopian tube, or peritoneal cancer (NCT01540565), or solid neoplasms, including high-grade serous ovarian cancer and *BRCA*-mutated breast cancer (NCT01853306) (Table 2). In addition, a pilot study is evaluating the effects of talazoparib on patients with ovarian, fallopian tube, or peritoneal cancer (NCT02316834). To the best of our knowledge, the results of the clinical trial NCT02009631 (evaluating the clinical profile of veliparib in advanced solid tumors) have not yet been released. (http://www.clinicaltrials.gov).

According to official sources (http://www.clinicaltrials.gov), 52 ongoing clinical trials have been launched worldwide to evaluate the safety and tolerability of PARP inhibitors in combination with conventional radio- or chemotherapy (Table 2).

PARP inhibitors employed in Phase III interventional studies include (1) olaparib, which is being combined with paclitaxel in individuals with gastric cancer who have progressed

Table 2. Ongoing clinical trials recently launched to evaluate the safety and efficacy of PARP inhibitors in cancer patients.

Agent	Indication(s)	Phase	Status	Notes	Ref.
BGB-290	Advanced solid tumors	I	Recruiting	As single agent	NCT02361723
E7016	Melanoma	II	Active, not recruiting	Combined with temozolomide	NCT01605162
Iniparib	Advanced solid tumors	III	Active, not recruiting	Alone or combined with others chemotherapeutics, including carboplatin, doxorubicin, gemcitabine, irinotecan, paclitaxel, and topotecan	NCT01593228
Niraparib	Breast cancer	III	Recruiting	As single agent *vs.* 4 standard of care metastatic breast cancer chemotherapies ($HER2^-$)	NCT01905592
	Ewing sarcoma	I	Recruiting	Combined with temozolomide	NCT02044120
	Ovarian cancer	I/II	Not yet recruiting	Alone or combined with bevacizumab	NCT02354131
		II	Not yet recruiting	As single agent	NCT02354586
		III	Recruiting	As single agent	NCT01847274
Olaparib	Advanced solid tumors	I	Recruiting	As single agent	NCT01894243
			Recruiting	As single agent	NCT01894256
			Recruiting	Combined with anastrozole, letrozole, or tamoxifen	NCT02093351
			Recruiting	Combined with AZD5363	NCT02338622
			Active, not recruiting	As single agent	NCT01921140
			Active, not recruiting	As single agent	NCT01851265
			Active, not recruiting	Combined with itraconazole	NCT01900028
			Active, not recruiting	Combined with rifampicin	NCT01929603
		I/II	Recruiting	Combined with AZD6738	NCT02264678
	Breast cancer	I	Recruiting	Combined with RT	NCT02227082
		III	Recruiting	As single agent	NCT02032823
			Recruiting	As single agent *vs.* capecitabine, eribulin or vinorelbine	NCT02000622
	Breast or female reproductive system cancer	I/II	Recruiting	Combined with AZD2014 and AZD5363	NCT02208375
	Breast or ovarian cancer	I	Recruiting	Combined with BKM120	NCT01623349
	Ewing sarcoma	I	Recruiting	Combined with temozolomide	NCT01858168
		II	Active, not recruiting	As single agent	NCT01583543
	Gastric cancer	III	Recruiting	Combined with paclitaxel	NCT01924533
	Head and neck cancer	I	Not yet recruiting	Combined with cisplatin and intensity modulated RT	NCT02308072
			Recruiting	Combined with cetuximab and RT	NCT01758731
			Recruiting	Combined with RT	NCT02229656
	Non-small cell lung cancer	I	Recruiting	Combined with cisplatin and RT	NCT01562210
		II	Recruiting	As single agent	NCT01788332
	Esophageal cancer	I	Recruiting	Combined with RT	NCT01460888
	Ovarian cancer	II	Not yet recruiting	Combined with cediranib	NCT02340611
		III	Not yet recruiting	As single agent	NCT02392676
			Recruiting	As single agent	NCT01844986
			Recruiting	As single agent	NCT02282020
			Active, not recruiting	As single agent	NCT01874353
	Ovarian, fallopian tube or peritoneal cancer	I	Recruiting	Combined with bevacizumab, cisplatin, and paclitaxel	NCT02121990
		II	Not yet recruiting	Combined with cediranib	NCT02345265
	Ovarian or uterine cancer	I/II	Active, not recruiting	Combined with carboplatin and paclitaxel	NCT01650376
	Pancreatic cancer	III	Recruiting	As single agent	NCT02184195
	Prostate cancer	I	Not yet recruiting	As single agent or combined with degarelix	NCT02324998
		II	Recruiting	As single agent	NCT01682772
			Recruiting	Combined with abiraterone and prednisone/ prednisolone	NCT01972217
Rucaparib	Ovarian, fallopian tube, or peritoneal cancer	II	Recruiting	As single agent	NCT01891344
		III	Recruiting	As single agent	NCT01968213
	Pancreatic cancer	II	Recruiting	As single agent	NCT02042378

(*Continued*)

Table 2. (*Continued*)

Agent	Indication(s)	Phase	Status	Notes	Ref.
Talazoparib	Advanced solid tumors	I	Not yet recruiting	Combined with carboplatin and paclitaxel	NCT02317874
			Not yet recruiting	Combined with carboplatin and paclitaxel	NCT02358200
			Recruiting	Combined with temozolomide or irinotecan	NCT02049593
		I/II	Recruiting	As single agent	NCT01989546
			Recruiting	Combined with temozolomide	NCT02116777
		II	Recruiting	As single agent	NCT02286687
	Breast cancer	II	Not yet recruiting	As single agent	NCT02282345
			Recruiting	As single agent	NCT02034916
		III	Recruiting	As single agent *vs.* capecitabine, eribulin, gemcitabine, or vinorelbine	NCT01945775 270
	Childhood solid tumors	I	Not yet recruiting	Combined with irinotecan and temozolomide	NCT02392793
	Endometrial cancer	II	Not yet recruiting	As single agent	NCT02127151
	Ovarian cancer	II	Recruiting	As single agent	NCT02326844
	Ovarian, fallopian tube or peritoneal cancer	0	Not yet recruiting	As single agent	NCT02316834
Veliparib	Advanced solid tumors	I	Active, not recruiting	As single agent	NCT02210663
			Active, not recruiting	As single agent or combined with carboplatin and paclitaxel or with FOLFIRI	NCT02033551
	Breast cancer	I	Recruiting	Combined with RT	NCT01618357
			Active, not recruiting	Combined with RT	NCT01477489
		II	Recruiting	Combined with carboplatin, paclitaxel, and temozolomide	NCT01506609
		III	Recruiting	Combined with carboplatin, cyclophosphamide, doxorubicin, and paclitaxel	NCT02032277
			Recruiting	Combined with carboplatin and paclitaxel	NCT02163694
		Not provided	Recruiting	Combined with lapatinib	NCT02158507
	Breast cancer or ovarian cancer	I	Active, not recruiting	As single agent	NCT01853306
	Colorectal cancer	II	Recruiting	Combined with bevacizumab and FOLFIRI	NCT02305758
	Glioblastoma multiforme	II/III	Recruiting	Combined with temozolomide	NCT02152982
	Head and neck cancer	I/II	Recruiting	Combined with carboplatin, cisplatin, hydroxyurea, fluorouracil, paclitaxel, and RT	NCT01711541
	Hematologic neoplasms	I	Active, not recruiting	Combined with carboplatin and topotecan	NCT00588991
	Lung cancer	I	Recruiting	Combined with carboplatin and etoposide	NCT02289690
		I/II	Recruiting	Combined with cisplatin and etoposide	NCT01642251
		II	Recruiting	Combined with temozolomide	NCT01638546
		III	Recruiting	Combined with carboplatin, cisplatin, paclitaxel and pemetrexed	NCT02264990
			Recruiting	Combined with carboplatin and paclitaxel	NCT02106546
	Ovarian cancer	I/II	Recruiting	Combined with topotecan	NCT01690598
	Ovarian, fallopian tube, or peritoneal cancer	I	Recruiting	Combined with floxuridine	NCT01749397
		II	Active, not recruiting	As single agent	NCT01540565
	Pancreatic cancer	I	Recruiting	Combined with gemcitabine and RT	NCT01908478
		I/II	Recruiting	Combined with fluorouracil, leucovorin, and oxaliplatin	NCT01489865
		II	Recruiting	Combined with cisplatin and gemcitabine	NCT01585805
	Prostate cancer	II	Recruiting	Combined with abiraterone and prednisone	NCT01576172

*Not terminated, suspended, withdrawn, unknown or completed on the date of submission (March 20, 2015). Sources: http://www.clinicaltrials.gov, searching with the following terms: "PARP AND cancer" or "PARP1 AND cancer" or "NAME OF THE COMPOUND (e.g., olaparib) AND cancer"

following first-line therapy (NCT01924533), and (2) veliparib, which is being combined with carboplatin and paclitaxel or paclitaxel-based regimens in patients with breast (NCT02163694 and NCT02032277) or lung (NCT02264990 and NCT02106546) cancer. In addition, veliparib is being combined with temozolomide in a phase II/III study to treat patients with newly diagnosed glioblastoma multiforme with O-6-methylguanine-DNA methyltransferase (*MGMT*) promoter hypermethylation (NCT02152982) (Table 2).

The vast majority of phase II or I studies assessing the therapeutic profile of PARP inhibitors in combinatorial regimens involves olaparib or veliparib (Table 2).

Olaparib is being administered together with (1) anastrozole or letrozole (2 aromatase inhibitors currently used for the

treatment of breast cancer in postmenopausal women[271-273]) or tamoxifen (a nonsteroidal selective estrogen receptor modulator approved by the FDA for the treatment and prevention of breast cancer[273,274]) in patients with advanced solid tumors (NCT02093351); (2) itraconazole (an FDA-approved antifungal compound with antineoplastic activity[275-277]) in individuals with advanced solid neoplasms (NCT01900028); (3) rifampicin (a cytochrome P450, family 3, subfamily A, polypeptide 4, CYP3A4, inducer[278]) in subjects with solid tumors (NCT01929603); (4) radiotherapy or radiotherapy-based regimens in individuals with breast cancer (NCT02227082), in subjects with head and neck cancer (NCT02229656, NCT01758731 and NCT02308072), in patients with non-small cell lung cancer (NCT01562210), or in individuals with esophageal cancer (NCT01460888); (5) AZD2014 or AZD5363 (inhibitors of mammalian target of rapamycin complex 1/2 [mTORC1/2] or AKT, respectively, with antitumor activity[279-282]) in subjects with breast cancer or female reproductive system cancer (NCT02208375) or advanced solid tumors (NCT02338622); (6) BKM120 (a PI3K inhibitor[283] whose therapeutic potential is being evaluated in clinical studies) in breast or ovarian cancer patients (NCT01623349); (7) bevacizumab, cisplatin, and paclitaxel in individuals with ovarian, fallopian tube, or peritoneal cancer (NCT02121990); (8) carboplatin and paclitaxel in subjects with ovarian or uterine cancer (NCT01650376); (9) temozolomide in patients with Ewing sarcoma (NCT01858168); (10) abiraterone (an FDA-approved androgen biosynthesis inhibitor[284]) and prednisone/prednisolone (2 FDA-approved glucocorticosteroids[285,286]) in individuals with prostate cancer (NCT01972217); (11) degarelix (a gonadotropin-releasing hormone antagonistic approved by the FDA for the treatment of advanced prostate cancers[287,288]) in patients with prostate cancer prior to radical prostatectomy (NCT02324998); (12) cediranib in patients with ovarian, fallopian tube, peritoneal (NCT02345265) or ovarian (NCT02340611) cancer; and (13) AZD6738 (an ATR serine/threonine kinase inhibitor whose activity is being evaluated in some clinical trials http://www.clinicaltrials.gov) in subjects with advanced solid malignancies (NCT02264678) (Table 2).

Veliparib is being (1) combined with carboplatin and paclitaxel-based regimens in patients with head and neck cancer (NCT01711541); (2) used in combination with carboplatin and paclitaxel or either FOLFIRI (irinotecan, leucovorin, 5-flourouracil, and irinotecan) in advanced solid tumors (NCT02033551) or temozolomide in breast cancer (NCT01506609); (3) administered together with radiotherapy in individuals with breast cancer (NCT01477489 and NCT01618357); (4) given in combination with radiotherapy and gemcitabine in pancreatic cancer patients (NCT01908478); (5) combined with temozolomide in patients with lung cancer (NCT01638546); (6) used together with floxuridine (an antimetabolite that is metabolized to fluorouracil and other metabolites with antineoplastic activity[289]) in females with ovarian, fallopian tube, or peritoneal cancer (NCT01749397); (7) used in combination with topotecan and/or carboplatin in individuals with ovarian cancer (NCT01690598) and hematologic neoplasms (NCT00588991); (8) given together with 5-fluorouracil (an antimetabolite fluoropyrimidine commonly used for the adjuvant and palliative treatment of several neoplasms[290,291]), leucovorin (an active metabolite of folic acid approved by the FDA in combination with fluorouracil as palliative treatment in patients with advanced colorectal cancer[292,293]), and oxaliplatin (an FDA-approved cisplatin derivative[294,295]) in pancreatic cancer patients (NCT01489865); (9) combined with bevacizumab and FOLFIRI in subjects with colorectal cancer (NCT02305758); (10) used in combination with platinum-based agents and either etoposide (an FDA-approved inhibitor of topoisomerase II currently used for the treatment of patients affected by a variety of solid malignancies[296,297]) or gemcitabine in individuals with lung (NCT01642251 and NCT02289690) or pancreatic cancer (NCT01585805), respectively; and (11) administered together with abiraterone and prednisone in patients with prostate cancer (NCT01576172) (Table 2). In addition, an open-label pilot study is evaluating the effectiveness and safety of veliparib together with lapatinib (a tyrosine kinase inhibitor currently used in combination with capecitabine or letrozole to treat advanced or metastasized breast cancer[298-301]) in patients with metastatic, TNBCs (NCT02158507). To the best of our knowledge, the results of clinical trials NCT01589419 (evaluating the safety and efficacy of veliparib in combination with radiotherapy and capecitabine in colorectal cancer), NCT01657799 (determining the activity, safety, and tolerability of veliparib combined with whole-brain radiation therapy for brain metastases from non-small cell lung cancer), and NCT01560104 and NCT01617928 (both assessing the clinical profile of veliparib in combination with carboplatin and paclitaxel in advanced solid tumors) have not yet been released (http://www.clinicaltrials.gov). The recruitment status of the clinical trial NCT01495351 is unknown, while NCT01818063 has suspended participant recruitment due to lack of funding.

Regarding the other PARP inhibitors, niraparib and E7016 are being combined with temozolomide in subjects with Ewing sarcoma (NCT02044120) or melanoma (NCT01605162), respectively. Niraparib is also being administered alone or combined with bevacizumab in patients with ovarian cancer (NCT02354131). Finally, talazoparib is being used together with (1) carboplatin and paclitaxel in individuals with advanced solid tumors (NCT02317874) or in subjects with advanced BRCA-mutated solid tumors or metastatic TNBCs (NCT02358200); and (2) temozolomide and/or irinotecan in individuals with advanced solid tumors (NCT02049593 and NCT02116777) or in patients with childhood solid tumors (NCT02392793) (Table 2).

Concluding remarks

A large number of preclinical and clinical studies have demonstrated the safety and therapeutic benefits of PARP inhibitors alone or in combination with other cytotoxic drugs (mostly DNA damaging agents), in particular against breast and ovarian cancers harboring mutations in components of DNA repair pathways.

Nonetheless, the role of PARP1 in the preservation of genomic stability, the non-selective inactivation of PARP family members other than PARP1 ascribed to PARP inhibitors, the toxicity and limited efficacy of some (but not all) combinatorial regimens, and the development of resistance to synthetic lethal strategies based on PARP inhibitors may cast doubt on the use

of these agents for cancer therapy. It is important to note that the mechanisms of resistance to PARP inhibitors acquired by HR-deficient tumors include novel deletions or secondary mutations that restore the open reading frame (ORF), sequence and/or function of BRCA2;[302-304] somatic mutations of tumor protein p53 binding protein 1 (*TP53BP1* best known as *53BP1*) or loss of MAD2 mitotic arrest deficient-like 2 (MAD2L2, best known as REV7), which are believed to restore HR proficiency;[194,305-307] and upregulation of ATP-binding cassette, sub-family B (MDR/TAP), member 1 (*ABCB1*, also known as multidrug resistance protein 1, *MDR1*, or P-glycoprotein, *P-GP*), which increases drug efflux.[308] Moreover, besides being involved in DDR, PARP enzymes regulate many functions relevant for cancer, including DNA transcription,[309] energy metabolism,[11] metabolic checkpoints (*i.e.,* molecular mechanisms triggered in response to metabolic fluctuations),[310] cell death,[61-64] mitosis,[311-313] ploidy status,[314] cell migration,[315-317] angiogenesis,[318-320] and metastasis.[321] To add further layers of complexity, PARP enzymes have been linked to signaling pathways, including extracellular signal-regulated kinase (ERK), nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-kB), and wingless-type (Wnt)/β-catenin pathways.[322-325] PARP activity is also involved in cancer stem cell (CSC) maintenance,[326] whereas MARylation has been shown to regulate processes relevant to cancer, including the unfolded protein response (UPR).[6,327] Finally, recent evidence suggests a cytoprotective role of PARP1 and PAR in response to intrinsic or extrinsic perturbations.[6,14,190,328]

The recent approval of olaparib by the FDA as a maintenance therapy for patients with platinum-sensitive high-grade serous ovarian cancer and promising clinical evidence showing the efficacy of PARP inhibitors in the adjuvant setting[75] are both paving the way for the advancement of PARP1 inhibitors in clinics. Nevertheless, the results of large phase III trials are awaited in order to uncover the true potential of these agents for cancer therapy. Moreover, a better understanding of the biology of the PARP enzyme family and the identification of potential predictive biomarkers for PARP inhibitor-based therapies are urgently needed in order to increase the specificity and efficacy of these agents and expand the patient population that might benefit from these targeting strategies.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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