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REVIEW

Current status of poly(ADP-ribose) polymerase inhibitors and future directions

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Abstract: Inhibitors of poly(ADP-ribose) polymerases (PARPs), which play a key role in DNA damage/repair pathways, have been developed as antitumor agents based on the concept of synthetic lethality. Synthetic lethality is the idea that cell death would be efficiently induced by simultaneous loss of function of plural key molecules, for example, by exposing tumor cells with inactivating gene mutation of BRCA-mediated DNA repair to chemically induced inhibition of PARPs. Indeed, three PARP inhibitors, olaparib, rucaparib and niraparib have already been approved in the US or Europe, mainly for the treatment of *BRCA*-mutant ovarian cancer. Clinical trials of various combinations of PARP inhibitors with cytotoxic or molecular-targeted agents are also underway. In particular, expanded applications of PARP inhibitors are anticipated following recent reports that defects in homologous recombination repair (HRR) are associated with mutations in repair genes other than *BRCA1/BRCA2*, such as *ATM*, *ATR*, *PALB2*, *RAD51*, *CHEK1* and *CHEK2*, as well as with epigenetic loss of *BRCA1* function through promoter methylation or overexpression of the BRCA2-interacting transcriptional repressor EMSY. Current topics of interest include selection of the best agent in each clinical context, identification of new treatment targets for HRR-proficient cases, and development of PARP inhibitor-based regimens that are less toxic and that prolong overall survival as well as progression-free survival. In addition, potential long-term side effects and suitable biomarkers for predicting efficacy and mechanisms of clinical resistance are in discussion. This review summarizes representative preclinical and clinical data for PARP inhibitors and discusses their potential for future applications to treat various malignancies.

Keywords: PARP inhibitors, synthetic lethality, *BRCA* mutation, homologous recombination, drug resistance, biomarkers

Introduction

Poly(ADP-ribose) polymerases (PARPs) are important components of DNA damage/repair pathways, playing key roles in genomic stability and tumor cell survival. PARP inhibitors have attracted great interest as potential antitumor agents since the concept of synthetic lethality was introduced by Bryant et al[1] and Farmer et al[2] in 2005. This concept is based on the idea that simultaneous loss of function of two or more key gene products can cause cell death, even if a deficiency in only one of them is not lethal. Thus, for example, tumor cells with inactivating mutation of the *BRCA* DNA-repair genes, which is not lethal, might be killed if they are also exposed to chemical inhibition of PARPs. Indeed, preclinical and clinical studies have verified antitumor effects of PARP inhibition in *BRCA*-mutant tumors.[1–8] So far, three agents (olaparib, rucaparib and niraparib) have been approved by western regulatory agencies, and >70 clinical trials evaluating PARP inhibitors for various kinds of malignancies are underway.[9] Hereditary breast and ovarian cancer (HBOC) is a syndrome

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associated with germline mutations of *BRCA1/BRCA2* and is considered as the most suitable target for PARP inhibitors. A pooled analysis of 26 observational studies with a total of 3,879 ovarian cancer patients showed that germline *BRCA* mutations were associated with better survival, supporting the position of HBOC as a distinct clinical subtype.[10] Triple-negative breast cancer (TNBC), characterized by lack of expression of estrogen receptor, progesterone receptor and *HER2* gene amplification, is a pathologically and clinically aggressive entity and is considered as the most problematic for breast cancer patients and clinicians, in which hormone treatments or anti-HER2 agents are ineffective. Defects of DNA-repair pathways including *BRCA1* are reported in many TNBC cases, providing a rationale for PARP inhibitor treatment.[11] Defects in homologous recombination repair (HRR) genes other than *BRCA1/BRCA2* and acquired loss of *BRCA1* function through promoter methylation have also opened up the possibility of new indications for PARP inhibitor treatment.[12,13] However, only limited information is yet available about mechanisms of clinical resistance to these inhibitors or biomarkers to identify suitable cases for treatment. In this review, we summarize the current status of basic research and clinical trials on PARP inhibitors and discuss prospects for extending their applicability and improving clinical outcomes.

Mechanisms of action

PARP is a nuclear protein first reported in 1963 as a DNA-dependent polyadenylic acid-synthesizing nuclear enzyme, and to date, 17 members of the PARP protein family have been identified.[14,15] PARP members are involved in various cellular processes, such as DNA repair, cellular differentiation, gene transcription, inflammation, mitosis, cell death and metabolism.[16] Among them, PARP-1 accounts for >90% of the total PARP activity and is considered to be a key player in DNA base excision repair and repair of DNA single-strand breaks (SSBs).[16–18] PARP-1 binds to SSBs through a series of N-terminal zinc finger DNA-binding domains and catalyzes the polymerization of ADP-ribose (PARylation) with NAD^+ as a substrate, resulting in the production of variable-sized polymers of ADP-ribose (PAR).[15,19,20] The amount of PAR production is regulated by the balance between PARP-1 and poly(ADP-ribose) glucohydrolase, which hydrolyzes PAR.[21] PAR recruits SSBs repair scaffolding proteins, such as X-ray repair cross-complementing protein 1 (XRCC1), DNA ligase III and DNA polymerase beta, and concurrently modifies chromatin structure around lesions.[15,19] PARP-2, which accounts for 5%–10% of the total PARP activity, is also essential for DNA base excision repair, in collaboration with PARP-1.[22] Accumulation of SSBs due to inhibition of PARylation or base excision repair produces DNA double-strand breaks (DSBs) through replication fork collapse.[23] HRR and nonhomologous end joining (NHEJ) are the main types of repair mechanisms for DSBs.[3,15,21,24] HRR is an accurate process conducted using a homologous DNA sequence and is composed of gene conversion and single-strand annealing pathways. On the other hand, NHEJ is an inaccurate process in which broken DNA ends are directly connected without using a homologous sequence. The former process occurs exclusively during the S and G2 phases of the cell cycle, while the latter is cell cycle independent.[15] While HRR normally takes a leading role in the repair of DSBs, deficiency of this process often leads to alternative NHEJ activation, and some of the genetic alterations introduced by NHEJ promote carcinogenesis by cancer-driver genes.[12,24,25] PARP-1 affects repair of DSBs and SSBs through activating ATM in the HRR pathway and inactivating DNA-dependent protein kinase in the NHEJ pathway, and thus PARP occupies a central position in the whole picture of DNA damage control and repair.[26,27] Interactions between PARP, HRR and NHEJ are concisely illustrated in a review by O'Sullivan et al.[26] PARP-1 expression and activity are increased in actively proliferating cells, and high PARP-1 expression is a feature of various tumors.[28] A preclinical study using 318 cell lines from 30 cancer types showed that PARP-1 mRNA expression was extremely high in small cell lung cancer (SCLC), in addition to hematologic malignancies. These results might provide clues to new treatment approaches for intractable tumors such as SCLC or neuroendocrine carcinomas derived from other organs, which are unresponsive to conventional molecular-targeting agents.[29]

In contrast to the limited efficacy of PARP inhibition alone, the combination of PARP inhibition with DNA-repair defects involving other signaling pathways is often lethal to tumor cells.[30] This synthetic lethality is powerful, because *BRCA*-deficient tumor cells have shown >1,000-fold greater sensitivity to PARP inhibitors in preclinical models.[1,2] Inactivation of BRCA1 and BRCA2, which are essential for HRR, increases the importance of PARP1 for maintaining genomic stability, and addition of PARP inhibition thus leads to cell cycle arrest and apoptosis through stimulating inaccurate NHEJ.[30,31] In addition to germline *BRCA*-mutant tumors, BRCA deficiency is observed in somatic *BRCA*-mutant tumors or tumors with epigenetic loss of function through *BRCA1* promoter methylation or overexpression of the *BRCA2* transcription suppressor

EMSY.[12,32] In addition, large-scale genomic data showed that some *BRCA*-proficient tumors have defects in HRR genes such as *ATM*, *ATR*, *CHK1*, *CHK2*, *PALB2*, *RAD51* and *PTEN*.[13] These gene products are linked in the HRR signaling pathway as follows: ATM recruited in response to DSBs produces γH2AX and concurrently phosphorylates and activates CHK2, while ATR activated by replication protein A phosphorylates and activates CHK1, and PALB2 facilitates invasion of the BRCA2–RAD51 complex into damaged DNA by localizing BRCA2 to DSBs.[12,16] As mentioned earlier, tumors with acquired loss of BRCA1 function or defects in HRR genes share clinical and biological features with germline *BRCA*-mutant tumors and are known as BRCAness phenotype tumors.[12,13,24,33] Recent genomic data indicate that the frequency of BRCAness phenotype tumors is not negligible, and thus, the concept of synthetic lethality is adaptable to more cases than might have been expected. Pennington et al[34] analyzed germline or somatic mutations of 30 genes, including *BRCA1/BRCA2* and other HRR genes, in 390 ovarian cancer patients and showed that 31% of patients possess some deleterious alterations in HRR genes. Mateo et al[35] also conducted targeted sequencing of DNA-repair genes, including *BRCA1/BRCA2*, *ATM*, and *CHEK2* and Fanconi anemia genes in 49 patients with castration-resistant prostate cancer and identified homozygous deletions or deleterious alterations in 33% of the cases. Large-scale integrated genomic analyses of ovarian cancer by The Cancer Genomic Atlas (TCGA) project found gene alterations in HRR genes in 51% of 316 cases.[36] These data highlight BRCAness phenotype tumors as a clinically promising target of PARP inhibitors. In addition to inhibiting PARylation, the inhibitors trap PARP1/PARP2 enzymes at sites of DNA damage and induce cytotoxic PARP–DNA complexes.[30] The effects of these agents depend mainly on the degree of PARP trapping rather than the ability to inhibit PARylation.[22,24,37] However, it remains unclear whether an agent with stronger PARP-trapping activity would have greater clinical benefits, and prospective clinical trials are warranted to address this question.

It should be noted that DNA-repair function is intrinsically decreased in tumor cells compared with normal cells, and this disparity accounts for the high selectivity of PARP inhibitors.[3,38] Nevertheless, it remains important to develop inhibitors with high potency and low toxicity. The clinical efficacy of PARP inhibitors as single agents is actually only moderate, except for *BRCA*-mutant or BRCAness tumors, and therefore, combination therapy is a reasonable approach to improve the utility of these inhibitors, which should sensitize cells to DNA damage caused by various cytotoxic agents, exhibiting synthetic lethality in the clinical context.[3] Some combined regimens have been tested, but it appears that the combination effects are dependent on the partner cytotoxic agent used.[24,39] In in vitro preclinical studies, olaparib showed better synergy than veliparib with temozolomide (TMZ), whereas rucaparib showed the strongest combination effect with topotecan but the weakest effect with paclitaxel (PTX) or gemcitabine (GEM).[39–41] In terms of mechanisms, accumulated DNA damage and increased PARP dependency for repair are suggested for the combinations with platinum agents or topoisomerase-1 inhibitors, elevated PARP1 trapping for the combinations with TMZ, and induced BRCAness phenotype for the combinations with taxanes.[42] The next step in evaluating such combinations would be in vivo studies or clinical trials.

Some preclinical studies have recently demonstrated a unique and promising combination effect between PARP inhibitors and alkylating agent TMZ in *isocitrate dehydrogenase 1 (IDH1)*-mutant tumors.[43,44] The synthesis of NAD^+ as a substrate PARylation is reduced in *IDH1*-mutant cases, and this depletion of NAD^+ is speculated to result in enhancement of PARP inhibition. Here, TMZ promotes PARP recruitment through inducing DNA damage, reasonably explaining interaction of above two agents, which indicates a broader application of PARP inhibitors in various malignancies with NAD metabolic defects, including glioma.

Clinical applications of PARP inhibitors

Clinical applications of PARP inhibitors are the most advanced in ovarian cancer, and so far, olaparib, rucaparib and niraparib are commercially available in the US or Europe. However, many clinical trials are underway, including malignancies such as breast cancer and prostate cancer, as well as ovarian cancer, and tumors without *BRCA* mutations, such as BRCAness phenotype tumors. In this section, we review clinical evidence of the efficacy of five PARP inhibitors (olaparib, talazoparib, rucaparib, veliparib and niraparib; Table 1).

Olaparib

Fong et al[45] conducted the first Phase I trial of olaparib (AZD-2281; AstraZeneca plc, Cambridge, UK) in 60 patients including 22 *BRCA*-mutant cases, and the maximum tolerated dose (MTD) was established as 400 mg twice daily. An additional cohort study of 50 patients with *BRCA*-mutant ovarian cancer showed that the overall clinical

Table 1 Summary of Phase II/III trials of PARP inhibitors

Agent	Phase	Number of patients	Tumor type	ORR	Median PFS	Median OS
Olaparib[31]	2	50	Metastatic castration-resistant prostate cancer	33% (entire cohort), 88% (genomic defects positive cases in DNA-repair genes), 6% (genomic defects negative cases in DNA-repair genes)	9.8 months (genomic defects positive cases in DNA-repair genes), 2.7 months (genomic defects negative cases in DNA-repair genes)	13.8 months (genomic defects positive cases in DNA-repair genes), 7.5 months (genomic defects negative cases in DNA-repair genes)
Olaparib[41]	2	57	Recurrent *BRCA*-mutant ovarian cancer	33% (400 mg twice daily), 13% (100 mg twice daily)	5.8 months (400 mg twice daily), 1.9 months (100 mg twice daily)	Not reported
Olaparib[42]	2	298	Recurrent *BRCA*-mutant cancer	26% (entire cohort), 31% (ovarian), 13% (breast), 22% (pancreatic), 50% (prostate)	7.0 months (ovarian), 3.7 months (breast), 4.6 months (pancreatic), 7.2 months (prostate)	16.6 months (ovarian), 11 months (breast), 9.8 months (pancreatic), 18.4 months (prostate)
Olaparib[43]	2	64	Advanced HGSOC or TNBC	41% (*BRCA* mutant), 24% (*BRCA* wild)	7.2 months (ovarian), 1.8 months (breast)	Not reported
Olaparib[44]	2	265	Recurrent platinum-sensitive HGSOC	12% (olaparib), 4% (placebo)	8.4 months (olaparib), 4.8 months (placebo)	29.7 months (olaparib), 29.9 months (placebo)
Olaparib[46]	2	54	Recurrent *BRCA*-mutant breast cancer	41% (400 mg twice daily), 22% (100 mg twice daily)	5.7 months (400 mg twice daily), 3.8 months (100 mg twice daily)	Not reported
Rucaparib[49]	2	35	Recurrent *BRCA*-mutant ovarian cancer	65%	Not reached	Not reported
Rucaparib[50]	2	206	Recurrent platinum-sensitive high-grade ovarian cancer	80% (*BRCA* mutant), 29% (*BRCA* wild/LOH high), 10% (*BRCA* wild/LOH low)	12.8 months (*BRCA* mutant), 5.7 months (*BRCA* wild/LOH high), 5.2 months (*BRCA* wild/LOH low)	Not reported
Veliparib[52]	2	50	Persistent or recurrent *BRCA*-mutant epithelial ovarian, fallopian tube or primary peritoneal cancer	26%	8.2 months	Not reached
Niraparib[54]	3	553	Recurrent platinum-sensitive ovarian cancer	Not reported	21.0 months vs 5.5 months (germline *BRCA* mutant vs placebo), 12.9 months vs 3.8 months (*BRCA* wild/HRD positive vs placebo), 9.3 months vs 3.9 months (overall *BRCA* wild vs placebo)	Not reported

Abbreviations: PARP, poly(ADP-ribose) polymerase; ORR, overall response rate; PFS, progression-free survival; OS, overall survival; HGSOC, high-grade serous ovarian cancer; TNBC, triple-negative breast cancer; LOH, loss of heterozygosity; HRD, homologous recombination deficiency.

benefit rate (CBR) as a composite radiological and tumor marker factor and the overall response rates (ORRs) were 46% and 28%, respectively, and there was a significant association between CBR and platinum-free interval, defined as the period from last platinum administration to disease progression (platinum sensitive, 69%; platinum resistant, 45%; platinum refractory, 23%).[46] In a Phase II trial in 57 patients with recurrent BRCA-mutant ovarian cancer, ORR was 33% in the 400 mg twice daily cohort and 13% in the 100 mg twice daily cohort; ie, higher dose administration of olaparib gave a better clinical outcome.[47] Kaufman et al also conducted a Phase II trial in 298 patients with recurrent *BRCA*-mutant cancers, including 193 ovarian cancers, 62 breast cancers, 23 pancreatic cancers and 8 prostate cancers. They reported that ORR was 26% in the entire cohort, while the values were 31%, 13%, 22% and 50% in patients with ovarian, breast, pancreatic and prostate cancers, respectively.[4] Another Phase II trial in 64 patients with recurrent high-grade serous ovarian cancer (HGSOC) or TNBC showed a higher ORR in patients with *BRCA*-mutant ovarian cancer than in ovarian cancer patients without mutation (41% vs 24%).[5] These clinical data led to accelerated approval of olaparib by the US Food and Drug Administration (FDA) in 2014 for fourth-line or later treatment of *BRCA*-mutant ovarian cancer. Some impressive data also support the value of olaparib maintenance treatment. Ledermann et al[6] conducted a randomized placebo-controlled Phase II trial in 265 patients with recurrent platinum-sensitive HGSOC and reported that progression-free survival (PFS) as a primary end point was significantly longer in olaparib-receiving patients (median PFS: 8.4 months vs 4.8 months; hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.25–0.49; $P<0.001$). Moreover, the preplanned retrospective analysis for this cohort revealed that PFS benefit was greater in *BRCA*-mutant ovarian cancer (median PFS: 11.2 months vs 4.3 months; HR, 0.18; 95% CI, 0.10–0.31; $P<0.0001$).[48] Based on the above results, the European Medicines Agency (EMA) approved olaparib as a maintenance therapy in 2014 for platinum-sensitive relapsed *BRCA*-mutant HGSOC. Currently, three Phase III trials, termed SOLO1 (NCT01844986), SOLO2 (NCT01874353) and SOLO3 (NCT02282020), are in progress for *BRCA*-mutant ovarian cancer using the primary end point of PFS. Briefly, SOLO1 is a placebo-controlled Phase III trial in which newly diagnosed patients are randomized to olaparib maintenance (300 mg twice per day) or placebo after a platinum-based regimen. In SOLO2, the usefulness of olaparib maintenance for recurrent platinum sensitive-patients is being evaluated. SOLO3 also targets recurrent platinum-sensitive cases, comparing olaparib maintenance (300 mg twice per day) with physician's choice single-agent chemotherapy (PTX, topotecan, pegylated liposomal doxorubicin or GEM). These Phase III trials are expected to yield definite conclusions as to the clinical efficacy of olaparib.

Clinical investigations of olaparib are in progress for patients with breast and prostate cancers, as well as ovarian cancer. Tutt et al[49] conducted a Phase II trial in 54 patients with recurrent BRCA-mutant breast cancer and reported that the ORR was 41% in the 400 mg twice daily cohort and 22% in the 100 mg twice daily cohort. While ORR in *BRCA*-mutant cases was generally similar for patients with ovarian cancer and those with breast cancer, the Phase II trial by Tutt et al[49] found no responders among *BRCA*-wild breast cancer patients, in contrast to an ORR of 24% in *BRCA*-wild ovarian cancer patients.[5] The poor sensitivity of *BRCA* wild-type breast cancer patients might be explained by the biological heterogeneity of breast cancer. Mateo et al[35] performed a Phase II trial in 50 cases with metastatic castration-resistant prostate cancer, resulting in an ORR of 33% in the entire cohort. Among them, 16 cases with homozygous deletions, deleterious alterations or both in DNA-repair genes had an ORR of 88%, including 100% in seven patients with *BRCA2* loss and 80% in five cases with *ATM* aberrations. Based on these clinical data, olaparib received FDA breakthrough designation in 2016 for patients with *BRCA* or *ATM*-mutant castration-resistant prostate cancer, who have progressed on prior taxane-based chemotherapy and abiraterone or enzalutamide as a new-generation hormonal agent.

Talazoparib

Talazoparib (BMN-673; Medivation, San Francisco, CA, USA) has stronger PARP-trapping activity than other PARP inhibitors.[50] In the Phase I trial for patients with advanced solid tumor, MTD was established at 1.0 mg/day and gave ORR values of 50%, 42%, 9%, 20% and 0% in patients with *BRCA*-mutant breast cancer, *BRCA*-mutant ovarian cancer, SCLC, pancreatic cancer and Ewing sarcoma, respectively.[51] The Phase III EMBRACA trial comparing talazoparib with physician's choice is underway for patients with locally advanced and/or metastatic germline *BRCA*-mutant breast cancer (NCT01945775).

Rucaparib

In a Phase I/II study in patients with advanced solid tumors performed by Kristeleit et al,[52] the MTD was established as 600 mg twice per day and the disease control rate (complete response [CR] + partial response [PR] + stable disease

[SD] ≥24 weeks) was 70% in germline *BRCA*-mutant breast cancer patients receiving rucaparib (AG014699; Clovis Oncology, Boulder, CO, USA) ≥300 mg once per day. A Phase II trial in 35 patients with recurrent *BRCA*-mutant ovarian cancer gave an ORR of 65% in the entire cohort.[53] Swisher et al[7] conducted the Phase II ARIEL2 trial in 206 patients with recurrent, platinum-sensitive, high-grade ovarian cancer, where patients were classified into *BRCA* mutant, *BRCA* wild type plus genomic loss of heterogenity (LOH) high and *BRCA* wild-type plus LOH low groups using next-generation sequencing. In this trial, the cutoff value of LOH was defined as 14%. PFS as a primary end point was significantly longer in the BRCA-mutant group and the LOH high/BRCA wild group compared with the LOH low/BRCA wild group (HR, 0.27; 95% CI, 0.16–0.44; $P<0.0001$, 0.62; 95% CI, 0.42–0.90; $P=0.011$, respectively). Their study is clinically useful in demonstrating that genomic LOH, as well as BRCA-mutant status, is helpful for identifying rucaparib responders. Based on these trial data, rucaparib obtained FDA breakthrough designation in 2015 for *BRCA*-mutant ovarian cancer in third-line or later treatment. The Phase III ARIELE3 trial (NCT01968213) is currently in progress for patients with platinum-sensitive ovarian cancer, in which rucaparib maintenance is being compared with placebo with PFS as the primary end point.

Veliparib

Veliparib (ABT-888; AbbVie, North Chicago, IL, USA) is an oral inhibitor possessing relatively weak PARP-trapping activity.[50] In a Phase I trial in patients with *BRCA*-mutant cancer, *BRCA*-wild type platinum-refractory ovarian cancer or basal-like breast cancer, MTD was established at 400 mg twice per day and the ORR values were 23% in *BRCA*-mutant and 4% in *BRCA* wild-type patients.[54] In a Phase II trial by Coleman et al,[55] 50 patients with persistent or recurrent *BRCA*-mutant epithelial ovarian, fallopian tube or primary peritoneal cancer were enrolled to receive veliparib 400 mg twice per day; ORR was 26% in the entire cohort, 20% in platinum-resistant patients and 35% in platinum-sensitive cases.

Niraparib

In the Phase I trial in patients with advanced solid tumor, 300 mg once per day was established as the MTD.[56] Mirza et al conducted the randomized Phase III NOVA trial for a maintenance situation in 553 recurrent platinum-sensitive ovarian cancer patients, who were divided into two groups based on germline *BRCA* mutation and HRR deficiency (HRD) status using BRACAnalysis and myChoice HRD test (Myriad Genetics, Salt Lake City, UT, USA), respectively. Niraparib (MK4827; Tesaro, Waltham, MA, USA) maintenance (300 mg once per day) was compared with placebo with PFS as the primary end point.[8] Remarkably, patients receiving niraparib had a longer PFS, irrespective of germline *BRCA* mutation and HRD status (*BRCA*-mutant cohort: median PFS 21.0 months vs 5.5 months; HR, 0.27; 95% CI, 0.17–0.41; $P<0.001$; non-*BRCA*-mutant and HRD-positive cohort: 12.9 months vs 3.8 months; HR, 0.38; 95% CI, 0.24–0.59; $P<0.001$ and overall non-*BRCA*-mutant cohort: 9.3 months vs 3.9 months; HR, 0.45; 95% CI, 0.34–0.61; $P<0.001$). Based on the promising results of the NOVA trial, the FDA approved niraparib for recurrent platinum-sensitive ovarian cancer regardless of *BRCA* mutation and HRD status in March 2017.

In summary, olaparib is currently the best-established agent for *BRCA*-mutant cases, and this agent is available for prostate cancer and ovarian cancer cases. Rucaparib is promising due to its higher ORR for *BRCA*-mutant cases, and niraparib is the first agent demonstrating PFS prolongation for *BRCA*-wild cases in a Phase III trial. Veliparib has modest activity as a single agent, and so combination therapies are expected to become the mainstream of its clinical development. Talazoparib showed strong cytotoxicity in preclinical models, and further evidence is needed in this respect. In addition to these representative agents, clinical evidence has been gradually accumulated for other PARP inhibitors, including iniparib.[57]

Combination therapy with PARP inhibitor and cytotoxic or molecular-targeted agents

Combination trials of PARP inhibitors are actively underway, usually with cytotoxic agents. Veliparib is considered the most suitable for combination trials because of its modest hematopoietic toxicity.[58] Currently, the Phase III GOG PARTNERS 3005 trial (NCT02470585) is in progress for newly diagnosed ovarian cancer cases. Patients are randomized to the combination of carboplatin (CBDCA)/PTX and veliparib (150 mg twice per day) or CBDCA/PTX alone, followed by maintenance monotherapy with veliparib (400 mg twice per day) or placebo, with PFS as the primary end point.

There are also some impressive data for olaparib combinations. Oza et al[59] conducted a Phase II trial for patients with recurrent platinum-sensitive ovarian cancer, in which patients were randomized to the combination of CBDCA/PTX and olaparib (200 mg twice per day), followed by maintenance

monotherapy with olaparib (400 mg twice per day) or CBDCA/PTX alone, with PFS as the primary end point. PFS was significantly longer in the combination group (median PFS 12.2 months vs 9.6 months; HR, 0.51; 95% CI, 0.34–0.77; *P*=0.0012), and it was prominent in *BRCA*-mutant cases (HR, 0.21; 95% CI, 0.08–0.55; *P*=0.0015). In the randomized Phase II trial by Bang et al,[60] 123 patients with recurrent or metastatic gastric cancer were randomized to the combination of olaparib (200 mg twice per day) and PTX or PTX alone, followed by maintenance monotherapy with olaparib (200 mg twice per day) or placebo. While PFS prolongation (primary end point) was not clearly detected, overall survival (OS) was significantly better in the combination group (median OS: 13.1 months vs 8.3 months; HR, 0.56; 80% CI, 0.41–0.75; *P*=0.005), and the benefit was especially marked in cases with low ATM protein level (median OS: not reached vs 8.2 months; HR, 0.35; 80% CI, 0.22–0.56; *P*=0.002). Although further consideration of the discrepancy between PFS and OS is needed, this trial is noteworthy for demonstrating the impact of BRCAness phenotype in the clinical situation.

In spite of the low PARP-inhibitory activity of iniparib (BSI201, Sanofi S.A., Paris, France) as a single agent, the open-label Phase II trial by O'Shaughnessy et al[61] found that combination therapy with iniparib and GEM/CBDCA improved not only CBR as a primary end point but also OS compared with GEM/CBDCA alone (56% vs 34%; *P*<0.01, median OS: 12.3 months vs 7.7 months; HR, 0.57; 95% CI, 0.36–0.90; *P*=0.01).[62,63] However, the subsequent Phase III trial for patients with metastatic TNBC failed to demonstrate prolongation of OS (median OS: 11.8 months vs 11.1 months; HR, 0.88; 95% CI, 0.69–1.12; *P*=0.28), and further evaluation of the survival benefits of this agent is needed.[63,64]

Combinations with molecular-targeted agents and cytotoxic agents are under investigation and in some cases have moved to the clinical trial phase. Angiogenesis inhibitors seem to be attractive, in that this class of agents downregulates HRR genes through constructing a hypoxic tumor environment.[65] Liu et al[66] reported a randomized Phase II trial of cediranib, which is an oral tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptor (VEGFR)1, VEGFR2 and VEGFR3. In their trial, 90 patients with recurrent platinum-sensitive ovarian cancer were randomized to the combination group of olaparib (200 mg twice per day) and cediranib (30 mg per day) or the olaparib (400 mg twice per day) alone group. PFS was significantly longer in the combination group (median PFS: 17.7 months vs 9.0 months; HR, 0.42; 95% CI, 0.23–0.76; *P*=0.005), and in response to this promising result, Phase III trials of a combination regimen of olaparib and cediranib are underway (NCT2502266, NCT02446600, ICON9). Clinical trials of combination regimens of PARP inhibitors with cytotoxic agents, molecular-targeted agents or immunotherapies that are currently in progress are summarized in Table 2.

Toxicity profiles of PARP inhibitors

The grade 3–4 toxicity profiles in patients receiving five PARP inhibitors at their MTDs are shown in Table 3. According to previous reports on the aforementioned five inhibitors, nausea and fatigue were detected in >50% of cases in common, but the percentage of grade 3–4 events was <10%. The frequency of hematological toxicity varied depending on the agent and was conspicuous in clinical trials of talazoparib and niraparib.[8,51] In a Phase III trial of niraparib, grade 3–4 thrombocytopenia, anemia and neutropenia were detected in >20% of the patients.[8] On the other hand, in a Phase II trial of veliparib, these events were detected in <2% of the cases. Thus, the moderate hematopoietic toxicity of veliparib could be advantageous for developing combinations with cytotoxic agents.[55] Moreover, rucaparib increased aspartate transaminase (AST) and alanine aminotransferase (ALT), but these changes were asymptomatic and normalized over time during continuous administration.[7] PARP inhibitors are newcomers in the field of oncology, and detailed toxicity profiles for long-term administration of PARP inhibitors remain to be established. Clinical trial data indicate that the onset of treatment-related myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are serious issues.[67] According to the US Package Insert for olaparib, MDS/AML was reported in 22 of 2,618 patients (0.8%), of which 17 cases were fatal, and the duration from olaparib initiation to the onset of MDS/AML ranged from <6 months to >2 years.[68] Because all patients had received previous chemotherapy with platinum agents and/or other DNA-damaging agents, it is not clear whether olaparib directly caused MDS/AML. It is possible that the combined effects of PARP inhibition and DNA damage due to cytotoxic agents or the innate defect of *BRCA* might promote the onset of MDS/AML. DNA-repair inhibitors such as PARP inhibitors might increase intratumor genomic mutation rates and induce evolution of metastatic or resistant clones.[69] As for other agents, MDS/AML was reported in two of 377 patients (0.5%) treated with rucaparib and seven of 751 patients (0.9%) treated with niraparib.[70,71] Therefore, clinicians should monitor each patient's complete blood count carefully and stop the inhibitor administration immediately if MDS/AML is clinically suspected. Moreover, preclinical models suggested an association of PARP1 with

Table 2 Ongoing trials of PARP inhibitor combinations

PARP inhibitor	Combination agents	Phase	Types of malignancies	NCT identifier
Olaparib	AZD2014 (mTORC 1/2 inhibitor) or AZD5363 (AKT inhibitor)	I	Breast cancer, malignant female reproductive system tumors	NCT02208375
Olaparib	Prexasertib	I	Solid tumors	NCT03057145
Olaparib	AZD2281, AZD5363, AZD1775 or AZD2014	II	Tumors	NCT02576444
Olaparib	AT13387 (heat shock protein 90 inhibitor)	I	Ovarian cancer, fallopian tube cancer, peritoneal cancer and TNBC	NCT02898207
Olaparib	Cediranib, MEDI4736 (anti-PD-L1 antibody)	I/II	Lung cancer, breast cancer, ovarian cancer, colorectal cancer, prostate cancer and TNBC	NCT02484404
Olaparib	Temozolomide	I	Ewing sarcoma	NCT01858168
Olaparib	AZD1775 (tyrosine kinase WEE1 inhibitor)	I	Ovarian cancer, breast cancer and SCLC	NCT02511795
Olaparib	Temozolomide	I	Brain and central nervous system tumors	NCT01390571
Olaparib	CRLX101 (nanoparticle camptothecin)	I/II	SCLC	NCT02769962
Olaparib	Neoadjuvant carboplatin and paclitaxel	II/III	TNBC and germline *BRCA*-positive breast cancer	NCT03150576
Talazoparib	Decitabine	I/II	Acute myeloid leukemia	NCT02878785
Talazoparib	Temozolomide	I/II	Solid tumors	NCT02116777
Veliparib	VX-970 (ATR) and cisplatin	I	Tumors	NCT02723864
Veliparib	Intraperitoneal floxuridine	I	Fallopian tube cancer, ovarian cancer and primary peritoneal cancer	NCT01749397
Veliparib	Carboplatin and paclitaxel	III	*BRCA*-mutant breast cancer	NCT02163694
Veliparib	FOLFIRI or modified FOLFIRI	II	Pancreatic cancer	NCT02890355
Veliparib	Carboplatin and paclitaxel	III	Ovarian cancer, fallopian tube cancer and peritoneal cancer	NCT02470585
Veliparib	Topotecan hydrochloride	I/II	Solid tumors	NCT01012817
Niraparib	Temozolomide or irinotecan	I	Ewing sarcoma	NCT02044120
Niraparib	Pembrolizumab	I/II	Ovarian cancer, fallopian tube cancer, peritoneal cancer and TNBC	NCT02657889
Fluzoparib	Apatinib and paclitaxel	I	Gastric cancer	NCT03026881
Fluzoparib	Apatinib	I	Ovarian cancer and TNBC	NCT03075462
BGB-290	BGB-A317 (anti-PD-1 monoclonal antibody)	I	Solid tumors	NCT02660034

Abbreviations: FOLFIRI, folinic acid/fluorouracil/ irinotecan; NCT, National Clinical Trial; PD-1, programmed death-1; PD-L1, programmed death-ligand1; TNBC, triple-negative breast cancer; SCLC, small cell lung cancer.

cardiovascular diseases and long-term memory formation, and long-term observation is required to examine the effects on the cardiovascular system and on mental health.[31]

Identification of biomarkers predicting suitable cases

Identification of responders to PARP inhibitors is important for providing maximum clinical benefit to suitable cases and for preventing development of drug resistance and is also desirable from a cost–benefit point of view. However, there are no established strategies for identifying relevant candidates, although combinations of various kinds of biomarkers with clinicopathological features have been investigated with a focus on detecting HRR-deficient cases.[33] According to the Phase I trial conducted by Fong et al,[46] platinum-free interval was significantly associated with CBR for olaparib

Table 3 Grade 3–4 toxicity profiles of PARP inhibitors

Grade 3–4 adverse events	Olaparib (n=298)[42]	Talazoparib (n=71)[47]	Rucaparib (n=204)[50]	Veliparib (n=50)[52]	Niraparib (n=367)[54]
Nausea	0%	0%	4%	4%	3%
Vomiting	2%	Not reported	2%	0%	2%
Fatigue	6%	Not reported	9%	Not reported	8%
Abdominal pain	6%	Not reported	2%	Not reported	1%
Thrombocytopenia	Not reported	18%	2%	2%	34%
Anemia	17%	23%	22%	0%	25%
Neutropenia	Not reported	10%	7%	2%	20%
Hypertension	Not reported	Not reported	Not reported	Not reported	8%
Increased AST/ALT	Not reported	Not reported	12%	Not reported	Not reported

Abbreviations: AST, aspartate transaminase; ALT, alanine aminotransferase; PARP, poly(ADP-ribose) polymerase.

administration, and Cochrane's review of 599 patients with epithelial ovarian cancer noted that PARP inhibitors appeared to improve PFS in recurrent platinum-sensitive disease, whereas clinical significance for platinum-resistant disease was undetermined.[72] These data highlight platinum sensitivity as a clinical surrogate marker predicting PARP inhibitor's responsiveness. Assays for the HRR pathway include targeted sequencing, whole-genome sequencing, copy number analyses, gene-expression profiling, protein expression assays and functional assays.[69]

Genomic analysis is a direct and comprehensive approach for predicting suitable cases and has already been embedded in clinical trials, but it is relatively expensive for routine use in many institutions and requires frozen or formalin-fixed paraffin-embedded (FFPE) tumor specimens for analysis, as well as bioinformatic support from experts.[33] In addition, this approach is often affected by different analytical approaches and genomic heterogeneity among tumor specimens; also, genomic alterations do not necessarily cause functional changes in proteins.[73,74] Genomic scars (accumulated patterns of DNA damage and repair) are unique in HRR-deficient cases, and these characteristic signatures are caused by large genomic deletions and LOH owing to the activation of inaccurate NHEJ. Telli et al[75] defined an HRD score composed of LOH, telomeric allelic imbalance and large-scale state transitions and reported that this index predicted response to neoadjuvant platinum-based regimen in cases with TNBC, regardless of *BRCA*-mutant status. In a prospective trial setting, two indexes (LOH and HRD score) were adopted for the ARIEL2 trial of rucaparib and the NOVA trial of niraparib, confirming the position of HRD score as an independent prognostic factor.[7,8] Previous studies indicate that the total number of exome alterations, including nonsynonymous ones, was also associated with clinical outcomes in *BRCA*-mutant ovarian cancers.[69]

In terms of functional biomarkers, the detection of RAD51 foci with immunofluorescence is useful because of its rapidity. While administration of PARP inhibitors increases expression of RAD51 foci in HRR-proficient tumors, RAD51 foci remain absent in HRR-deficient tumors, indicating a role of RAD51 as a key player in the HRR signaling pathway.[12,76] One weakness of this method is that we cannot predict the change in RAD51 foci prior to actual drug exposure.[12] PARP1 is an essential substrate for PARylation, and immunohistochemical analysis by von Minckwitz et al[77] showed that high cytoplasmic PARP expression predicted high sensitivity to chemotherapy in breast cancer samples. Moreover, elevated PAR levels detected by Western blot or immunohistochemistry or E26 transformation-specific sequence (ETS) gene fusions observed in Ewing's sarcoma and prostate cancer are promising biomarkers.[78,79] However, the usefulness of the aforementioned factors for the identification of PARP inhibitor responders has mainly been demonstrated in preclinical models, and their clinical relevance needs to be properly assessed in clinical trials.

Mechanisms of clinical resistance

Development of drug resistance is a major problem in patients receiving the same treatment regimen for a long period. Resistance to PARP inhibitors can appear at many steps of the DNA-repair pathways. A conceptual diagram of resistance mechanisms, classified into increased HRR capacity, decreased activity of PARP-1 and decreased intracellular availability of PARP inhibitor, is shown in Figure 1.[80]

Recovery of HR is an important mechanism. Edwards et al[81] examined *BRCA2* c.6174delT mutation of a BRCA2-deficient human pancreatic cancer cell line (CAPAN1) and reported that this frameshift mutation resulted in normalization of the functions of BRCA2 protein. Sakai et al[73] established seven subclones with restored BRCA2 protein and seven subclones without BRCA2 protein from CAPAN1 and found that the sensitivity to PARP inhibitors was lower in clones with secondary *BRCA2* mutation than in those without *BRCA2* mutation. Barber et al[82] compared genomic information for primary and metastatic samples from a male breast tumor patient developing resistance to olaparib and detected a secondary *BRCA2* c.9106C > G mutation leading to the functional restoration of BRCA2 protein. In the context of cisplatin resistance, Swisher et al[83] compared recurrent platinum-resistant and platinum-sensitive tumors and reported that four of six in the former group developed secondary genetic changes in *BRCA1* leading to functional BRCA1 protein restoration, whereas none of three in the latter group developed *BRCA1* sequence alterations. Norquist et al[84] reviewed 46 recurrent ovarian cancer patients and reported that the percentage of secondary mutations restoring BRCA1/BRCA2 was significantly higher in platinum-resistant cases than in platinum-sensitive ones (46% vs 5%, P=0.003). Dhillon et al[85] proposed an interesting model of secondary BRCA restoration from a primary chemotherapy-sensitive tumor. First, BRCA-restored subclones coincidentally arise from initially BRCA-deficient or chemotherapy-sensitive tumor as a result of increased mutation rates associated with DNA-damaging agents. Next, these clones spread through selective pressure from repeated drug administrations. This theory might reasonably explain the induction of PARP inhibitor resistance during repeated cisplatin administrations.

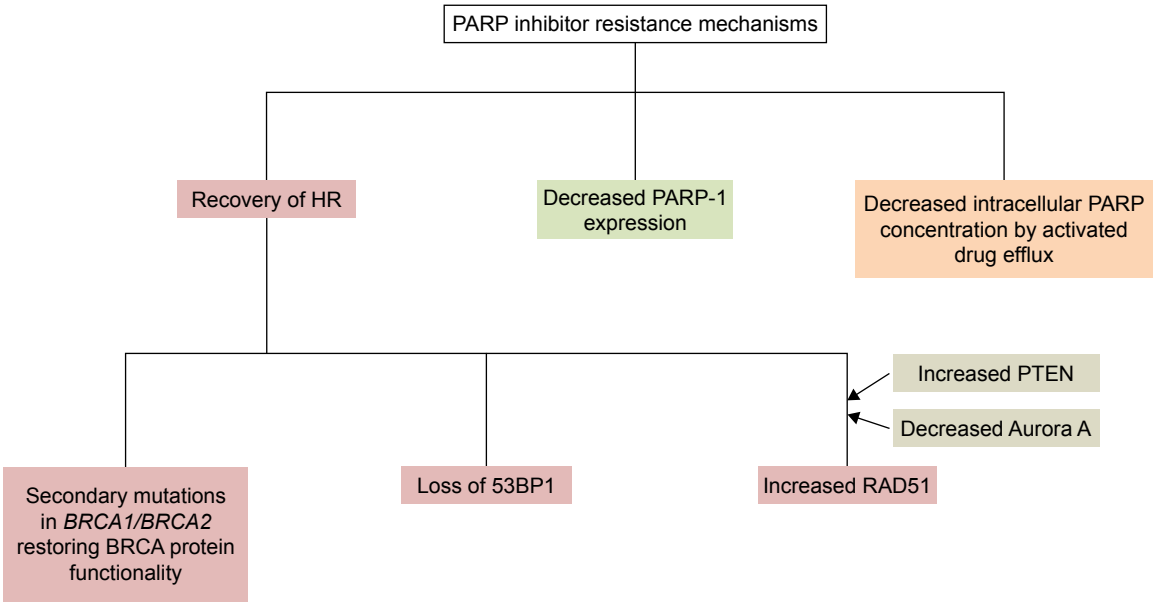

Figure 1 Conceptual diagram of resistance mechanisms to PARP inhibitors.
Notes: These processes are categorized into three groups (recovery of HRR, decreased PARP-1 expression, and decreased intracellular PARP concentration due to activation of drug efflux). Secondary mutations in *BRCA1/BRCA2*, loss of 53BP1 and increased RAD51 finally result in recovery of HRR, where PTEN or Aurora A indirectly regulate RAD51 activity.
Abbreviations: PARP, poly(ADP-ribose) polymerase; HRR, homologous recombination repair.

As for other HRR-related factors, P53-binding protein 1 (53BP1) plays a key role in DNA-repair responses and checkpoint control, and loss of 53BP1 promotes ATM-dependent resection of broken DNA ends in BRCA1-deficient cells and finally restores HRR.[86,87] An association between increased RAD51 activity and resistance to PARP inhibitors is also indicated, and Aurora A and PTEN modulate RAD51 activity indirectly.[80,88,89] Aurora A inhibits the recruitment of RAD51 to DNA damage sites, while PTEN deficiency causes a reduction in RAD51 expression. RAD51 forms a complex with BRCA2, and its combination with damaged DSB is indispensable to HRR, so that increased RAD51 activity leads to resistance to PARP inhibitors.[90] Kondrashova et al[91] recently sequenced HRR pathway genes in PARP inhibitor pretreatment and post-progression tumor samples from patients enrolled in the ARIEL2 trial and detected secondary mutations in *RAD51C* and *RAD51D* associated with PARP inhibitor resistance.

P-Glycoprotein (P-gp; multi-drug resistance protein) acts as a drug efflux pump to decrease intracellular drug concentration and is associated with resistance to various kinds of agents. An in vivo model by Rottenberg et al[92] showed upregulation of the P-gp-encoding *ABCB1A/B* genes after long-term PARP administration. In addition, preclinical studies suggest other possibilities, including regulation by micro RNA, epigenetic re-expression of BRCA1, phosphorylation of PARP1 by c-Met and overexpression of HOX family members.[93–97]

Large-scale genomic data also revealed the genomic backgrounds of refractory or resistant cases. Patch et al[98] performed whole-genome sequencing of 92 ovarian cancer patients with primary refractory, resistant, sensitive and matched acquired resistant disease and identified several molecular events associated with acquired resistance, including reverse germline *BRCA1/BRCA2* mutation, loss of BRCA1 promoter methylation and *ABCB1* rearrangement. The practical relevance of these mechanisms should be considered in future clinical trials.

Conclusion and prospects for the future

The concept of synthetic lethality led to great interest in PARP inhibitors as candidate antitumor agents, and clinical applications of this class of agents have so far focused mainly on *BRCA*-mutant ovarian cancer. Olaparib, rucaparib and niraparib are already available under US health insurance. Detailed assays for HRR repair pathway components, including genomic analysis, are broadening the applicability of PARP inhibitors in HRR-deficient cases, and future investigations are expected to focus on HRR-proficient cases and various kinds of malignancies other than ovarian, prostate and breast cancers (Figure 2). Considering the variety of patients who may receive clinical benefit from PARP inhibitors, we consider that intergroup studies will be essential to improve and extend current clinical outcomes.

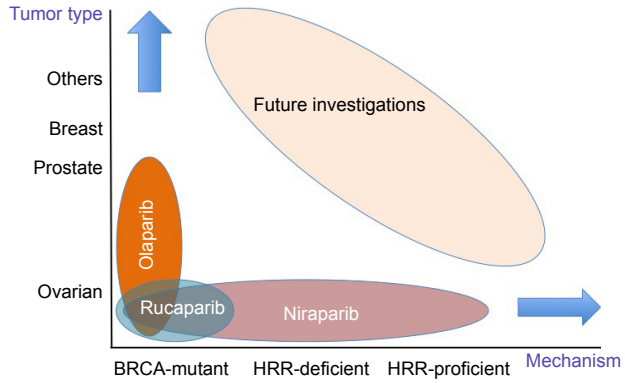

Figure 2 Current indications for olaparib, rucaparib, and niraparib.
Notes: The differences among these agents, which are available under US health insurance, probably reflect the characteristics of patients who participated in the relevant clinical trials. Future investigations should be focused on HRR-proficient cases and malignancies other than ovarian, prostate and breast cancers.
Abbreviation: HRR, homologous recombination repair.

In addition to the need for well-established biomarkers to predict suitable cases and resistance mechanisms, there are several areas where further work is needed to realize the full potential of PARP inhibitors (Figure 3). First, although clinical evidence for each agent has been accumulating gradually, direct comparative data of the available agents are lacking, and we cannot draw a clear conclusion as to which agent is the best option in each clinical context. In this sense, further accumulation of preclinical data and further randomized clinical trials are essential to establish the status of each agent. Second, the FDA approved the first PARP inhibitor, olaparib, in 2014, so that only about 3 years have passed since marketing. Therefore, potential long-term toxicities, including secondary malignancies, are not clear, and further follow-up data in clinical trials and postmarketing surveillance are indispensable to uncover the toxicity profile of this agent. Third, clinical effects on HRR-proficient tumors are not evident, except for niraparib. In addition, it would be desirable to discover new cascades other than the HRR pathway to provide additional indications for PARP inhibitors. Fourth, clinical trials so far performed have not demonstrated OS prolongation, in spite of PFS benefit. The current gold standard for assessment of efficacy of new agents is a statistically significant and clinically meaningful improvement in OS and quality of life (QOL). The surrogacy of PFS for OS is established only in advanced colorectal and ovarian cancers, and the clinical meaning of PFS in other types of tumors is not yet clear.[99] A longer follow-up period is required for assessment of OS, and at the same time, development of powerful combination regimens is expected to bring better clinical benefits. Interestingly, the olaparib trial data showed that high-dose olaparib gave a higher ORR, and

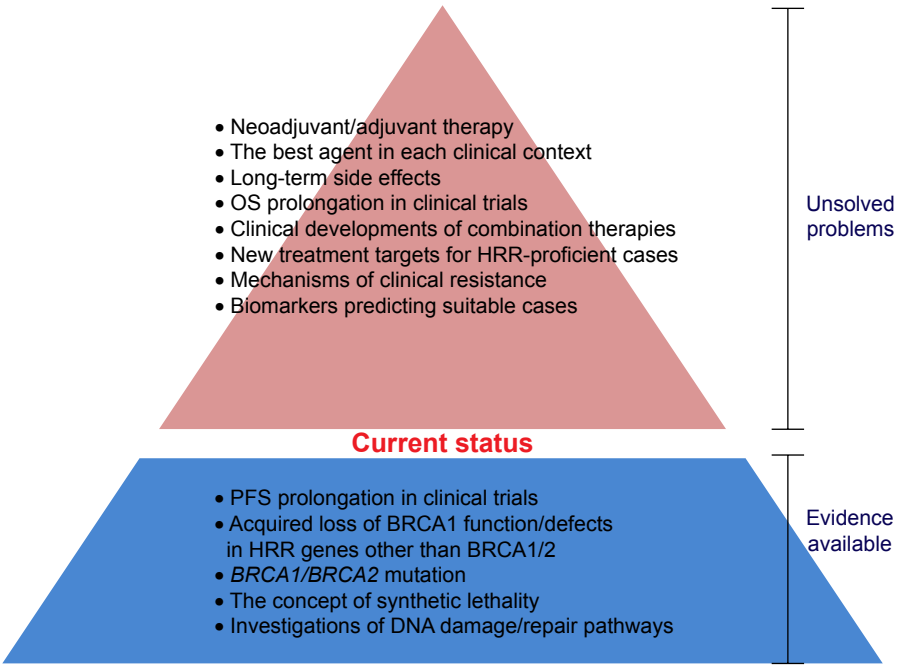

Figure 3 Current status of PARP inhibitors.
Notes: Recent advances in preclinical models have provided fundamental data on synthetic lethality and HRR pathways, and clinical trials have shown PFS prolongation with a focus on *BRCA*-mutant tumors. On the other hand, several issues remain, such as discovering new treatment targets for HRR-proficient cases or selecting the best agent in each clinical context. In the future, it will be important to demonstrate OS prolongation as a real clinical end point through development of PARP inhibitor combination regimens or neoadjuvant/adjuvant therapies.
Abbreviations: PARP, poly(ADP-ribose) polymerase; HRR, homologous recombination repair; PFS, progression-free survival; OS, overall survival.

the combination of high-dose olaparib with relatively low-dose cytotoxic agents seems to be an appropriate approach to concurrently achieve efficacy and tolerance.[42,47,49] However, clinical benefits need to be comprehensively evaluated from the viewpoints of QOL and cost-effectiveness, as well as OS. Finally, further accumulation of evidence about PARP inhibitors may lead to expanded adoption for neoadjuvant or adjuvant therapy in operable patients or preventive administration in *BRCA* mutation carriers in the future. Based on favorable trial data for pancreatic cancer, clinical development for intractable cancers, including this disease, might be promising.[4,51] PARP inhibitors are considered advantageous for these adaptations in that the target population is small and well-defined and the risk is unlikely to outweigh the clinical benefit, since the complications resulting from the use of this class of agents are mild.[100]

Disclosure

The authors report no conflicts of interest in this work.

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