Review

Clinical Cancer Research

PARP Inhibitors: Extending Benefit Beyond *BRCA*-Mutant Cancers

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Abstract

A mounting body of evidence now indicates that PARP inhibitors have the potential to be used as a foundation for both monotherapy and combination strategies across a wide spectrum of molecular backgrounds and tumor types. Although PARP inhibitors as a class display many similarities, critical differences in structure can translate into differences in tolerability and antitumor activity that have important implications for the clinic. Furthermore, while PARP inhibitors have demonstrated a clear role in treating tumors with underlying homologous recombination deficiencies, there is now biological and early clinical evidence to support their use in other molecular subsets of cancer, including tumors associated with high levels of replication stress such as small-cell lung cancer. In this article, we highlight the key similarities and differences between individual PARP inhibitors and their implications for the clinic. We discuss data that currently support clinical strategies for extending the benefit of PARP inhibitors beyond *BRCA*-mutant cancers, toward broader populations of patients through the use of novel biomarkers of homologous recombination repair deficiency (HRD), as well as predictive biomarkers rooted in mechanisms of sensitivity outside of HRD. We also explore the potential application of PARP inhibitors in earlier treatment settings, including neoadjuvant, adjuvant, and even chemoprevention approaches. Finally, we focus on promising combination therapeutic strategies, such as those with other DNA damage response (DDR) inhibitors such as ATR inhibitors, immune checkpoint inhibitors, and non–DDR-targeted agents that induce "chemical BRCAness."

Introduction

The establishment of the relationship between the tumor-suppressive genes *BRCA*1 and *BRCA2* (*BRCA1/2*) and hereditary breast and ovarian cancer syndrome (HBOC) revolutionized clinical cancer genetics, and led to increased research focused on germline variant testing, risk stratification, early detection, and cancer prevention for *BRCA1/2* mutation carriers (1). BRCA1 and BRCA2 are key proteins in the DNA Damage Response (DDR), and over the past two decades, key advances in next-generation sequencing, as well as epigenetic and expression-level profiling technologies have rapidly expanded our understanding of the role of DDR pathway deficiencies and associated genomic instability in cancer initiation and evolution. Critically, they have also informed the field on how they can be rationally targeted for cancer therapy (2). Preclinical and clinical studies have revealed key gene networks that may directly or indirectly influence DDR, and which now include molecular aberrations beyond *BRCA1/2* mutations, as well as tumor types outside of breast and ovarian cancers (3–6). Previously, the identification of a germline *BRCA1/2* mutation generally only impacted cancer screening and prevention practices for that patient and their relatives; however, the discovery that small-molecule inhibitors of PARP selectively killed *BRCA1/2*-mutant cancer cells has now led to new therapeutic approaches in the clinic for patients with DDR gene aberrations (7–10). In this article, we review the PARP inhibitors currently in the clinic with respect to their known mechanism(s) of action, current single-agent applications, key similarities and differences, predictive biomarkers of response and resistance, and rational combinatorial strategies with other anticancer agents.

Targeting PARP in Cancer

DNA damage activates a complex range of processes, including DDR signaling, DNA repair, cell-cycle regulation, and potentially also an immunologic response, all of which have been extensively reviewed previously (6, 7, 11–14). Briefly, DNA single-strand breaks resulting from processes that remove misincorporated rNTP incorporation, dNTP mismatches, or bases following oxidative damage are the most common; however, DNA double-strand breaks (DSB) are the most cytotoxic. The high-fidelity homologous recombination repair (HRR) pathway faithfully repairs DNA DSBs by using the replicated sister chromatid DNA when available, and the activities of key molecules including BRCA1/2 and RAD51 among others (15). If an undamaged

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Clin Cancer Res 2019;25:3759–71

doi: 10.1158/1078-0432.CCR-18-0968

template DNA is unavailable, then the more rapid but error-prone nonhomologous end joining (NHEJ) repair pathway is the primary method of DNA DSB repair in the cell, utilizing essentially a direct ligation approach (16). The PARP family of proteins plays a key role in a variety of cellular processes that includes DNA repair, chromatin modulation, and aspects of the replication stress response (7, 17). With regard to DNA repair, PARP1 and PARP2 play critical roles in DNA strand break repair through multiple DDR pathways, with HRR-deficient cells showing a greater reliance on PARP activity to maintain cell survival (7).

The primary activity of PARP1, and the closely related PARP2 protein, is the poly-ADP ribosylation (PARylation) of key components of chromatin and DDR as well as auto-PARylation (18). PARP1 activity both opens up chromatin and facilitates recruitment of downstream DNA repair factors to damaged sites (18). After completing this recruitment role, PARP auto-PARylation triggers the release of bound PARP from DNA to allow access for other DNA repair proteins to complete repair. Thus, the binding of PARP to damaged sites, its catalytic activity, and its eventual release from DNA are all necessary steps for a cancer cell to respond to DNA breaks introduced by certain chemotherapies, radiation, and various forms of endogenous damage (7). It has been shown that preclinical models with biallelic loss of *PARP* show viability under normal conditions, but are exquisitely sensitive to alkylating chemotherapy and DNA-damaging radiation.

Synthetic lethality describes a bimodal dependency whereby the loss-of-function of just one component in a cell or organism does not have a significant impact on viability, yet the combined loss of both components results in cell death due to the interdependent and/or compensatory nature of the two pathways (7). The finding that single-agent PARP inhibition selectively killed *BRCA1* (8) or *BRCA2* (9)-deficient cells was a pivotal discovery that ushered in new synthetic lethal therapeutic approaches in clinical oncology. This was soon followed by the demonstration that non-BRCA deficiencies in the HRR pathway also resulted in PARP inhibitor single-agent sensitivity (19). In this cardinal example of DDR-based synthetic lethality, it is the PARP inhibitor that can trap PARP protein onto the DNA at the single-strand break (SSB) as the initiating event. If the inhibitor stays bound within the PARP-active site and the PARP protein is trapped on the DNA long enough to be encountered by the replication machinery, this can result in a stalling of the replication fork, its collapse, and the generation of a DNA DSB. In cancer cells deficient for HRR, classical NHEJ is employed, generating error-prone repair which, after multiple rounds of DNA replication, can lead to unsustainable levels of genomic instability and cancer cell death. Conversely, normal cells with functional HRR are able to deal with the DSBs accurately and effectively. This example of PARP inhibitor synthetic lethality in HRR-deficient cancer cells heralded the promise of cancer cell–specific killing and importantly, an opportunity for a wide therapeutic window (2).

Progress of PARP Inhibitors in the Clinic

Currently, six small-molecule PARP inhibitors are available in the clinic—olaparib (the first PARP inhibitor to test the synthetic lethality concept in the clinic), rucaparib, niraparib, talazoparib, veliparib, and pamiparib (Fig. 1). Olaparib, rucaparib, and niraparib have all obtained FDA and/or EMA approval in ovarian cancer in different settings. Olaparib, and very recently talazoparib, are currently the only FDA-approved PARP inhibitors for metastatic *BRCA1/2*-mutant breast cancer (20, 21). Although pamiparib only recently entered phase I trial testing, a favorable safety profile and preliminary antitumor activity have resulted in the initiation of randomized phase III trials versus placebo for maintenance therapy in both platinum-sensitive gastric and ovarian cancers (22). Veliparib does not yet have an approved label, and its use is being investigated mostly in combination with chemotherapy or targeted agents. The likely reason for this is described below.

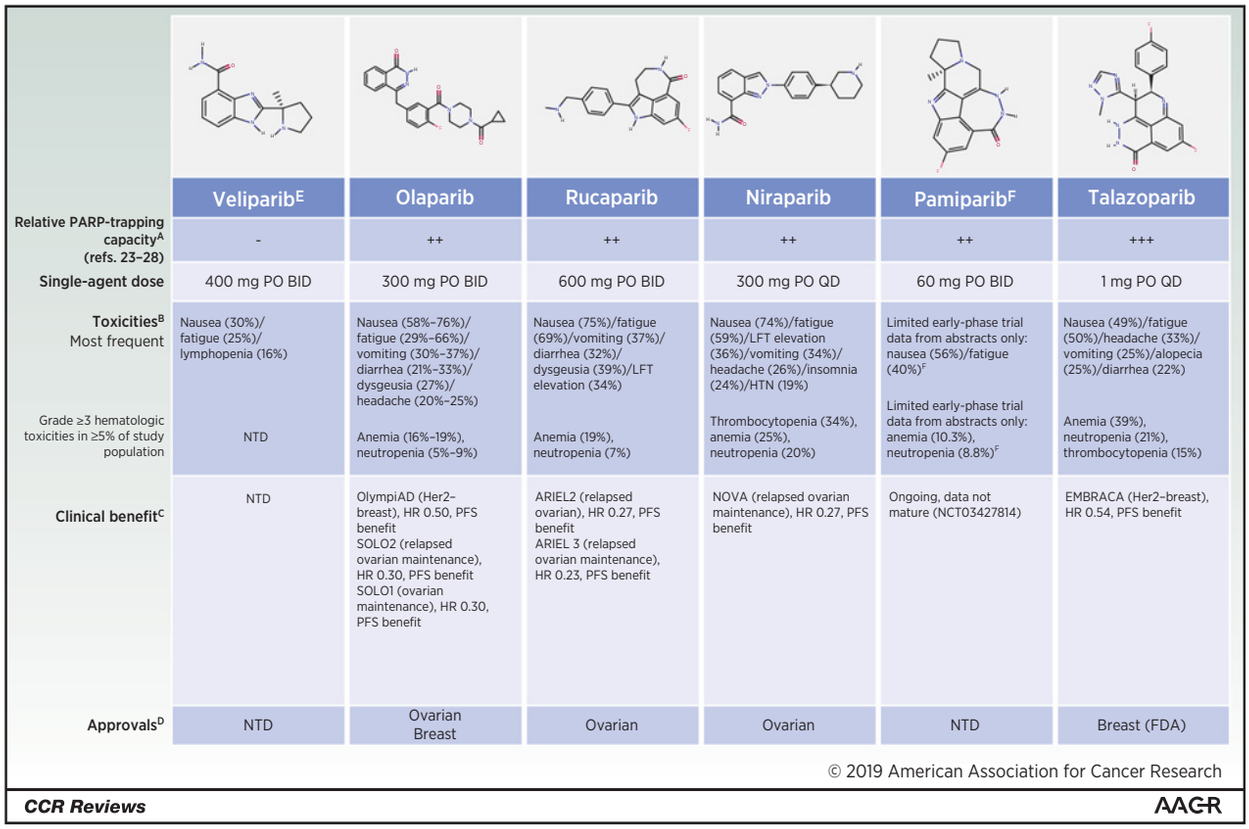
Are All PARP Inhibitors Created Equally?

Preclinical and clinical data so far on the different PARP inhibitors have revealed many similarities, but also notable differences, resulting from the different chemical structures of each PARP inhibitor (Fig. 1; refs. 23, 24). In addition, sequential tumor and/or liquid biopsies in PARP inhibitor–treated preclinical models and patients are giving researchers a better understanding of the underlying mechanisms of sensitivity and resistance to this class of drugs, potentially paving the way forward for the development of functional biomarkers for rational patient selection.

Preclinical studies

The PARP inhibitors currently approved for clinical use and those still under trial development all share a similar capacity to outcompete NAD^+ binding to the PARP catalytic domain and to inhibit the acute PARylation of downstream substrates and PARP itself, with anticatalytic activity seen in the nanomolar range for each drug (Fig. 1; refs. 24, 25). Clinical studies of PARP inhibitors have used the quantification of PAR chain formation in peripheral blood lymphocytes as a pharmacodynamic biomarker, demonstrating that they can cause the acute and complete inhibition of PARP enzymatic activity, even at subtherapeutic doses. Importantly, such abrogation of enzymatic activity was not found to correlate with clinical responses, and the reasons behind this have not at this time been satisfactorily explained.

Despite the mechanistic similarities in anticatalytic function, the six PARP inhibitors differ in their chemical structure, preclinical potency, and clinical doses used for patients (Fig. 1). With respect to chemical structure, veliparib is the smallest of the PARP inhibitors, whereas talazoparib is the largest in size and possesses a more rigid structure (25). These differences in size and rigidity are thought to be the basis for the off-rate of each PARP inhibitor, and therefore the distinct capacity of each drug to prevent the release of bound PARP1/2 from chromatin—a phenomenon known as "PARP trapping" (25). However, PARP inhibitors do not trap PARP to DNA simply by inhibiting the catalytic activity and auto-PARylation of PARP in the short term; otherwise the class of PARP inhibitors would not display such different PARP-trapping abilities and single-agent cytotoxicities. Rather, as described above, PARP trapping, in addition to the inhibition of catalytic activity, also requires a slow "off-rate," and as long as the inhibitor is bound to the active site, NAD cannot be utilized for auto-PARylation and DNA dissociation. Talazoparib is able to bind chromatin and create these trapped PARP–DNA complexes to an approximately 100-fold greater degree than rucaparib, niraparib, or olaparib, whereas veliparib displays negligible PARP-trapping ability (23–26). Although preclinical data on pamiparib is more limited than the other PARP inhibitors, a



	Veliparib[E]	Olaparib	Rucaparib	Niraparib	Pamiparib[F]	Talazoparib
Relative PARP-trapping capacity[A] (refs. 23–28)	-	++	++	++	++	+++
Single-agent dose	400 mg PO BID	300 mg PO BID	600 mg PO BID	300 mg PO QD	60 mg PO BID	1 mg PO QD
Toxicities[B] Most frequent	Nausea (30%)/ fatigue (25%)/ lymphopenia (16%)	Nausea (58%–76%)/ fatigue (29%–66%)/ vomiting (30%–37%)/ diarrhea (21%–33%)/ dysgeusia (27%)/ headache (20%–25%)	Nausea (75%)/fatigue (69%)/vomiting (37%)/ diarrhea (32%)/ dysgeusia (39%)/LFT elevation (34%)	Nausea (74%)/fatigue (59%)/LFT elevation (36%)/vomiting (34%)/ headache (26%)/insomnia (24%)/HTN (19%)	Limited early-phase trial data from abstracts only: nausea (56%)/fatigue (40%)[F]	Nausea (49%)/fatigue (50%)/headache (33%)/ vomiting (25%)/alopecia (25%)/diarrhea (22%)
Grade ≥3 hematologic toxicities in ≥5% of study population	NTD	Anemia (16%–19%), neutropenia (5%–9%)	Anemia (19%), neutropenia (7%)	Thrombocytopenia (34%), anemia (25%), neutropenia (20%)	Limited early-phase trial data from abstracts only: anemia (10.3%), neutropenia (8.8%)[F]	Anemia (39%), neutropenia (21%), thrombocytopenia (15%)
Clinical benefit[C]	NTD	OlympiAD (Her2–breast), HR 0.50, PFS benefit SOLO2 (relapsed ovarian maintenance), HR 0.30, PFS benefit SOLO1 (ovarian maintenance), HR 0.30, PFS benefit	ARIEL2 (relapsed ovarian), HR 0.27, PFS benefit ARIEL 3 (relapsed ovarian maintenance), HR 0.23, PFS benefit	NOVA (relapsed ovarian maintenance), HR 0.27, PFS benefit	Ongoing, data not mature (NCT03427814)	EMBRACA (Her2–breast), HR 0.54, PFS benefit
Approvals[D]	NTD	Ovarian Breast	Ovarian	Ovarian	NTD	Breast (FDA)

Figure 1.

Comparison of PARP inhibitors under clinical development. **A,** Relative PARP trapping taken from multiple preclinical studies (23–26). **B,** Most frequent adverse events when given as single agent, followed by occurrence of grade 3 or higher cytopenias when given as single agent. **C,** Clinical benefit as derived from mature phase III data. **D,** Tumor types with both FDA/EMA approvals unless noted. **E,** Mature phase III data on single-agent veliparib are not available or being pursued at this time; side effects obtained from phase II study (114). **F,** Pamiparib has only been through phase I testing to date; phase III trials registered as noted. BID, twice a day; HTN, hypertension; LFT, liver function test; NTD, none to date; PFS, progression-free survival; PO, orally; QD, every day.

study in cell line models showed that this drug is able to form PARP–DNA complexes at an IC_{50} of 13 nmol/L. In addition, pamiparib displayed 10-fold greater potency and antitumor activity in a *BRCA1*-mutant breast cancer xenograft compared with olaparib (27, 28). However, while sufficient PARP trapping is required for single-agent activity in HRR-deficient cancers, it does not directly correlate with clinical efficacy. This is because the stronger PARP trappers often have to be used at lower doses in the clinic due to lower MTD achieved (25).

Novel insights are now emerging that may help to explain the basis of the balance between efficacy, specificity, and tolerability profiles in the clinic. For example, a recent study by Leo and colleagues comparing all aforementioned PARP inhibitors, apart from pamiparib, showed that the cytotoxic potential of each of the five PARP inhibitors differs between HRR-deficient (HRD) and HRR-proficient isogenic cell lines, whereby olaparib showed the most HRD-specific sensitivity, and talazoparib was the most agnostic to HRR status with regard to its cytotoxicity. Veliparib displayed the least efficacy in both the HRD and HRR-proficient lines (24).

Clinical studies

Each of the PARP inhibitors have shown generally favorable safety profiles in clinical trials, with the most common side effects including fatigue, gastrointestinal (GI) symptoms, and bone marrow suppression. Anecdotally, PARP inhibitor–related toxicities, such as GI symptoms and fatigue, have interestingly been observed to improve over time while on therapy. Although the underlying mechanisms for this clinical phenomenon are still unclear, they have important implications for encouraging patients and physicians to continue PARP inhibitor therapy at their starting doses while optimizing supportive therapies. The frequency and grade of cytopenias do seem to differ between PARP inhibitors in clinical trials carried out to date, with talazoparib arguably showing the highest occurrence of cytopenias, particularly anemia and neutropenia (20), followed by niraparib (24, 29), with high rates of grade 3 or greater thrombocytopenia and neutropenia in particular, and then olaparib (21, 30, 31) and rucaparib (32) with similar lower rates of all cytopenias versus talazoparib and niraparib. Although a direct comparison between these trials is not possible given that they are in distinct patient populations, it is notable that the rate of occurrence of grade 3 or higher bone marrow suppression tends to mirror the respective PARP-trapping ability of these PARP inhibitors. Late-phase testing of pamiparib is currently underway, thus adverse event data are not mature, but early-phase data (33) did show that the most

common grade 3 toxicities were anemia and neutropenia, in a similar vein to the other "PARP trappers."

Interestingly, a number of unique secondary paharmacology–based toxicities specific to each PARP inhibitor have also been observed in the clinic (Fig. 1). For example, niraparib leads to hypertension in approximately 19% of patients (29), which is thought to be due to the off-target inhibition of dopamine transporters, among others (34). It is important for clinicians to be aware of such distinctive PARP inhibitor–specific toxicities, so that they can be managed effectively in the clinic if they arise, and also to guide the selection of the most appropriate PARP inhibitor to use to minimize any overlapping toxicities when designing combinations with other antitumor agents, which come with their own side effects.

Although there have not been any direct head-to-head comparisons of PARP inhibitors in clinical trials, the phase III monotherapy data of olaparib, niraparib, rucaparib, and talazoparib have been published, while phase III trial data involving veliparib in combination with chemotherapy have also been presented (Fig. 1). The clinical data so far have been encouraging for olaparib, rucaparib, niraparib, and talazoparib, mostly centered around their single-agent use in patients with ovarian or breast cancer harboring *BRCA1/2* mutations. Importantly, statistically significant clinical benefit of maintenance olaparib, rucaparib, or niraparib extended to all patients with platinum-sensitive high-grade serous ovarian cancer, regardless of DDR gene mutation status or HRD as determined by specific genomic assays, likely due to the high incidence of HRR deficiency and continued platinum sensitivity of the cancers being treated in this patient population (29, 31, 35). The very recent SOLO1 data (36), where olaparib was given daily as a first-line maintenance therapy in advanced ovarian cancer harboring *BRCA1/2* mutations, suggest that these agents are going to transform ovarian cancer patient outcomes. The 5-year survival rate for ovarian cancer is only 40%, with 70% of patients progressing within 3 years following their first line of platinum-based chemotherapy (36). However, in the SOLO1 trial, 60% of patients had not progressed after 3 years, in contrast to less than 30% on placebo, even though olaparib therapy in many cases had only been given for 2 years (36). These data far outweighed the expected benefits going from second-line maintenance to this earlier line of therapy. Moreover, there was no significant reduction in quality of life compared with the placebo arm, and 70% of patients remained on full doses of drug during the trial (36).

Concurrent chemotherapy combinations. Veliparib given in combination with carboplatin/paclitaxel chemotherapy for *BRCA1/2*-mutant metastatic breast cancer in the BROCADE-2 trial showed some promise in phase II with an overall response rate (ORR) 77.8% in the veliparib arm and 61.3% in the placebo arm (37). However, there was no benefit in progression free survival (PFS) with the addition of veliparib in BROCADE-2, and phase III results are currently pending (BROCADE-3) (37). Phase III results available thus far including veliparib in combination with carboplatin/paclitaxel chemotherapy for 1) patients with treatment-naive metastatic smoking-related non-small-cell-lung cancer (NCT02106546) and 2) neoadjuvant veliparib in combination with carboplatin/paclitaxel for TNBC (NCT02032277) failed to meet their primary endpoints of improved overall survival (OS), and improved complete response (pCR), respectively (38, 39). A recent phase II study of veliparib in combination with temozolomide for recurrent small-cell lung cancer (SCLC) showed improved ORR for the veliparib arm versus placebo (39% vs. 14%); however, a median OS and progression-free survival (PFS) benefit were only seen in patients with overexpression of schlafen11 (SLFN11), an emerging biomarker of PARP inhibitor response that is discussed later in this review (40).

In SCLC xenograft studies, single-agent talazoparib displayed striking single-agent activity, similar to cisplatin (41). In another xenograft study, talazoparib was shown to be superior in its radiosensitizing capacity compared with veliparib, probably due to the enhanced PARP-trapping ability of talazoparib (42). In this study, talazoparib was shown to synergize with temozolomide independent of SLFN11 status in preclinical SCLC models (42). Thus, while phase II trial data for veliparib look promising in recurrent SCLC, the more potent PARP-trapping drugs may prove to be more adept therapies in this setting, although overlapping toxicities with chemotherapy, including bone marrow suppression, are likely to be dose limiting. There is currently a trial underway combining olaparib and temozolomide (NCT02446704), which has shown encouraging preliminary activity in phase I testing with an ORR of 46% in patients with SCLC (43). Novel strategies are being developed to mitigate toxicities observed with PARP inhibitor and chemotherapy combinations. For example, in preclinical studies, by conjugating talazoparib to a low-pH–sensing peptide, it was possible to selectively deliver the PARP inhibitor across the membrane of tumor cells and achieve target engagement in the tumor without free drug detected in the systemic circulation, thus having the potential to reduce chemotherapy combination bone marrow toxicity (44).

Although clinical benefit has been observed for olaparib in the aforementioned patient populations with breast or ovarian cancers, a phase III study of paclitaxel with or without olaparib for patients with metastatic gastric cancer failed to meet statistical significance in its primary endpoint of improved OS, even in those harboring a predicted biomarker of response—low ATM protein expression (45). This lack of efficacy is likely multifactorial, including a lack of standardization in the IHC assay to quantify loss of ATM protein expression, not enriching for patients with true HRD, the absence of an olaparib monotherapy arm as a comparator, as well as a suboptimal dose of olaparib and lack of synergy between PARP inhibition and paclitaxel, all of which may have been contributing factors. Further studies of PARP inhibitors and associated biomarkers are currently being pursued in gastric cancer.

PARP inhibitors are also under active investigation as part of treatment regimens for primary brain cancers such as glioblastoma (GBM), as well as metastatic brain disease. The ability of the drug to cross the blood–brain barrier (BBB) is different for each PARP inhibitor. A phase I study of olaparib in combination with temozolomide for patients with relapsed GBM showed a high incidence of grade 3 or higher toxicities (~70% of 35 evaluable patients), predominantly myelosuppression (46). The study did show that olaparib was present in both core and margin GBM tissue specimens, despite olaparib not being able to penetrate the BBB at clinically relevant doses in preclinical xenograft models with an intact BBB. The 6-month PFS was 45% in 13 evaluable patients, providing supporting evidence to proceed to late-phase trial testing of olaparib in combination with radiotherapy ± temozolomide for newly diagnosed GBM (PARADIGM-2; ref. 47). In contrast to olaparib, niraparib was shown to effectively

penetrate the BBB in preclinical models and have a significant antitumor effect in germline *BRCA2*-mutant intracranial xenografts at clinically relevant doses (48). In preclinical studies, talazoparib sensitized GBM cells to temozolomide *in vitro* and in flank GBM xenografts; however, there was no benefit for the addition of talazoparib in the intracranial xenograft models (49). In this study, talazoparib demonstrated poor penetration across the BBB because of multidrug-resistant 1 (MDR1) efflux activity at the barrier (49). However, in the EMBRACA trial, the PFS benefit of talazoparib extended to patients with central nervous system metastases in subgroup analysis (20). Xenograft studies of rucaparib showed a similar discordance in efficacy between *in vitro* and flank xenografts compared with intracranial xenografts, also due to drug efflux transporter activity leading to poor BBB penetration (50). Veliparib despite synergizing with temozolomide in temozolomide-resistant GBM lines *in vitro*, did not display efficacy at clinically relevant doses *in vivo*, even in a flank xenograft model (51).

Although it is unlikely that there will be a clinical trial comparing PARP inhibitors head-to-head in the near future, it is evident from preclinical data and clinical studies conducted so far that the success of a specific PARP inhibitor may ultimately be influenced by the specific biomarker-selected population being targeted. Although the synthetic lethal relationship between PARP inhibition and HRR deficiency resulting from *BRCA1/2* deficiency is known, there are also cancer cell types that display other forms of PARP-dependency, including mechanisms that result in an HRD-like phenotype. For example, deleterious variants in non-BRCA HRR genes such as *ATM*, *PALB2*, and *RAD51* lead to functional HRR deficiency and sensitivity to PARP inhibition. Outside of canonical HRR pathway genes, mutations in Krebs cycle genes such as *IDH1* or *FH* lead to oncometabolite production that results in reduced expression of HRR gene activity (52, 53). In addition, mutations in key chromatin regulators, such as *ARID1A* (54) and *BAP1* (55, 56), give way to an HRD phenotype via loss of sustained DDR signaling and ubiquitylation activity that is needed in DSB repair. Finally, there are biomarkers of PARP inhibitor sensitivity that are distinct from HRD altogether as further discussed below.

Predictive Biomarkers Beyond HRD

With the incorporation of PARP inhibitors in multiple ongoing trials, a wide range of companion biomarkers that relate to HRD, beyond *BRCA1/2* mutations, are also under development, as previously discussed and extensively reviewed (6, 57).

Although the rationale for targeting *BRCA1/2*- and HRD-associated malignancies with PARP inhibitors is well described, several additional tumor types, including Ewing sarcoma, some aggressive variant prostate cancers, and SCLC, display increased sensitivity to PARP inhibitors in spite of a seemingly intact HRR pathway. The best characterized of these non-HRD examples is probably SCLC, where previous proteomic characterization has identified high expression of not only PARP itself, but also a number of additional DDR-related proteins including ATM, ATR, CHK1, and CHK2 (58). The unique genomic profile of SCLC includes the nearly ubiquitous genetic loss of *TP53* and *RB1*, and thus the loss of the tumor-suppressive roles that these proteins play in response to DNA damage (59). In addition, SCLC is known to display frequent *MYC* amplification, thereby providing additional oncogenic stresses during the tumor cell cycle (59). The net effect of these genomic alterations is a rapidly dividing tumor under immense replication stress due to checkpoint loss and thus, a tumor that is heavily dependent on a robust DDR to maintain its survival (34). The loss of RB1 assists in enhancing DDR capacity due to the absence of the inhibitory effects of RB1 on the E2F1 transcription factor responsible for the expression of *PARP1* and many other DDR-related genes (58). Relative to NSCLC, SCLC models showed increased sensitivity to olaparib *in vitro* in terms of cytotoxicity, but also reductions in PAR levels (58). Despite the initially robust DDR machinery in SCLC, PARP inhibitor treatment resulted in broad downregulation of multiple DDR proteins, likely due to the role of PARP1 as a coactivator of the aforementioned E2F1 (58). Thus, in SCLC, PARP inhibition is capable not only of abrogating the role of PARP itself but of reversing much of the DDR protein upregulation that maintains DNA integrity amidst high levels of replication stress in this cancer (Fig. 2).

It is now clear, however, that the sensitivity of SCLC and other high replication stress tumors to PARP inhibitors is not ubiquitous. For example, while a phase I trial of talazoparib in patients with advanced cancers reported robust responses in patients with *BRCA1/2*-mutant breast and ovarian cancers, objective responses were only observed in 2 of 23 patients with SCLC, and 2 of 10 patients with pancreatic cancer, and no objective responses in small populations of patients with Ewing sarcoma and metastatic castration-resistant prostate cancer (60). Significant efforts have been made to identify predictive biomarkers of response to PARP inhibitors and combinations in SCLC, with varying degrees of clinical success. *In vitro*, analyses in SCLC cell lines and cell line–derived xenografts identified expression of the DNA-PKcs protein, as well as a 5-gene expression score (*GLS*, *UBEC2*, *HACL1*, *MSI2*, *LOC100129585*), which predicted sensitivity to veliparib (61). In a separate preclinical study, a DNA repair score developed on the basis of the overexpression of 17 DDR proteins, rather than deficiency in DDR proteins, predicted sensitivity to talazoparib in SCLC *in vitro* models (41). Multiple studies have also identified baseline PI3K/mTOR pathway activation as a marker of PARP inhibitor resistance in SCLC and demonstrated that PARP inhibition itself leads to PI3K activation (41, 62). Another potential predictor of PARP inhibitor sensitivity in SCLC includes high expression of E-cadherin (63). However, none of these biomarkers have so far been supported by clinical data.

One of the most promising predictive biomarkers to emerge recently is the expression of SLFN11 (Fig. 2); this putative DNA/RNA helicase protein has been identified by different research groups as a predictor of sensitivity to multiple PARP inhibitors, as well as platinum chemotherapy, in both *in vitro* and patient-derived xenograft models (63–66). The predictive role of SLFN11 for talazoparib responses *in vitro* appears to extend beyond SCLC across the NCI-60 collection of cell lines, where SLFN11 expression is second only to BRCA inactivation in its correlation with drug sensitivity (67). Furthermore, SLFN11 is under transcriptional control of the EWS–FLI1 fusion protein that defines Ewing sarcoma and has been linked to PARP inhibitor sensitivity (68). SLFN11 helps orchestrate the DDR by binding to chromatin in response to replication stress through association with RPA (34), thus blocking replication fork progression. In the absence of SLFN11, this irreversible and lethal replication inhibition does not occur (67). SLFN11 expression is dynamic, owing to silencing by promoter methylation, which is responsible both for innate and acquired SLFN11-dependent resistance (69), although

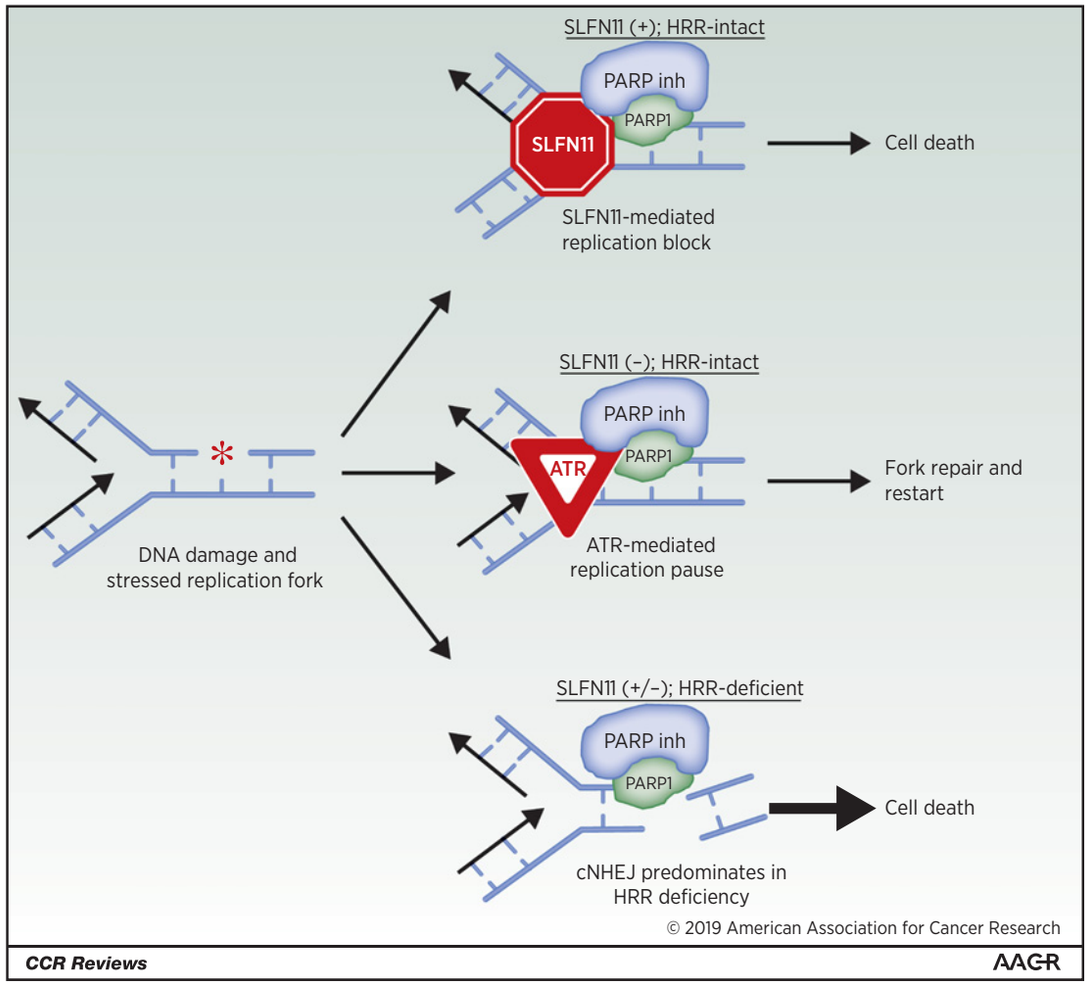


Figure 2.

Multiple paths to PARP inhibitor vulnerability. HRR-intact tumors that express high levels of SLFN11 experience irreversible replication block and cell death in response to unrepaired SSBs and PARP entrapment after PARP inhibitor addition (top right). HRR-intact tumors lacking SLFN11 instead undergo only temporary replication pause, mediated by ATR, in response to same DNA damage, which allows for eventual fork repair and replication restart (middle right). In HRR-deficient tumors, regardless of SLFN11 status, PARP trapping leads to DSBs that cannot be resolved accurately due to absence of HRR and result in genome instability and cell death (bottom right). PARP inh, PARP inhibitor.

treatment with EZH2 and HDAC inhibitors may be capable of restoring SLFN11 expression, and therefore PARP inhibitor sensitivity (70, 71).

Efforts to analytically validate existing biomarkers and to identify new ones to predict PARP inhibitor response are ongoing, including novel strategies utilizing circulating tumor cells (CTC) and CTC-derived xenograft (CDX) models (72). In this study, patients enrolled on a phase I/II trial of temolozomide and olaparib for previously treated SCLC had blood collected at multiple time points prior to, during, and following trial therapy. These blood samples were subjected to CTC enrichment using the CTC-iChip microfluidic device and the resultant CTCs injected into mice to generate longitudinal CDX models. Preliminary analysis from this ongoing study revealed that basal protein PARylation distinguishes sensitive CDX models from both intermediate and resistant models, while PARylation, like SLFN11 expression, appears to decrease with treatment and the development of resistance (72). A similar CDX-based approach investigating the combination of olaparib with or without the WEE1 inhibitor adavosertib (AZD1775) identified multiple additional biomarker candidates, including inducers and markers of replication stress, such as MYC-family proteins, phospho-RPA, and cyclinE1 (73). Given the relative dearth of tissue available in SCLC and other tumors not commonly managed via surgical resection, approaches such as these may shape the next era of biomarker discovery for PARP inhibitors and beyond.

Extending the Clinical Benefits of PARP Inhibitors

Moving PARP inhibition into earlier treatment settings

Neoadjuvant and adjuvant treatment strategies. As highlighted above, there have been multiple positive late-phase trials and subsequent regulatory approvals for the use of PARP inhibitors in

pretreated patients with metastatic *BRCA1/2*-mutant cancers. Neoadjuvant studies exploit the possibility of PARP inhibitors to potentially spare patients the detrimental toxicities and likely impact on quality of life of chemotherapy, while also obtaining vital information on the underlying tumor biology and responsiveness to PARP-targeted therapy. Recent phase II neoadjuvant trial data for the use of single-agent neoadjuvant talazoparib for patients with *BRCA1/2* mutant, HER2 normal (predominantly triple negative) operable breast cancer were very encouraging, with 53% of women on study achieving a pathologic complete response, and over 60% ORR reported during preliminary analysis (74). Toxicities observed were similar to those reported in studies of talazoparib administered in the metastatic setting, including grade 4 thrombocytopenia in 1 of 18 patients, and dose reductions were required in 9 of 18 patients. Pretreatment and postoperative tissue profiling are expected to provide additional novel insights into how PARP inhibition alters genomic stability, DDR and oncogene pathway function, and the immune microenvironment in this unique patient population. A small phase II study of veliparib plus carboplatin added to a standard neoadjuvant backbone regimen of paclitaxel and adriamycin/cyclophosphamide for localized TNBC patients appeared to show improved pathologic complete response rates. However, the subsequent phase III BriGHTness trial failed to meet its primary endpoint, demonstrating that the addition of carboplatin alone to the standard chemotherapy regimen was sufficient to benefit patients, without the need for veliparib (38). The failure of veliparib in this setting may be multifactorial, but its value as a PARP inhibitor in the context of available, more potent "PARP trapping" agents remains questionable.

In the adjuvant setting, results are pending from the phase III OlympIA trial, which is assessing olaparib as adjuvant therapy for patients with *BRCA1/2*-mutant localized breast cancer who have completed neoadjuvant chemotherapy and definitive treatment.

Chemoprevention strategies. Given the relationship between PARP inhibitors and germline *BRCA1/2* mutation carriers, chemoprevention strategies have also been assessed in *BRCA*-mutant preclinical models (75). These studies showed that physiologic doses of veliparib or olaparib were able to delay mammary gland tumor onset in *BRCA1*-deficient mice, with olaparib showing an improved delay in tumor onset and also improved overall survival in the mice even when given intermittently rather than continuously. However, it is important to note that these mice had biallelic loss of *BRCA1* and all still eventually developed tumors, thus implying that PARP inhibition delayed, but did not prevent cancer in this mammary tumor model. Moreover, the efficacy and risk-benefit of the use of PARP inhibitors in the case of monoallelic loss or haplo-insufficiency of *BRCA1/2*, as is the case in patients with germline mutations in these genes who have not yet developed a cancer, is not currently clear. In addition, given that: (i) not every patient with a HBOC-associated mutation will develop a cancer, (ii) clinical trials have shown that not all patients with *BRCA1/2*-mutant cancers respond to PARP inhibition, and (iii) long-term toxicities of PARP inhibitor use have not been fully elucidated (76, 77), such chemoprevention strategies still require thoughtful discussion and study. In particular, it is still unclear if the rare (<1%) incidence of acute myeloid leukemia and myelodysplasia observed in long-term ovarian cancer maintenance treatment can be attributed to PARP inhibition, or if it is due to prior platinum-based chemotherapy. Given the high risk of cancer in germline *BRCA1/2* mutation carriers, chemoprevention with PARP inhibitors may warrant investigation, perhaps starting with an assessment of the potential to delay or prevent secondary cancers in such carriers.

Rational PARP Inhibitor Combination Strategies

In addition to the aforementioned strategy of combining PARP inhibitors with DNA-damaging chemotherapy and/or radiation, preclinical evidence has led to multiple biologically informed clinical trials combining PARP inhibitors with (i) other DDR inhibitors, such as those that target ATR, CHK1/2, or WEE1, (ii) agents that target oncogenes, and (iii) immune checkpoint therapy (Fig. 3).

DDR inhibitor combinations

Acquired or innate resistance to single-agent PARP inhibitors is frequently observed in both preclinical models and the clinic. Multiple potential mechanisms for resistance to PARP inhibitors have been described with the majority linked to routes by which HRR capability is restored (78). The mechanisms have been extensively previously reviewed (7, 78, 79), and include reversion to wild-type mutations in *BRCA* and other HRR genes, promoter demethylation of suppressed DDR genes, mitigation of replication stress, mutations in PARP itself, and/or drug efflux pumps, among others. This overarching mechanism of HRR restoration has been highlighted in multiple preclinical PDX studies of PARP inhibition in TNBC (15, 80–82), where functionality of HRR in virtually all cases was implied by the presence of RAD51 foci in untreated tumor samples, suggesting this could represent a useful clinical biomarker for PARP inhibitor response and/or resistance. Emerging data also suggest that these olaparib-resistant cancer models can be resensitized to olaparib when combined with a WEE1 inhibitor or an ATR inhibitor (67, 73, 83–85). Preclinical studies suggest that PARP inhibitor–resistant, *BRCA*-deficient cells have an increased reliance on ATR signaling for fork stabilization (83, 84), while synthetic lethal screens identified ATR as a target that was able to overcome PARP inhibitor resistance, leading to early-phase clinical trials combining ATR and PARP inhibitors (NCT02723864, NCT03462342, NCT03682289, NCT02576444; ref. 85). In addition to reversing PARP inhibitor resistance, WEE1 inhibitors may serve as a promising partner to PARP inhibitors, with the synergy dependent on the PARP-trapping ability of the PARP inhibitor (86). Encouragingly, in preclinical chemosensitive and chemorefractory SCLC models, the combination of olaparib and adavosertib provided superior efficacy versus the standard combination of cisplatin and etoposide (73).

The cytotoxic mechanism of action of these DDR inhibitor combinations is multifactorial, with contributions from an overreliance on alternative DDR pathways in PARP-inhibitor–resistant cells, as well as catastrophic replication stress and nucleotide resource depletion when PARP inhibitors are combined with ATR inhibitors or WEE1 inhibitors. There are also other DDR inhibitors targeting multiple points along the cascade in clinical development, including ATM, CHK1/2, DNA-PK, and POLθ, which all have the potential for effective combinations with PARP inhibitors (78). Importantly, in designing these DDR–DDR inhibitor combinations, one must consider the potential for overlapping

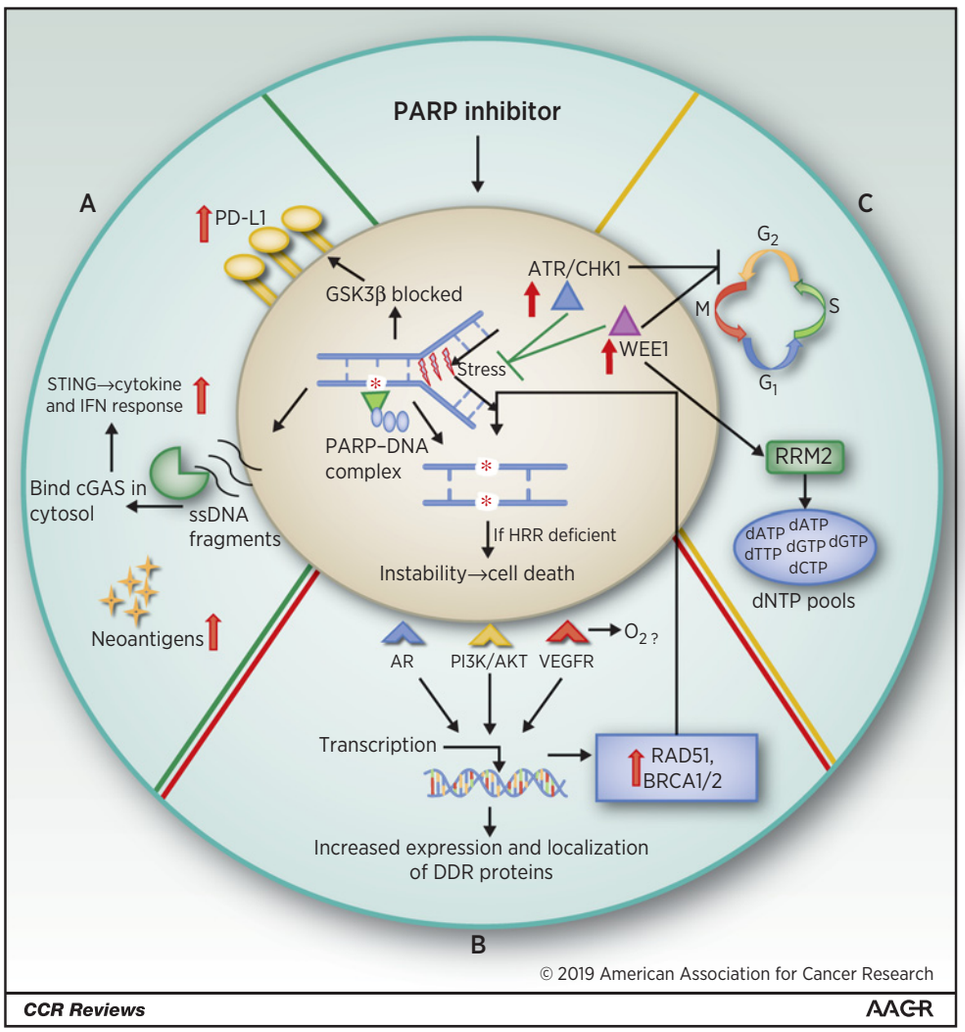


Figure 3.

PARP inhibitor–based combination treatment strategies. Broad categories of PARP inhibitor–based combination treatment strategies include PARP inhibition in combination with: **A,** Immune checkpoint therapy, with PARP inhibition increasing genomic instability, immune pathway activation, and PD-L1 expression on the cancer cell. Examples of active clinical trials include MEDIOLA (olaparib + durvalumab) and TOPACIO (niraparib + pembrolizumab); **B,** Antioncogenic-targeted therapy, with the antioncogenic inhibitor inducing DDR deficiency and susceptibility to PARP inhibition. Examples of active trials include NCT01972217 (olaparib + abiraterone) and NCT01116648 (olaparib + cediranib); **C,** Other DDR inhibitors, with PARP inhibition creating increased reliance in the cancer cell on other DDR genes (e.g., *ATR/WEE1*) for regulation of DNA DSB repair, cell-cycle checkpoints, dNTP pools, and replication fork stability. Examples of active trials include OLAPCO (olaparib + AZD6738 and olaparib + AZD1775). RRM2, Ribonucleotide Reductase Regulatory Subunit M2, STING, stimulator of interferon gene.

bone marrow toxicity. Further studies are thus warranted to establish the appropriate doses, schedule, and sequence of these therapies.

Molecularly targeted agent combinations

A major theme of PARP inhibitor resistance from preclinical studies is oncogene-driven expression of HRR genes and rescue of repair activity. For example, androgen receptor (AR) signaling has been shown to alter HRR and cell-cycle gene expression in castration-resistant prostate cancer (CRPC), with DDR genes upregulated at progression, and PARP1 required for maximal AR function (87, 88). The rational combination of AR blockade and PARP inhibition has thus been explored in preclinical models and clinical trials (89). Enzalutamide was shown to reduce BRCA1 expression in CRPC cell lines, inducing a "chemical BRCAness" phenotype, potentially resulting in the synergy observed with the combination of enzalutamide and olaparib in preclinical models. These findings were regardless of DDR gene mutation status, whereby lead-in therapy with enzalutamide reduced HRR capacity, increased apoptosis, and had antitumor effects in prostate cancer models (87, 89). The recently published phase II trial of abiraterone/prednisone with or without olaparib showed a clinical benefit for the addition of olaparib with improved radiographic PFS (13.8 vs. 8.2 months; ref. 90). Importantly, in an exploratory analysis, this benefit appeared to extend to patients who did not have DDR gene alterations, though less than half of

the study population had the appropriate DNA sequencing performed and the study was not designed to detect differences in DDR gene mutation carriers (90). Unlike the aforementioned olaparib trial, a phase II multicenter trial of abiraterone/prednisone with or without veliparib for patients with pretreated CRPC did not show any benefit for veliparib over placebo (91). The selection of the specific PARP inhibitor to use in combination with targeted agents is clearly important and must be informed by preclinical mechanistic data.

The combination of PI3K/mTOR inhibition and PARP inhibition has also been suggested to result in efficacy in preclinical studies of various cancer types via multiple mechanisms centered on inducing HRD, including the suppression of DNA DSB repair protein SUV39H1, a histone methyltransferase, and suppression of HRR gene expression (92). An early-phase clinical trial of olaparib in combination with buparlisib, a pan-PI3K inhibitor, showed approximately 30% response rate for the combination (93). However, multiple dose reductions of buparlisib for treatment-related toxicities led to the discontinuation of this particular combination. Subsequently, olaparib was combined with a more specific PI3Kalpha inhibitor, alpelisib, and showed an ORR of 36% in patients with advanced ovarian cancer, who were largely platinum-resistant (94). Importantly, the benefit extended to patients with and without germline DDR gene mutations (94).

RAS-mutant cancers are notoriously difficult to target; however, preclinical evidence has shown that mitogen-activated protein kinase inhibitors reduce HRR gene expression and DNA damage checkpoint activation, increase FoxO3a expression, and synergize with PARP inhibition for antiproliferative activity in *RAS*-mutant cells (95). A phase I/II trial of selumetinib and olaparib for patients with RAS-altered cancers, as well as PARP-inhibitor–resistant ovarian cancers is underway (NCT03162627), among others in development. The combination of anti-VEGF small molecules with PARP inhibitors has also shown promise in patients with recurrent ovarian cancer. Phase II trial data of cedirinib in combination with olaparib showed a PFS benefit versus single-agent olaparib (16.5 vs. 8.2 months) in a platinum-sensitive, *BRCA* wild-type patient population. However, grade 3 or higher toxicities were frequent (75%; ref. 96). The mechanism of synergy with this combination is not as well understood, with the current thinking being that antiangiogenic therapy may create tumor hypoxia, which has been shown to alter DDR gene expression (97). Interestingly, patients with *BRCA1/2* mutations derived no benefit from the addition of cedirinib to olaparib versus olaparib alone, suggesting that this combination may best be reserved for the patients with an intact HRR phenotype (96).

BET bromodomain (BRD4) protein promotes oncogene transcription, and BET inhibitors have been shown to suppress DDR genes, including TOPBP1, WEE1, and DNA DSB repair protein CtiP in some cell line models (98). The combination of BRD4 and PARP inhibition demonstrated enhanced activity in multiple tumor lineages, regardless of *BRCA1/2*, *TP53*, *RAS*, or *BRAF* mutation status both *in vitro* and *in vivo* (98). Consequently, BET inhibitors in combination with PARP inhibitors may have wide application in the clinical setting and are under active early-phase clinical trial investigation.

Preclinical studies are rapidly uncovering new targets that can induce HRD and/or overcome PARP inhibitor resistance with biologically informed clinical trials evolving from these novel mechanistic insights. The goal in the clinic is now to minimize overlapping toxicities by optimizing dose and schedule, for example, concurrent versus alternating versus sequential dosing, determine the order of drugs in the treatment sequence, and to limit the use of combinations to those patients who would not otherwise obtain the same benefit from PARP inhibitor monotherapy. Patient selection approaches incorporating tumor type and molecular profiles specific to each unique PARP inhibitor–based combination will also be essential to optimize efficacy, while minimizing toxicity of these rationale strategies. Although it is likely that combinations involving three or more agents are feasible, we will need to establish safety and efficacy in doublet combinations first before moving to assess strategies involving multiple drugs.

Immune checkpoint inhibitor combinations

Patients with cancers harboring innate deficiencies in canonical DDR genes, including mismatch repair and HRR genes, have been shown to have increased $CD8^+$ T-cell infiltration and improved ORR to immune checkpoint therapy (13). The intertwined relationship between immunotherapies and DDR pathways is extensive, and the synergy between DDR deficiency and immune activation against cancer cells is multifactorial (13, 99–101). Preclinical and clinical data indicate that neoantigen burden primarily drives this response in patients with hypermutated tumors, such as in the case of MMR and POLE deficiencies (102–104). For patients with HRR gene aberrations where mutational burdens are lower than in MMR (105), there is also likely to be a contribution from the generation of S-phase–specific DNA damage resulting from collapsed replication forks or underreplicated DNA, leading to the accumulation of cytosolic DNA, which in turn can activate the cGAS–STING innate immune pathway and type I IFN signaling (Fig. 3; ref. 106). Interestingly, PARP inhibition has also been shown in preclinical models to inactivate GSK3β and upregulate PD-L1 in a dose-dependent manner, suppressing T-cell activation and increasing cancer cell killing (107). These effects were observed in rucaparib-, olaparib-, and talazoparib-treated cancer models; and subsequent combination therapy with anti–PD-L1 blockade induced PARP inhibitor sensitization and led to antitumor activity to a greater degree than either drug alone (107).

A phase II trial of durvalumab in combination with olaparib for selected advanced solid cancers (MEDIOLA) showed that this combination is well tolerated with no significant overlapping toxicities (108–111). Clinical response measured as disease control rate at 12 weeks was 29%, 80%, and 81% in patients with advanced SCLC, germline *BRCA1/2*-mutant HER2-normal breast cancer, and germline *BRCA1/2*-mutant platinum-sensitive ovarian cancer, respectively (109–111). This same combination was also assessed in patients with CRPC, and reported a 12-month PFS of 51% in a population unselected for DDR variants (112). In molecularly driven tumor types where PARP inhibitor monotherapy activity is already observed, the hope is that such a combination will lead to deeper and more durable responses in a greater proportion of patients, including long-lasting complete responses.

Given the increasing importance of immunotherapy for the management of cancer patients with multiple tumor types, one of the most clinically important questions just beginning to be answered is to what extent PARP inhibitors may enhance response to immune checkpoint blockade or other immunotherapy approaches. Ongoing and future trials will determine

the degree to which the therapeutic targeting of DNA repair by PARP inhibition or other DDR inhibitors may similarly enhance responses, and the underlying mechanisms through which this occurs. Finally, as with other targeted agents, optimal biomarkers to predict benefit and resistance from PARP inhibitors and specific combinations will be essential to enable the rational expansion of this class of drugs to the additional patient populations who may benefit.

Preliminary safety and efficacy data from the phase II trial of niraparib and pembrolizumab for patients with advanced platinum-resistant ovarian cancer (TOPACIO) demonstrated no additive toxicities, an ORR of 25%, and disease control rate (including stable disease) of 68% (113). A subgroup analysis of patients with *BRCA1/2* mutations revealed that their disease control rate (73%) did not differ significantly from the general study population; however, the ORR in *BRCA1/2*-mutant patients was 45% (113). It is not yet clear which specific PARP inhibitor, or even other DDR inhibitors, may combine best with immune checkpoint blockade, and what the optimal predictive biomarker strategy is, that is, if there will be efficacy independent of HRD status. Nevertheless, the data reported from these early studies are certainly encouraging for this novel combination strategy.

Conclusions

PARP inhibitors are the first approved DDR-targeted medicines and have already transformed treatment paradigms for subgroups of patients with ovarian and breast cancers (20, 21, 29, 30, 32). DDR deficiencies are common in cancer and indeed have been postulated to be a necessary component of tumorigenesis, but they also represent an Achilles' heel that can now be targeted (2). It is likely that with the significant improvement in patient benefit observed in earlier therapeutic settings, along with the likelihood of long-term tolerability of PARP inhibitors, there is great potential for this drug class to become a foundation treatment for ovarian cancer, and for its impact to extend to multiple other cancers and far beyond *BRCA1/2*-mutant tumors. Preclinical mechanistic studies are now guiding hypothesis-testing, biomarker-driven clinical trials that look beyond *BRCA1/2* mutations, toward a broader view of HRD phenotypes, and even beyond HRD itself to maximize the number of individuals who may benefit from PARP inhibition.

If we also take into account the potential to reverse acquired PARP inhibitor monotherapy resistance using PARP inhibitor–DDR inhibitor combinations (through a "PARP-after-PARP" inhibitor approach), while broadening the patient populations beyond what is obtainable through monotherapy via combinations with other targeted agents such as inhibitors of VEGFR, PI3K pathways, other oncogenic drivers such as AR and immunotherapy, as well as other DDR-targeted agents, it is clear that PARP inhibitor benefits have the potential to go well beyond the initial impressive advances experienced in recent years.

Disclosure of Potential Conflicts of Interest

L.A. Byers reports receiving other commercial research support from and is a consultant/advisory board member for AbbVie and AstraZeneca. M.J. O'Connor is a shareholder in AstraZeneca. T.A. Yap reports receiving other commercial research support from AstraZeneca, Bayer, Pfizer, Tesaro, Jounce, Eli Lilly, Seattle Genetics, Kyowa, Constellation, and Vertex Pharmceuticals, speakers bureau honoraria from AstraZeneca, Merck, Pfizer, and Tesaro, and is a consultant/advisory board member for Aduro, Almac, AstraZeneca, Atrin, Bayer, Bristol-Myers Squibb, Calithera, Clovis, Cybrexa, EMD Serono, Ignyta, Janssen, Merck, Pfizer, Roche, Seattle Genetics, and Vertex Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

Acknowledgments

The University of Texas MD Anderson Cancer Center (Houston, TX) is supported by an NIH Cancer Center Support Grant (CA016672; to P.G. Pilié, C.M. Gay, L.A. Byers, and T.A. Yap).

Received November 23, 2018; revised January 4, 2019; accepted February 8, 2019; published first February 13, 2019.

References

1. King MC, Marks JH, Mandell JB; New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302:643–6.
2. O'Connor MJ. Targeting the DNA damage response in cancer. Mol Cell 2015;60:547–60.
3. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 2004;4:814–9.
4. Mandelker D, Zhang L, Kemel Y, Stadler ZK, Joseph V, Zehir A, et al. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs. guideline-based germline testing. JAMA 2017;318:825–35.
5. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443–53.
6. Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer 2016;16:110–20.
7. Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. Science 2017;355:1152–8.
8. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917–21.
9. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005;434:913–7.
10. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009;361:123–34.
11. Brown JS, Kaye SB, Yap TA. PARP inhibitors: the race is on. Br J Cancer 2016;114:713–5.
12. Brown JS, O'Carrigan B, Jackson SP, Yap TA. Targeting DNA repair in cancer: beyond PARP inhibitors. Cancer Discov 2017;7:20–37.
13. Mouw KW, Goldberg MS, Konstantinopoulos PA, D'Andrea AD. DNA damage and repair biomarkers of immunotherapy response. Cancer Discov 2017;7:675–93.
14. Brown JS, Sundar R, Lopez J. Combining DNA damaging therapeutics with immunotherapy: more haste, less speed. Br J Cancer 2018;118:312–24.
15. Ter Brugge P, Kristel P, van der Burg E, Boon U, de Maaker M, Lips E, et al. Mechanisms of therapy resistance in patient-derived xenograft models of BRCA1-deficient breast cancer. J Natl Cancer Inst 2016;108:djw148.
16. Radhakrishnan SK, Jette N, Lees-Miller SP. Non-homologous end joining: emerging themes and unanswered questions. DNA Repair 2014;17:2–8.
17. Forment JV, O'Connor MJ. Targeting the replication stress response in cancer. Pharmacol Ther 2018;188:155–67.
18. Bai P. Biology of poly(ADP-ribose) polymerases: the factotums of cell maintenance. Mol Cell 2015;58:947–58.
19. McCabe N, Turner NC, Lord CJ, Kluzek K, Bialkowska A, Swift S, et al. Deficiency in the repair of DNA damage by homologous recombination

and sensitivity to poly(ADP-ribose) polymerase inhibition. Cancer Res 2006;66:8109–15.
20. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Goncalves A, Lee KH, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 2018;379:753–63.
21. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 2017;377:523–33.
22. Ciardiello F, Bang Y, Bendell J, Cervantes A, Brachmann R, Zhang Y, et al. P-094 A phase 3, double-blind, randomized study of pamiparib versus placebo as maintenance therapy in patients with inoperable, locally advanced, or metastatic gastric cancer that responded to platinum-based first-line chemotherapy - trial in progress. Ann Oncol 2018;29(suppl_5): mdy151.093.
23. Murai J, Huang SY, Das BB, Renaud A, Zhang Y, Doroshow JH, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res 2012;72:5588–99.
24. Leo E, Johannes J, Illuzzi G, Zhang A, Hemsley P, Bista MJ, et al. A head-to-head comparison of the properties of five clinical PARP inhibitors identifies new insights that can explain both the observed clinical efficacy and safety profiles [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2018; 2018 Apr 14–18; Chicago, IL. Philadelphia (PA): AACR; 2018. Abstract nr LB-273.
25. Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med 2016;8: 362ps17.
26. Murai J, Huang SY, Renaud A, Zhang Y, Ji J, Takeda S, et al. Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol Cancer Ther 2014;13:433–43.
27. Tang Z, Jiang B, Shi Z, Gong W, Liu Y, Wang X, et al. BGB-290, a novel PARP inhibitor with unique brain penetration ability, demonstrated strong synergism with temozolomide in subcutaneous and intracranial xenograft models [abstract]. In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research; 2015 Apr 18–22; Philadelphia, PA. Philadelphia (PA): AACR; 2015. Abstract nr 1651.
28. Tang Z, Liu Y, Zhen Q, Ren B, Wang H, Shi Z, et al. BGB-290: A highly potent and specific PARP1/2 inhibitor potentiates anti-tumor activity of chemotherapeutics in patient biopsy derived SCLC models [abstract]. In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research; 2015 Apr 18–22; Philadelphia, PA. Philadelphia (PA): AACR; 2015. Abstract nr 1653.
29. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016;375:2154–64.
30. Kim G, Ison G, McKee AE, Zhang H, Tang S, Gwise T, et al. FDA approval summary: olaparib monotherapy in patients with deleterious germline BRCA-mutated advanced ovarian cancer treated with three or more lines of chemotherapy. Clin Cancer Res 2015;21:4257–61.
31. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1274–84.
32. Balasubramaniam S, Beaver JA, Horton S, Fernandes LL, Tang S, Horne HN, et al. FDA approval summary: rucaparib for the treatment of patients with deleterious BRCA mutation-associated advanced ovarian cancer. Clin Cancer Res 2017;23:7165–70.
33. Lickliter JD, Gan HK, Meniawy T, Yang J, Wang L, Luo L, et al. A phase I dose-escalation study of BGB-290, a novel PARP1/2 selective inhibitor in patients with advanced solid tumors. J Clin Oncol 34, 2016 (suppl; abstr e17049).
34. Murai J, Tang SW, Leo E, Baechler SA, Redon CE, Zhang H, et al. SLFN11 blocks stressed replication forks independently of ATR. Mol Cell 2018;69: 371–84.
35. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:1949–61.
36. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2018;379:2495–505.
37. Han H, Diéras V, Robson M, Palácová M, Marcom P, Jager A, et al. Efficacy and tolerability of veliparib (V; ABT-888) in combination with carboplatin (C) and paclitaxel (P) vs. placebo (Plc)+C/P in patients (pts) with *BRCA1* or *BRCA2* mutations and metastatic breast cancer: a randomized, phase 2 study [abstract]. In: Proceedings of the 2016 San Antonio Breast Cancer Symposium; 2016 Dec 6–10; San Antonio, TX. Philadelphia (PA): AACR; 2017. Abstract nr S2-05.
38. Loibl S, O'Shaughnessy J, Untch M, Sikov WM, Rugo HS, McKee MD, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol 2018;19: 497–509.
39. AbbVie Announces Topline Results from Two Phase 3 Studies Investigating Veliparib in Combination with Chemotherapy for the Treatment of Patients with Advanced or Metastatic Squamous Non-Small Cell Lung Cancer and Early-Stage Triple-Negative Breast Cancer [news release]. North Chicago, IL: AbbVie; April 19, 2017. https://news.abbvie.com/news/abbvie-announces-topline-results-from-two-phase-3-studies-investigating-veliparib-in-combination-with-chemotherapy-for-treatment-patients-with-advanced-or-metastatic-squamous-non-small-cell-lung-cancer-and-early-stage-triple-negative-breast-cancer.htm. Accessed April 12, 2019.
40. Pietanza MC, Waqar SN, Krug LM, Dowlati A, Hann CL, Chiappori A, et al. Randomized, double-blind, phase II study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer. J Clin Oncol 2018;36: 2386–94.
41. Cardnell RJ, Feng Y, Diao L, Fan YH, Masrorpour F, Wang J, et al. Proteomic markers of DNA repair and PI3K pathway activation predict response to the PARP inhibitor BMN 673 in small cell lung cancer. Clin Cancer Res 2013;19:6322–8.
42. Laird JH, Lok BH, Ma J, Bell A, de Stanchina E, Poirier JT, et al. Talazoparib is a potent radiosensitizer in small cell lung cancer cell lines and xenografts. Clin Cancer Res 2018;24:5143–52.
43. Farago AF, Drapkin BJ, Charles A, Yeap B, Heist RS, Azzoli CG, et al. Phase 1/2 study of olaparib tablets and temozolomide in patients with small cell lung cancer (SCLC) following failure of prior chemotherapy [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1–5; Washington, DC. Philadelphia (PA): AACR; 2017. Abstract nr CT048.
44. Aiello R, Marshall D, Csengery J, Bourassa P, Zhang Q, Robinson B, et al. Development of tumor-targeted PARP inhibitors for the treatment of solid cancers [abstract]. In: Proceedings of the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium; 2018 Nov 13–16; Dublin, Ireland. Eur J Cancer 2018;103S1:e21–e48.
45. Bang YJ, Xu RH, Chin K, Lee KW, Park SH, Rha SY, et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18: 1637–51.
46. Halford SER, Cruickshank G, Dunn L, Erridge S, Godfrey L, Herbert C, et al. Results of the OPARATIC trial: a phase I dose escalation study of olaparib in combination with temozolomide (TMZ) in patients with relapsed glioblastoma (GBM). Neuro Oncol 2017;19:vi4.
47. Fulton B, Short SC, James A, Nowicki S, McBain C, Jefferies S, et al. PARADIGM-2: two parallel phase I studies of olaparib and radiotherapy or olaparib and radiotherapy plus temozolomide in patients with newly diagnosed glioblastoma, with treatment stratified by MGMT status. Clin Transl Radiat Oncol 2018;8:12–6.
48. Mikule K, Wilcoxen K. The PARP inhibitor, niraparib, crosses the blood brain barrier in rodents and is efficacious in a BRCA2-mutant intracranial tumor model [abstract]. In: Proceedings of the AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; 2015 Nov 5–9; Boston, MA. Philadelphia (PA): AACR; 2015. Abstract nr B168.
49. Kizilbash SH, Gupta SK, Chang K, Kawashima R, Parrish KE, Carlson BL, et al. Restricted delivery of talazoparib across the blood–brain barrier

limits the sensitizing effects of PARP inhibition on temozolomide therapy in glioblastoma. Mol Cancer Ther 2017;16:2735–46.
50. Parrish KE, Cen L, Murray J, Calligaris D, Kizilbash S, Mittapalli RK, et al. Efficacy of PARP inhibitor rucaparib in orthotopic glioblastoma xenografts is limited by ineffective drug penetration into the central nervous system. Mol Cancer Ther 2015;14:2735–43.
51. Gupta SK, Mladek AC, Carlson BL, Boakye-Agyeman F, Bakken KK, Kizilbash SH, et al. Discordant *in vitro* and *in vivo* chemopotentiating effects of the PARP inhibitor veliparib in temozolomide-sensitive versus -resistant glioblastoma multiforme xenografts. Clin Cancer Res 2014;20:3730–41.
52. Sulkowski PL, Corso CD, Robinson ND, Scanlon SE, Purshouse KR, Bai H, et al. 2-Hydroxyglutarate produced by neomorphic IDH mutations suppresses homologous recombination and induces PARP inhibitor sensitivity. Sci Transl Med 2017;9:pii: eaal2463.
53. Sulkowski PL, Sundaram RK, Oeck S, Corso CD, Liu Y, Noorbakhsh S, et al. Krebs-cycle-deficient hereditary cancer syndromes are defined by defects in homologous-recombination DNA repair. Nat Genet 2018;50:1086–92.
54. Shen J, Peng Y, Wei L, Zhang W, Yang L, Lan L, et al. ARID1A deficiency impairs the DNA damage checkpoint and sensitizes cells to PARP inhibitors. Cancer Discov 2015;5:752–67.
55. Ismail IH, Davidson R, Gagne JP, Xu ZZ, Poirier GG, Hendzel MJ. Germline mutations in BAP1 impair its function in DNA double-strand break repair. Cancer Res 2014;74:4282–94.
56. Parrotta R, Okonska A, Ronner M, Weder W, Stahel R, Penengo L, et al. A novel BRCA1-associated protein-1 isoform affects response of mesothelioma cells to drugs impairing BRCA1-mediated DNA repair. J Thorac Oncol 2017;12:1309–19.
57. Thomas A, Murai J, Pommier Y. The evolving landscape of predictive biomarkers of response to PARP inhibitors. J Clin Invest 2018;128:1727–30.
58. Byers LA, Wang J, Nilsson MB, Fujimoto J, Saintigny P, Yordy J, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov 2012;2:798–811.
59. George J, Lim JS, Jang SJ, Cun Y, Ozretic L, Kong G, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47–53.
60. de Bono J, Ramanathan RK, Mina L, Chugh R, Glaspy J, Rafii S, et al. Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline BRCA1/2 mutations and selected sporadic cancers. Cancer Discov 2017;7:620–9.
61. Owonikoko TK, Zhang G, Deng X, Rossi MR, Switchenko JM, Doho GH, et al. Poly (ADP) ribose polymerase enzyme inhibitor, veliparib, potentiates chemotherapy and radiation in vitro and in vivo in small cell lung cancer. Cancer Med 2014;3:1579–94.
62. Cardnell RJ, Feng Y, Mukherjee S, Diao L, Tong P, Stewart CA, et al. Activation of the PI3K/mTOR pathway following PARP inhibition in small cell lung cancer. PLoS One 2016;11:e0152584.
63. Allison Stewart C, Tong P, Cardnell RJ, Sen T, Li L, Gay CM, et al. Dynamic variations in epithelial-to-mesenchymal transition (EMT), ATM, and SLFN11 govern response to PARP inhibitors and cisplatin in small cell lung cancer. Oncotarget 2017;8:28575–87.
64. Lok BH, Gardner EE, Schneeberger VE, Ni A, Desmeules P, Rekhtman N, et al. PARP inhibitor activity correlates with SLFN11 expression and demonstrates synergy with temozolomide in small cell lung cancer. Clin Cancer Res 2017;23:523–35.
65. Polley E, Kunkel M, Evans D, Silvers T, Delosh R, Laudeman J, et al. Small cell lung cancer screen of oncology drugs, investigational agents, and gene and microRNA expression. J Natl Cancer Inst 2016;108:djw122.
66. Teicher BA, Silvers T, Selby M, Delosh R, Laudeman J, Ogle C, et al. Small cell lung carcinoma cell line screen of etoposide/carboplatin plus a third agent. Cancer Med 2017;6:1952–64.
67. Murai J, Feng Y, Yu GK, Ru Y, Tang SW, Shen Y, et al. Resistance to PARP inhibitors by SLFN11 inactivation can be overcome by ATR inhibition. Oncotarget 2016;7:76534–50.
68. Tang SW, Bilke S, Cao L, Murai J, Sousa FG, Yamade M, et al. SLFN11 is a transcriptional target of EWS-FLI1 and a determinant of drug response in Ewing sarcoma. Clin Cancer Res 2015;21:4184–93.
69. Nogales V, Reinhold WC, Varma S, Martinez-Cardus A, Moutinho C, Moran S, et al. Epigenetic inactivation of the putative DNA/RNA helicase SLFN11 in human cancer confers resistance to platinum drugs. Oncotarget 2016;7:3084–97.
70. Gardner EE, Lok BH, Schneeberger VE, Desmeules P, Miles LA, Arnold PK, et al. Chemosensitive relapse in small cell lung cancer proceeds through an EZH2-SLFN11 axis. Cancer Cell 2017;31:286–99.
71. Smith TE, Pond CD, Pierce E, Harmer ZP, Kwan J, Zachariah MM, et al. Accessing chemical diversity from the uncultivated symbionts of small marine animals. Nat Chem Biol 2018;14:179–85.
72. Drapkin BJ, George J, Stanzione M, Yeap BY, Mino-Kenudson M, Christensen CL, et al. Co-clinical trial of olaparib and temozolomide in SCLC PDX models uncovers new biomarkers of sensitivity [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2018; 2018 Apr 14–18; Chicago, IL. Philadelphia (PA): AACR; 2018. Abstract nr 2972.
73. Lallo A, Frese KK, Morrow CJ, Sloane R, Gulati S, Schenk MW, et al. The combination of the PARP inhibitor olaparib and the WEE1 inhibitor AZD1775 as a new therapeutic option for small cell lung cancer. Clin Cancer Res 2018;24:5153–64.
74. Litton JK, Scoggins M, Ramirez DL, Murthy RK, Whitman GJ, Hess KR, et al. A feasibility study of neoadjuvant talazoparib for operable breast cancer patients with a germline BRCA mutation demonstrates marked activity. NPJ Breast Cancer 2017;3:49.
75. To C, Kim EH, Royce DB, Williams CR, Collins RM, Risingsong R, et al. The PARP inhibitors, veliparib and olaparib, are effective chemopreventive agents for delaying mammary tumor development in BRCA1-deficient mice. Cancer Prev Res 2014;7:698–707.
76. Sonnenblick A, de Azambuja E, Azim HA Jr, Piccart M. An update on PARP inhibitors–moving to the adjuvant setting. Nat Rev Clin Oncol 2015;12:27–41.
77. Moore KN, Mirza MR, Matulonis UA. The poly (ADP ribose) polymerase inhibitor niraparib: management of toxicities. Gynecol Oncol 2018;149:214–20.
78. Pilie PG, Tang C, Mills GB, Yap TA. State-of-the-art strategies for targeting the DNA damage response in cancer. Nat Rev Clin Oncol 2019;16:81–104.
79. Ashworth A, Lord CJ. Synthetic lethal therapies for cancer: what's next after PARP inhibitors? Nat Rev Clin Oncol 2018;15:564–76.
80. Cruz C, Castroviejo-Bermejo M, Gutierrez-Enriquez S, Llop-Guevara A, Ibrahim YH, Gris-Oliver A, et al. RAD51 foci as a functional biomarker of homologous recombination repair and PARP inhibitor resistance in germline BRCA-mutated breast cancer. Ann Oncol 2018;29:1203–10.
81. Castroviejo-Bermejo M, Cruz C, Llop-Guevara A, Gutierrez-Enriquez S, Ducy M, Ibrahim YH, et al. A RAD51 assay feasible in routine tumor samples calls PARP inhibitor response beyond BRCA mutation. EMBO Mol Med 2018;10:pii: e9172.
82. Dev H, Chiang TW, Lescale C, de Krijger I, Martin AG, Pilger D, et al. Shieldin complex promotes DNA end-joining and counters homologous recombination in BRCA1-null cells. Nat Cell Biol 2018;20:954–65.
83. Yazinski SA, Comaills V, Buisson R, Genois MM, Nguyen HD, Ho CK, et al. ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells. Genes Dev 2017;31:318–32.
84. Kim H, George E, Ragland R, Rafial S, Zhang R, Krepler C, et al. Targeting the ATR/CHK1 axis with PARP inhibition results in tumor regression in BRCA-mutant ovarian cancer models. Clin Cancer Res 2017;23:3097–108.
85. Haynes B, Murai J, Lee JM. Restored replication fork stabilization, a mechanism of PARP inhibitor resistance, can be overcome by cell cycle checkpoint inhibition. Cancer Treat Rev 2018;71:1–7.
86. Parsels LA, Karnak D, Parsels JD, Zhang Q, Velez-Padilla J, Reichert ZR, et al. PARP1 trapping and DNA replication stress enhance radiosensitization with combined WEE1 and PARP inhibitors. Mol Cancer Res 2018;16:222–32.
87. Asim M, Tarish F, Zecchini HI, Sanjiv K, Gelali E, Massie CE, et al. Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. Nat Commun 2017;8:374.

88. Karanika S, Karantanos T, Li L, Wang J, Park S, Yang G, et al. Targeting DNA damage response in prostate cancer by inhibiting androgen receptor-CDC6-ATR-Chk1 signaling. Cell Rep 2017;18:1970–81.
89. Li L, Karanika S, Yang G, Wang J, Park S, Broom BM, et al. Androgen receptor inhibitor-induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. Sci Signal 2017;10:pii: eaam7479.
90. Clarke N, Wiechno P, Alekseev B, Sala N, Jones R, Kocak I, et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2018;19:975–86.
91. Hussain M, Daignault-Newton S, Twardowski PW, Albany C, Stein MN, Kunju LP, et al. Targeting androgen receptor and DNA repair in metastatic castration-resistant prostate cancer: results from NCI 9012. J Clin Oncol 2018;36:991–9.
92. Mo W, Liu Q, Lin CC, Dai H, Peng Y, Liang Y, et al. mTOR inhibitors suppress homologous recombination repair and synergize with PARP inhibitors via regulating SUV39H1 in BRCA-proficient triple-negative breast cancer. Clin Cancer Res 2016;22:1699–712.
93. Matulonis UA, Wulf GM, Barry WT, Birrer M, Westin SN, Farooq S, et al. Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (ADP ribose) polymerase (PARP) inhibitor olaparib for the treatment of high-grade serous ovarian and breast cancer. Ann Oncol 2017;28:512–8.
94. Konstantinopoulos PA, Barry WT, Birrer M, Westin SN, Farooq S, Cadoo K, et al. Phase I study of the alpha specific PI3-Kinase inhibitor BYL719 and the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib in recurrent ovarian and breast cancer: Analysis of the dose escalation and ovarian cancer expansion cohort [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1–5; Washington, DC. Philadelphia (PA): AACR; 2017. Abstract nr CT008.
95. Sun C, Fang Y, Yin J, Chen J, Ju Z, Zhang D, et al. Rational combination therapy with PARP and MEK inhibitors capitalizes on therapeutic liabilities in RAS mutant cancers. Sci Transl Med 2017; 9:pii: eaal5148.
96. Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol 2014;15:1207–14.
97. Kumareswaran R, Ludkovski O, Meng A, Sykes J, Pintilie M, Bristow RG. Chronic hypoxia compromises repair of DNA double-strand breaks to drive genetic instability. J Cell Sci 2012;125:189–99.
98. Sun C, Yin J, Fang Y, Chen J, Jeong KJ, Chen X, et al. BRD4 inhibition is synthetic lethal with PARP inhibitors through the induction of homologous recombination deficiency. Cancer Cell 2018;33:401–16.
99. Hartlova A, Erttmann SF, Raffi FA, Schmalz AM, Resch U, Anugula S, et al. DNA damage primes the type I interferon system via the cytosolic DNA sensor STING to promote anti-microbial innate immunity. Immunity 2015;42:332–43.
100. Xu Y. DNA damage: a trigger of innate immunity but a requirement for adaptive immune homeostasis. Nat Rev Immunol 2006;6:261–70.
101. Sato H, Niimi A, Yasuhara T, Permata TBM, Hagiwara Y, Isono M, et al. DNA double-strand break repair pathway regulates PD-L1 expression in cancer cells. Nat Commun 2017;8:1751.
102. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–20.
103. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409–13.
104. McGrail DJ, Federico L, Li Y, Dai H, Lu Y, Mills GB, et al. Multi-omics analysis reveals neoantigen-independent immune cell infiltration in copy-number driven cancers. Nat Commun 2018;9:1317.
105. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415–21.
106. Parkes EE, Walker SM, Taggart LE, McCabe N, Knight LA, Wilkinson R, et al. Activation of STING-dependent innate immune signaling by S-phase-specific DNA damage in breast cancer. J Natl Cancer Inst 2017;109:djw199.
107. Jiao S, Xia W, Yamaguchi H, Wei Y, Chen MK, Hsu JM, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res 2017;23:3711–20.
108. Lee JM, Cimino-Mathews A, Peer CJ, Zimmer A, Lipkowitz S, Annunziata CM, et al. Safety and clinical activity of the programmed death-ligand 1 inhibitor durvalumab in combination with poly (ADP-ribose) polymerase inhibitor olaparib or vascular endothelial growth factor receptor 1–3 inhibitor cediranib in women's cancers: a dose-escalation, phase I study. J Clin Oncol 2017;35:2193–202.
109. Domchek S, Postel-Vinay S, Bang Y-J, Park Y, Alexandre J, Delord J-P, et al. An open-label, multitumor, phase II basket study of olaparib and durvalumab (MEDIOLA): results in germline *BRCA*-mutated (g*BRCA*m) HER2-negative metastatic breast cancer (MBC) [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5–9; San Antonio, TX. Philadelphia (PA): AACR; 2018. Abstract nr PD6-11.
110. Krebs M, Ross K, Kim S, De Jonge M, Barlesi F, Postel-Vinay S, et al. P1.15-004 an open-label, multitumor phase II basket study of olaparib and durvalumab (MEDIOLA): results in patients with relapsed SCLC. J Thorac Oncol 2017;12:S2044–5.
111. Drew Y, de Jonge M, Hong SH, Park YH, Wolfer A, Brown J, et al. An open-label, phase II basket study of olaparib and durvalumab (MEDIOLA): results in germline *BRCA*-mutated (*gBRCA*m) platinum-sensitive relapsed (PSR) ovarian cancer (OC). Gynecol Oncol 2018;149: 246–7.
112. Karzai F, Madan RA, Owens H, Couvillon A, Hankin A, Williams M, et al. A phase 2 study of olaparib and durvalumab in metastatic castrate-resistant prostate cancer (mCRPC) in an unselected population. J Clin Oncol 36, 2018 (suppl 6S; abstr 163).
113. Konstantinopoulos PA, Munster P, Forero-Torez A, Holloway RW, Schwartzberg L, Matulonis UA, Wang J, et al. Topacio: preliminary activity and safety in patients (pts) with platinum-resistant ovarian cancer (PROC) in a phase 1/2 study of niraparib in combination with pembrolizumab. Gynecol Oncol 2018;149 Suppl 1:246.
114. Somlo G, Frankel PH, Arun BK, Ma CX, Garcia AA, Cigler T, et al. Efficacy of the PARP inhibitor veliparib with carboplatin or as a single agent in patients with germline BRCA1- or BRCA2-associated metastatic breast cancer: California Cancer Consortium Trial NCT01149083. Clin Cancer Res 2017;23:4066–76.