CHAPTER

11

PARP Inhibition to Enhance Response to Chemotherapy

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Abstract

The inhibition of poly(ADP-ribose) polymerase (PARP) enzymes is a relatively new anticancer therapeutic strategy designed to impair the ability of tumor cells to repair DNA damage. PARP inhibitors induce synthetic lethality in cells lacking the ability to repair DNA breaks through homologous recombination, such as those with mutations in *BRCA1/2* genes. Furthermore, the combination of DNA-damaging chemotherapies with PARP inhibitors may potentiate the DNA damage caused by these agents and lead to enhanced antitumor activity. An additional mechanism of action of PARP inhibitors, known as PARP trapping, has been shown to result in double-strand breaks in DNA, further expanding the potential of these drugs in causing DNA damage accumulation and ultimately apoptosis. While clinical trials testing the combination of PARP inhibitors with chemotherapeutic agents have been challenging due to enhanced toxicity, a number of studies have demonstrated clinical benefits using this strategy. This chapter will review the current status of PARP inhibitor development and discuss the lessons that have been learned from novel chemotherapy combination studies.

ABBREVIATIONS

AML	Acute myeloid leukemia
A-T	Ataxia-telangiectasia
ATM	Ataxia-telangiectasia mutated
ATR	Ataxia-telangiectasia and Rad3 related
AUC	Area under the curve; BER, Base excision repair
CHK	Checkpoint kinase
CR	Complete response
CTEP	Cancer Therapy Evaluation Program
DLT	Dose-limiting toxicity
DSB	Double-strand break
FA	Fanconi anemia
FANCD2	Fanconi anemia complementation group D2

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FDA	Food and Drug Administration
FLT3-ITD	fms-like tyrosine kinase 3-internal tandem duplication
GBM	Glioblastoma multiforme
HGSOC	High-grade serous ovarian cancer
HI	Hematologic improvement
HR	Homologous recombination
HRD	Homologous recombination deficiency
H2AX	Histone 2A family member X
IV	Intravenous
LOH	Loss of heterozygosity
MGMT	O6-methylguanine DNA-methyltransferase
MMR	Mismatch repair
MTD	Maximum tolerated dose
NER	Nucleotide excision repair
NHEJ	Nonhomologous end-joining
NSCLC	Non-small cell lung cancer
OS	Overall survival
OvCa	Ovarian cancer
PARG	Poly(ADP-ribose) glycohydrolase
PARP	Poly(ADP-ribose) polymerase
PBMC	Peripheral blood mononuclear cells
pCR	Pathological complete response
PD	Pharmacodynamic
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PSA	Prostate-specific antigen
RR	Response rate
SCLC	Small cell lung cancer
SD	Stable disease
SSB	Single-strand break
TDP1	Tyrosyl-DNA-phosphodiesterase
TMZ	Temozolomide
TNBC	Triple-negative breast cancer

11.1 INTRODUCTION

Poly(ADP-ribose) polymerase (PARP) inhibitors have been under development for the last 10 years, with the first FDA approval in 2014 for olaparib (Astra Zeneca-Lynparza®, AZD 2281, KU 0059436), quickly followed by approval for rucaparib (Clovis-Rubraca®, PF-01367338, AGO14699) and niraparib (Tesaro-Zejula®, MK 4827). The success of these inhibitors is based on the synthetic lethality they induce in *BRCA1/2*-mutant cells. This effect was first demonstrated in preclinical models by two groups in 2005 [1,2]. Subsequently, this finding has been further advanced in human clinical trials, including in a phase I trial that analyzed the pharmacokinetic and pharmacodynamic characteristics of olaparib in a study population enriched for *BRCA1/2* mutation carriers [3]. The success in this population led to olaparib becoming the first PARP inhibitor to obtain regulatory approval as the fourth or later treatment line for germline *BRCA*-mutated high-grade serous ovarian cancer (HGSOC) [4].

In parallel to targeting existing homologous recombination deficiency (HRD), such as *BRCA1/2* mutation, to induce synthetic lethality, efforts have been made to combine PARP

inhibitors with other drugs to potentiate the DNA damage caused by cytotoxic chemotherapies or to induce HRD by targeted agents. Despite promising preclinical data, the combination of PARP inhibitors with cytotoxic chemotherapy has been quite challenging due to poor tolerability in patients, mainly because of myelosuppression. This unexpected result reflects the difficulty in predicting clinical tolerability using preclinical models of combination therapy. The Cancer Therapy Evaluation Program of the National Cancer Institute has sponsored a substantial number of PARP inhibitor combination trials, mostly with veliparib (ABT-888), to investigate novel chemotherapy combination strategies with PARP inhibitors based on sound preclinical data. This chapter focuses on reviewing the current status of PARP inhibitors and the progress that has been made in exploring potential combinations with chemotherapy, radiotherapy, and targeted agents as an anticancer therapeutic strategy. It will also provide perspectives regarding this strategy in the area of PARP inhibitor drug development.

11.2 TARGETING PARP TO INHIBIT DNA REPAIR

PARP-1 is a nuclear enzyme that catalyzes the formation of PAR polymers at DNA damage sites, promoting recruitment of repair proteins to single-strand DNA breaks and facilitating base excision repair (BER) [5–8]. More precisely, upon DNA strand breaks, the DNA-binding domain of PARP-1, which contains two zinc finger motifs, recognizes and binds to damaged sites. This binding results in the activation of the enzyme to generate long poly(ADP)-ribose from NAD^+ [9,10]. Polymer elongation leads to the catalysis and degradation activity of nuclear enzyme poly(ADP-ribose) glycohydrolase (PARG), which cleaves glycosidic bonds between ADP-ribose units, resulting in the removal and inactivation of PARP in preparation for further DNA damage [9].

When DNA damage occurs, DNA glycosylases remove damaged bases and generate apurinic/apyrimidinic sites, which are cleaved by endonucleases, leaving single-strand breaks (SSBs). As damaged base replacement involves recruitment of a DNA repair complex through PARP enzymatic activity, SSBs persist if PARP-1 is inhibited [10]. In the state of cell replication, an SSB will be converted into a double-strand break (DSB) at the replication fork, eventually inducing apoptosis if multiple DSBs persist in a cell. Homologous recombination (HR) is a major pathway for DSB repair and involves recruitment of ataxia-telangiectasia (A-T) mutated (ATM) or A-T and Rad3 related (ATR) proteins to the DSB. HR also involves activation and phosphorylation of a cascade of proteins, including checkpoint kinase (CHK)-1 and 2, histone H2A family member X (H2AX), the Fanconi anemia (FA) complementation group D2 (FANCD2) protein, and BRCA1 and BRCA2 [9]. If replicating cells have DSB repair deficiencies due to HR pathway mutations, these cells undergo apoptosis.

As a result of this role of PARP in DNA damage repair, PARP became an important target for pharmacological inhibition. When poly-ADP-ribosylation (PARylation) is inhibited, impairment of BER occurs and unrepaired SSBs accumulate, leading to widespread DSB formation and replication fork collapse. As mentioned above, DSBs are normally repaired by the HR repair pathway; this notion led to the idea of clinical development of PARP inhibitors in patients with germline *BRCA1/2* mutations. Of 17 known members of the PARP nuclear superfamily, only PARP-1 and PARP-2 are predominantly involved in DNA repair and can

impair the process if disrupted [8,11]. In addition, PARP enzymes have been implicated in several nuclear processes besides DNA repair, such as DNA replication, transcription, and modulation of chromatin structure [12].

Moreover, increasing efforts have been made in broadening the synthetic lethality concept beyond germline *BRCA* mutations. For example, in the setting of clinical trials, exploratory efforts have been made in identifying patients with defects in other proteins involved the HR pathway or in proteins that sense DNA damage and initiate or coordinate DNA repair [13–15]. This chapter will not discuss such PARP inhibitor development as monotherapy in these patients, but rather discuss the approach of combining PARP inhibitors with chemotherapy, which is intended to induce synergistic DNA damage or sensitize cells to chemotherapy through PARP inhibition.

Prior to the discussion of preclinical evidence for this combination approach, it is important to recognize an additional consequence of PARP inhibition. It has been shown that the binding of PARP to DNA strand breaks prevents the recombination machinery from working until PARP disassociates [16]. This finding has developed into the currently well-recognized concept of PARP trapping, the phenomenon in which, as a consequence of PARP inhibition, PARP does not disengage from the DNA break site, leading not only to unrepaired SSBs, but also to replication-dependent DSBs. It was elegantly demonstrated that PARP inhibitors have varying degrees of PARP trapping capability, with talazoparib being the strongest trapper [17]. The overall rationale of combining PARP inhibitors with chemotherapy stems from the idea that inhibition of PARP sensitizes tumor cells to chemotherapies that induce DNA damage. Damage that would normally be repaired through the BER system cannot be repaired in the presence of PARP inhibition. This rationale, which has driven multiple clinical trials, will be further discussed below.

11.3 RATIONALE FOR COMBINING WITH CHEMOTHERAPY

11.3.1 Chemosensitization Through PARP Inhibition by Impairing SSB or BER

Chemotherapy sensitization by causing enhanced DNA damage through PARP inhibition was considered as early as 1980 [18]. Notably, the rationale for the combination of a topoisomerase I (Topo1) inhibitor and a PARP inhibitor was extensively studied. Topo1 stabilizes the topoisomerase–DNA cleavable complexes in the nicked formation at the stage in which DNA breaks occur. Repair of DNA damage involves BER, in which the key BER protein XRCC1 is recruited to Topo1-dependent DNA breaks in association with PARP enzymes [19]. Consequently, tyrosyl-DNA-phosphodiesterase (TDP1), which removes Topo1 from DNA, is recruited to the break site [20]. Since PARP-1 is capable of interacting with Topo1 and repairing Topo1-dependent SSBs, inhibition of PARP enzymes sensitizes cells to Topo1 inhibition [21]. Topo1 inhibition leads to a need for DNA repair to prevent cell death, but this repair is impeded in cells in which PARP activity is inhibited [22,23].

Several studies have demonstrated the potentiation of Topo1 inhibitors in the presence of PARP inhibitors [24,25]. For example, Thomas et al. evaluated a panel of 42 potent PARP inhibitors for potential chemosensitization of temozolomide and topotecan using human colorectal cells *in vitro* and mouse xenograft models. The investigation to further delineate the mechanism of action for PARP inhibitor sensitization on topotecan cytotoxicity was expanded

to multiple cell-line models. It was revealed that this sensitization occurs at veliparib concentrations far below those required to substantially inhibit PARP synthesis and at least an order of magnitude lower than those involved in selective killing of HRD cells [26]. This preclinical work led to a phase I combination study of veliparib and topotecan in solid tumors and a phase I study of veliparib and irinotecan in solid tumors [27,28].

Temozolomide is an alkylating agent that has been recognized as a candidate for a PARP inhibitor combination. Temozolomide is a DNA alkylator that adds methyl adducts to N7-guanine, N3-adenine, and O6-guanine positions [29,30]. O6-methylguanine, which comprises 5% of the alkylated DNA products after temozolomide treatment, triggers a continuous cycle of futile mismatch repair (MMR), subsequently leading to apoptosis [31,32]. As O6-methylguanine is removed by O6-methylguanine DNA-methyltransferase (MGMT), MGMT overexpression is considered a potential mechanism of temozolomide resistance. However, N7-methylguanine and N3-methyladenine represent 80% of the alkylated DNA after temozolomide treatment, and these adducts are not susceptible to MGMT removal; they are instead excised by the BER pathway. Therefore, increased activity of the BER pathway may also contribute to temozolomide drug resistance. As PARP recruits and activates DNA repair proteins for the BER and nonhomologous end-joining (NHEJ) pathways [33], PARP inhibition is expected to enhance tumor sensitivity to temozolomide through inhibition of BER. For example, potentiation of temozolomide and topotecan in an *in vitro* cytotoxicity assay and in a clonogenic assay with PARP inhibitors was demonstrated in human tumor cell lines including lung, colon, ovary, and breast cancer [34]. In the B16F10 subcutaneous murine melanoma model, veliparib strongly potentiated the temozolomide antitumor effect [35]. In the 9L orthotopic rat glioma model, veliparib in combination with temozolomide significantly slowed tumor progression [35].

Veliparib and temozolomide combination efficacy was also tested in hematological malignancy preclinical models such as an AML model [36]. Both MMR-proficient and -deficient leukemia cells with varying MGMT activity were used to evaluate the veliparib sensitization effect on temozolomide growth inhibition. Interestingly, veliparib potentiation was most effective in MMR-deficient cells with low MGMT activity, whereas veliparib also potentiated temozolomide activity in MMR-deficient cells with elevated MGMT activity. A phase I clinical study to test this combination in AML patients was completed; the details of this study are discussed in Section 11.5.2 [37]. In solid tumors and lymphoma, veliparib and temozolomide combination efficacy was tested in multiple xenograft models representing various human tumors with different responses to temozolomide [38]. These xenograft tumors, including subcutaneous and orthotopic models and metastatic sites, were assessed by tumor burden, expression of poly(ADP-ribose) polymer, and MGMT. The combination had activity to various degrees across a broad histologic spectrum, including B-cell lymphoma, small and non-small-cell lung, pancreatic, ovarian, breast, and prostate cancer xenografts. More interestingly, efficacy in otherwise temozolomide-nonresponsive tumors suggests that temozolomide resistance may be overcome by PARP inhibition. However, the degree of sensitivity to this combination did not correlate with tumor MGMT, MMR status, or poly(ADP-ribose) (PAR) polymer levels.

Another class of agent that may be successfully combined with PARP inhibitors is platinum-based therapies. Preclinical evidence has demonstrated the potentiation of effects of platinum by PARP inhibitors, as well as synergism between PARP inhibitors and platinum

compounds, in *BRCA1*- or *BRCA2*-associated breast cancer models and in non-small cell lung cancer (NSCLC) models [39–41]. Particularly, the combination of carboplatin and a PARP inhibitor has been shown to result in enhanced DNA damage and antitumor activity, leading to a more significant reduction in tumor growth than cisplatin alone. These and other findings led to a clinical combination study of carboplatin, taxol, and veliparib in advanced solid tumors, since carboplatin and taxol are used in combination as standard of care [42]. Another triple combination of topotecan, carboplatin, and veliparib was tested in a phase I clinical trial in AML patients, based on the hypothesis that these agents act synergistically [43].

The concept of veliparib being combined with cyclophosphamide was also derived from preclinical data using the MX-1 breast xenograft model (*BRCA1* deletion and *BRCA2* mutation), in which veliparib in combination with cyclophosphamide showed tumor regression of established tumors, whereas cyclophosphamide alone resulted in only modest tumor inhibition [35]. Alkylating agents such as cyclophosphamide are known to form inter-strand cross-links, which are thought to result in cell death due to the formation of SSBs or DSBs during the DNA damage repair process. PARP inhibitors interfere with DNA repair and may potentiate the antitumor effects of cyclophosphamide.

By inhibiting BER, PARP inhibitors also enhance the cytotoxicity of floxuridine [44], an agent previously shown to have clinical activity in ovarian cancer.

11.3.2 Chemosensitization Through PARP Inhibition by Enhancing DNA Trapping

In addition to NAD(+)-competitive catalytic inhibition, which was the mechanism of action first defined for these agents, PARP inhibitors were recently found to also exhibit cytotoxic trapping of PARP–DNA complexes [17]. Although PARP inhibitors are potent catalytic inhibitors, PARP trapping is drug-specific. Murai et al. evaluated the cytotoxicity and molecular mechanisms of the combination of olaparib or veliparib with multiple agents: the Topo1 inhibitor camptothecin, the alkylating agent temozolomide, the cross-linking agent cisplatin, and the Topo2 inhibitor etoposide. PARP–DNA trapping and catalytic PARP inhibition were assessed in the genetically modified chicken B-cell lymphoma line DT40, human prostate DU145, and glioblastoma SF295 cancer cells. Topo1 inhibitor camptothecin combined with either veliparib or olaparib demonstrated highly synergistic effects due to catalytic PARP inhibition. However, PARP trapping was critical for the temozolomide combination, in which olaparib was more effective than veliparib. For other chemotherapeutic agent combinations, including cisplatin and etoposide, the olaparib combination was not effective due to the lack of PARP involvement in DNA repair following cisplatin- or etoposide-induced DNA damage. This paper elegantly illustrates the highly effective combination of catalytic PARP inhibitors, such as veliparib, with camptothecins, vs the effective combination of PARP-trapping inhibitors with temozolomide [45].

PARP inhibitors in combination with temozolomide have been shown to enhance antitumor activity in Ewing sarcoma xenograft and orthotopic models [46]. In these models, PARP inhibitor sensitivity is not due to an apparent HR DNA repair defect, but instead results from hypersensitivity to trapped PARP-1:DNA complexes. During cell replication, PARP-1:DNA complexes cause accumulation of DNA damage, subsequently leading to apoptosis; the potentiation of PARP inhibitors by temozolomide is associated with this process. Other

tumor cell lines, such as a subset of glioma, neuroblastoma, and melanoma cells, were also identified as particularly sensitive to a combination of temozolomide and PARP inhibitors by this mechanism [47]. Temozolomide potentiation of PARP inhibitor trapping was further investigated in a phase II three-arm randomized trial in breast cancer comparing veliparib plus temozolomide vs veliparib plus paclitaxel/carboplatin vs placebo plus paclitaxel/carboplatin [48].

11.4 PARP INHIBITORS

11.4.1 Iniparib

Iniparib (BSI 201) initially was thought to be a PARP inhibitor, whose inhibition of single-strand DNA break repair was dependent on PARP-1 expression. The initial excitement over this agent was driven by the activity of iniparib combined with carboplatin and gemcitabine in triple negative breast cancer, reported by O'Shaughnessy et al. [49]. While this phase II trial provided early evidence of the benefit of adding a PARP inhibitor to chemotherapy, the phase III trial did not meet the predefined criteria for the coprimary endpoints of progression-free survival (PFS) and overall survival (OS) [50]. As the phase III trial was commencing, data were released suggesting that iniparib may not be a true PARP inhibitor [51,52].

A phase II study was conducted to assess efficacy and tolerability of iniparib in patients with recurrent, germline *BRCA1/2*-mutated, advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer [53]. Among the 12 patients who received the study drug, no objective responses were seen [53]. The investigators admitted to learning two important lessons from this trial, which guided future early-phase studies. First, attention should be paid to seek out and understand the preclinical data prior to clinical investigations. Although there were basic science data reported from environmental and chemistry laboratories suggesting PARP-1 inhibition by iniparib prior to the clinical development of the drug, data from preclinical cancer models were not available. Studies showing the lack of efficacy of PARP inhibition with iniparib were reported in 2012, well after the completion of the phase II chemotherapy combination study. Second, although there had been favorable activity with the PARP inhibitor olaparib in heavily pretreated (3–4 regimens) germline *BRCA* mutation-associated ovarian cancer patients [54], similar results were not observed in the iniparib study, possibly due to the patients being further along in their disease course or the iniparib mechanism of action differing from direct PARP inhibition [53].

11.4.2 Olaparib

Olaparib is an oral PARP inhibitor approved in the United States as a monotherapy for patients with germline *BRCA*-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. It is known that women with germline mutations in *BRCA1*, *BRCA2*, or both have an increased risk of ovarian cancer, with the most common type being HGSOC. Approximately 15% of epithelial ovarian cancers are deficient in HR repair due to mutations in *BRCA1/2*, and olaparib induces synthetic lethality in

these HR-deficient tumor cells [4,55]. Clinical evidence of the efficacy of olaparib in patients with germline *BRCA* mutation-associated ovarian cancer was provided by several phase II trials [56–58]. Although the clinical benefits of olaparib are more dramatic in patients with *BRCA1/2* mutations, the drug was shown to have clinical activity in HGSOC patients regardless of *BRCA* status [58]. In 2014, olaparib was approved in the United States for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

A randomized, double-blind phase II trial (Study 19) was also conducted to evaluate the efficacy of olaparib monotherapy as maintenance treatment in patients with platinum-sensitive relapsed HGSOC who had achieved a response to their most recent platinum-based chemotherapy. Patients received olaparib 400 mg BID or placebo within 8 weeks after completion of chemotherapy. The primary endpoint was PFS, defined as the time from randomization to objective disease progression or death. PFS was significantly longer in the olaparib group, with a PFS of 8.4 months, compared to 4.8 months in the placebo group. The majority of adverse events were grade 1 or 2 and included nausea, vomiting, fatigue, and anemia; the most common adverse events leading to drug interruption or dose reduction were nausea, vomiting, and fatigue [4]. An updated analysis of this study was reported in 2016 and demonstrated that, although there was not a statistically significant improvement in OS, patients who received olaparib maintenance therapy seemed to have longer survival than patients who received placebo, without experiencing any additional safety issues [59]. The group deriving the most significant survival benefit was the *BRCA*-mutated group.

The SOLO-2 trial was designed to prospectively confirm the findings seen in Study 19 and was performed using a tablet form of olaparib, offering patients a reduced daily pill burden. The dose administered was 300 mg BID in tablets (four tablets per day) vs olaparib 400 mg BID in capsules (16 capsules per day). Overall, the safety profile of the tablet was shown to be similar to the capsule formulation. The only major difference in toxicity was an increased rate of anemia with the tablets, thought to be due to longer olaparib exposure in SOLO-2 compared to Study 19 (median duration of exposure of 588 days vs 206 days). Results from SOLO-2 confirmed an improvement in PFS with olaparib maintenance therapy in patients with *BRCA1/2*-mutated platinum-sensitive relapsed ovarian cancer [60]. In August 2017, the FDA approved olaparib tablets as a second indication for maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy [61–63].

11.4.3 Veliparib

The Division of Cancer Treatment and Diagnosis at the National Cancer Institute conducted the first phase 0 clinical trial in oncology of a therapeutic agent under the Exploratory Investigational New Drug Guidance of the FDA. It was a first-in-human study of the oral PARP inhibitor veliparib in patients with advanced malignancies. The trial looked not to determine a maximum tolerated dose (MTD) but to define a dose range and time course over which veliparib inhibited PARP activity. This analysis was done using a validated pharmacodynamic (PD) assay for PAR, a product of PARP. PAR measurements were performed on tumor cells and peripheral blood mononuclear cells (PBMCs), and pharmacokinetic (PK) data were

collected as well. A novel statistical approach was also developed, specifically for phase 0 trials, in which the endpoints are based on PD measurements rather than toxicity [64].

In the phase 0 trial, patients received a single oral dose of veliparib. There were five dose levels, with three patients on each dose level: 10, 25, 50, 100, and 150 mg. Planned serial blood sampling, pre- and post-drug administration, was performed for PD and PK analyses. Tumor biopsies were performed once significant inhibition of PARP activity was observed in PBMCs; this process reduced the likelihood of obtaining tumor biopsies from patients receiving doses unlikely to show drug effect. Statistically significant reductions in PAR levels were observed in both tumor and PBMC samples at the 25 and 50 mg dose levels. Veliparib was well tolerated, with no significant adverse effects reported. This study was pivotal in that, in about 5 months, data were available that showed molecular proof-of-mechanism: target inhibition by veliparib in patient tumor cells. Along with PK and PD data, these results were the foundation for subsequent combination studies of veliparib with DNA-damaging agents [64].

Veliparib is currently under extensive clinical development, both as a single agent and in combination trials. It is well suited for use in combination trials, as it has modest hematopoietic toxicity [15]. The first single-agent phase I/II trial of veliparib was performed in patients with germline *BRCA*-mutated or platinum-refractory ovarian cancer and *BRCA*-wild-type basal-like breast cancer. Greater clinical activity was demonstrated in patients with *BRCA*-mutated disease than in those with wild-type disease [65]. The toxicity profile of veliparib was found to be favorable and the phase II dose was established at 400 mg BID. A subsequent phase II trial using single-agent oral veliparib was reported by Coleman et al. [66], examining clinical activity in ovarian cancer patients with a germline *BRCA1* or *BRCA2* mutation. The overall response rate was 26%, and responses were seen in both platinum-sensitive and -resistant disease.

Veliparib is also being evaluated in other solid tumors, including rectal, pancreatic, head and neck, and testicular cancer. In November 2016, the FDA granted Orphan Drug Designation to veliparib for advanced squamous NSCLC [61]. Novel combination regimens of veliparib with different radiotherapy or chemotherapy treatments are being explored in various tumor types, such as with whole-brain radiation in brain metastasis, temozolomide in metastatic melanoma, cisplatin and etoposide in extensive stage SCLC, whole-abdominal radiation in peritoneal carcinomatosis, and carboplatin and paclitaxel in NSCLC, all with promising results [67–71]. However, reports of results from phase III veliparib–chemotherapy combination studies in NSCLC and triple-negative breast cancer (TNBC) have not indicated improvement in clinical activity for the veliparib combination arms [61,72].

11.4.4 Niraparib

Niraparib is a highly selective inhibitor of PARP-1/2, and its antitumor activity was initially demonstrated in a phase I dose escalation study, with the MTD being 300 mg daily. Objective clinical responses were observed in patients with ovarian cancer, with good tolerability [73].

These results led to the multinational phase III NOVA trial evaluating the efficacy and safety of niraparib vs placebo as maintenance treatment in platinum-sensitive recurrent

ovarian cancer. There were two cohorts, defined by the presence or absence of a germline *BRCA* mutation [74]. Archival tissue from the non-*BRCA* group was further analyzed using the myChoice HRD test (Myriad Genetics) to define the population of patients with HRD, as decreased rates of HR are associated with inefficient DNA repair. The primary endpoint of the study was the duration of PFS. The three predefined primary efficacy populations were: (1) the germline *BRCA* cohort, (2) a subgroup of the nongermline *BRCA* cohort positive for HRD, and (3) the overall nongermline *BRCA* cohort. The most common adverse events included thrombocytopenia, anemia, and neutropenia, all managed with dose reductions. However, the incidence of myelodysplastic syndrome was 1.4% in patients receiving niraparib, and there were three deaths occurring during the follow-up period (one MDS and one AML), which were considered to be treatment-related. The results demonstrated that niraparib provided significant clinical benefit, regardless of *BRCA* status or HRD status, in this group of platinum-sensitive patients. Niraparib is the first PARP inhibitor approved by the FDA for use regardless of *BRCA* mutation status; it is approved for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have a partial or complete response to platinum-based therapy without regard to *BRCA* status [74,75].

11.4.5 Rucaparib

Rucaparib is an oral PARP inhibitor that, in a phase I/II trial, demonstrated an objective response in 67% of women with platinum-sensitive relapsed high-grade ovarian carcinoma, who harbored a germline *BRCA* mutation [14].

ARIEL2 was a clinical trial that sought to help predict which *BRCA* wild-type cancers would respond to PARP inhibitor therapy. Several clinical trials reported antitumor activity and improvement in PFS with PARP inhibitors in patients without a *BRCA* mutation, implying that other HR deficiencies may be present. In ARIEL2, patients were classified into one of the three predefined HRD subgroups on the basis of tumor genetic analysis: (1) *BRCA* mutant (deleterious germline or somatic), (2) *BRCA* wild-type and loss of heterozygosity-high group (LOH-high), or (3) *BRCA* wild-type and LOH-low (LOH-low group) [14].

Patients in the ARIEL2 trial received rucaparib 600 mg BID for 28 days, with the primary endpoint being PFS. The most common grade 3 adverse events were decreased hemoglobin and elevations in alanine aminotransferase or aspartate aminotransferase. In patients with platinum-sensitive ovarian carcinoma tumors classified as *BRCA* mutant or *BRCA* wild-type and LOH-high, PFS was longer than in those patients with *BRCA*-wild type and LOH-low tumors. This suggests that assessment of tumor LOH could identify *BRCA* wild-type patients who might benefit from rucaparib, extending the benefit of this agent beyond those with *BRCA* mutation-associated tumors [14]. In 2016, rucaparib was granted FDA approval for treatment of patients with deleterious *BRCA* (germline and/or somatic) mutation-associated advanced ovarian cancer who have been treated with two or more chemotherapies.

In September 2017, data were reported from ARIEL3, a study in which patients with high-grade ovarian cancer who had responded to platinum-based therapy in the second or third line of treatment were randomized 2:1 to rucaparib maintenance therapy or placebo. The primary endpoint was PFS, which was measured sequentially in the following three groups if

benefit was found in the previous group: *BRCA* mutant, HR-deficient (*BRCA* mutant or *BRCA* wild-type with high LOH), or the entire study population. Rucaparib produced statistically significant improvement in PFS in all three groups, with the greatest improvement in the *BRCA*-mutated group. However, patients without BRCA mutations were divided based on LOH, and while patients with high LOH demonstrated more improvement in PFS than those with low LOH, rucaparib performed statistically better than placebo in both groups. Therefore, the LOH test was not able to successfully differentiate responders from nonresponders as the investigators had hoped [76].

11.4.6 Talazoparib

The PARP-1/2 inhibitor talazoparib was brought to a phase I first-in-human trial because it was demonstrated to be the most potent agent in terms of both *in vitro* PARP inhibition and *in vitro* trapping of PARP–DNA complexes at sites of single-strand DNA breaks. The phase I dose-escalation trial was done in patients with advanced malignancies, whereas the expansion cohort included patients with tumors harboring germline *BRCA1/2* mutations or predicted to be potentially sensitive to PARP inhibition based on preclinical data. Tumors in the expansion cohort included TNBC, HGSOC, fallopian tube or peritoneal cancers, and castration-resistant prostate and pancreatic cancers [77].

At the MTD of 1 mg daily, confirmed responses were observed in 7 of 14 patients with *BRCA*-mutated breast cancer, with one complete response (CR). In the ovarian cancer cohort, 5 of 12 responses occurred in patients with deleterious germline *BRCA1/2* mutations, including one CR. It should be noted that for all *BRCA*-mutated ovarian cancer patients treated at any dose level, the overall response rate was 55% in platinum-sensitive patients, when compared with 20% in platinum-resistant patients. Of the 13 pancreatic patients treated, two had a partial response (PR), one with a *BRCA2* mutation and one with a *PALB2* mutation.

Patients with Ewing sarcoma and SCLC were also included in the expansion cohort based on the strong preclinical rationale for use of a PARP inhibitor in these tumor types. The 23 SCLC patients were all treated with 1 mg/day, with two PRs. These two patients also had had an objective response to their last prior platinum therapy. No objective responses were seen in Ewing sarcoma patients [77].

Talazoparib was well tolerated overall, with the dose-limiting toxicity being thrombocytopenia. Myelosuppression was transient and reversible, managed with dose interruptions and/or dose reductions [77]. The findings from this study demonstrated the efficacy of single-agent talazoparib in patients with *BRCA1/2* or *PALB2* mutations in ovarian, breast, small-cell lung, and pancreatic cancers.

11.5 PARP INHIBITOR AND CHEMOTHERAPY COMBINATIONS

Based on the strong rationale and preclinical evidence supporting the combination of PARP inhibitors with chemotherapy, various clinical trials to evaluate patient response have been performed or are ongoing (Tables 11.1 and 11.2). However, these studies have been challenging due to severe adverse events, particularly myelosuppression. This increased frequency and severity of myelosuppression observed with combination treatment, especially with the

TABLE 11.1 Combination Studies of PARP Inhibitors With Other Agents: Phase I Trials

Trial Identifier	Disease	PARP Inhibitor	Other Agent(s)	Cycle Length	Combination MTD	Results[a]
NCT00553189	Refractory solid tumors and lymphomas	Veliparib	Topotecan	21 days	Veliparib 10 mg BID on days 1–5 + topotecan 0.6 mg/m^2/day on days 1–5	>75% reduction in PAR levels in all three paired tumor biopsies; >50% reduction in PAR levels in PBMCs from 19 of 23 patients with measurable levels (no data on clinical benefit reported) [27]
NCT01012817 (ongoing)	Metastatic or unresectable solid tumors	Veliparib	Topotecan	28 days	Veliparib 300 mg BID on days 1–3, 8–10, and 15–17 + topotecan 3 mg/m^2 on days 2, 9, and 16	Of 52 evaluable patients, 1 CR (2%), 3 PR (6%), and 6 SD for ≥8 cycles (12%); no response correlation to *BRCA* status [78]
NCT01445522	Refractory solid tumors and lymphomas	Veliparib	Cyclo-phosphamide	21 days	Veliparib 60 mg QD + cyclophosphamide 50 mg QD	Of 35 pts, 7 PR (20%) and 6 SD for ≥6 cycles (17%) [79]
NCT01085422	Metastatic castration-resistant prostate cancer	Veliparib	Temozolomide	28 days	Veliparib 40 mg BID on days 1–7 + TMZ 150–200 mg/m^2 QD on days 1–5	Of 25 pts, two had PSA response (8%; decline ≥30%), 13 had stable PSA (52%) [80]
NCT01139970	Acute myeloid leukemia	Veliparib	Temozolomide	28 days	Veliparib 150 mg BID × 9 days + TMZ 200 mg/m^2 QD × 7 days (veliparib beginning the day after temozolomide initiation)	Of 48 pts, 8 CR (17%) and 8 SD/HI (17%) [37]
NCT01642251	Extensive stage SCLC	Veliparib	Cisplatin and etoposide	21 days	Veliparib 100 mg BID on days 1–7 + cisplatin (75 mg/m^2 on day 1) and etoposide (100 mg/m^2 on days 1–3)	Of 7 pts, 1 CR (14%), 4 PR (57%), and 2 SD (29%) [69]
NCT01749397 (ongoing)	Metastatic epithelial ovarian, primary peritoneal cavity, or fallopian tube cancer	Veliparib	Floxuridine	21 days	MTD not yet established (testing treatment schedule: veliparib BID on days 1–10 + floxuridine on days 3–5)	Not yet available

NCT00678132	Advanced solid tumors	Olaparib	Cisplatin and gemcitabine	21 days	Olaparib 100 mg QD on day 1 + cisplatin 60 mg/m^2 on day 1 + gemcitabine 500 mg/m^2 on days 1 and 8	Of 21 pts, 2 PR (10%) and 13 SD (62%; median duration of 20 weeks) [81]
NCT00782574	Advanced solid tumors	Olaparib	Cisplatin	21 days	MTD not established; olaparib 50 mg BID on days 1–5 + cisplatin 60 mg/m^2 on day 1 deemed tolerable	Of 46 total pts, 19 PR (41%) and 19 SD (41%); of 25 pts with *BRCA* mutation, 15 PR (60%) and 10 SD (40%) [82]
NCT01445418	*BRCA*1/2-mutated ovarian and breast cancer	Olaparib	Carboplatin	21 days	MTD not reached; highest tested dose was olaparib 400 mg BID on days 1–7 + carboplatin AUC5 once per cycle	Of 42 pts, 1 CR (2%) and 21 PR (50%) [83]
NCT00707707	Metastatic TNBC	Olaparib	Paclitaxel	28 days	MTD not established; initial tested dose was olaparib 200 mg BID + paclitaxel 90 mg/m^2 on days 1, 8, and 15	Of 19 pts, 7 PR (37%) and 6 SD for ≥7 weeks (32%) [84]
NCT00516802	Advanced solid tumors	Olaparib	Dacarbazine	21 days	Olaparib 100 mg BID on days 1–7 + dacarbazine 600 mg/m^2 on day 1	Of 40 pts, 2 PR (5%; both in melanoma) and 8 SD (20%) [85]
NCT01116648	Recurrent ovarian or metastatic TNBC	Olaparib	Cediranib	28 days	Olaparib 200 mg BID + cediranib 30 mg QD	Of 18 OvCa pts, 1 CR (6%), 7 PR (39%), and 3 SD for ≥24 weeks (17%); of 11 *BRCA*-mutated OvCa pts, 1 CR (9%) and 4 PR (36%); of 7 TNBC pts, no responses and 2 SD for ≥24 weeks (29%) [86]
NCT01009190	Advanced solid tumors	Rucaparib	Carboplatin	21 days	Rucaparib (oral) 240 mg QD + carboplatin AUC 5	Of 33 pts, 3 PR (9%) and 18 SD for ≥12 weeks (55%) [87]

Abbreviations: AUC, area under the curve; BID, twice daily; CR, complete response; HI, hematologic improvement; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; OvCa, ovarian cancer; PAR, poly(ADP-ribose); PMBC, peripheral blood mononuclear cell; PR, partial response; PSA, prostate-specific antigen; pts, patients; QD, once daily; SCLC, small cell lung cancer; SD, stable disease; TMZ, temozolomide; TNBC, triple negative breast cancer.

[a] *The patient population used to determine the denominator (number of total patients) is defined differently depending on the study. In some studies, this number refers to evaluable patients in the expansion cohort only, whereas in other studies the number refers to the total number of patients in the trial, including all dose levels. Please see the cited reference for this information.*

TABLE 11.2 Phase II of combinations of PARP with other agents

Trial	Disease	PARP Inhibitor	Other Agent(s)	Cycle Length	Study Design/ Treatment Dose	Results
NCT00804908	Stage III unresectable or stage IV metastatic melanoma	Veliparib	Temozolomide	28 days	Randomized, double-blind TMZ (150–200 mg/m^2 QD on days 1–5) + placebo OR TMZ (150–200 mg/m^2 QD on days 1–5) + veliparib (20 mg or 40 mg BID on days 1–7)	Veliparib 20 and 40 mg increased median PFS vs placebo, but the difference did not reach statistical significance—3.7 months PFS in the 20 mg veliparib arm—3.6 months PFS in the 40 mg veliparib arm—2 months PFS in the placebo arm [68]
NCT01306032	*BRCA*-mutated ovarian (or high-grade serous ovarian, primary peritoneal, or fallopian tube cancer) triple-negative breast cancer	Veliparib	Cyclo-phosphamide	21 days	Randomized, open-label cyclo-phosphamide (50 mg QD) alone or combined with veliparib (60 mg QD)	Veliparib added to cyclophosphamide did not improve response rate or PFS In *BRCA*-mutated ovarian: cyclophosphamide alone (36 pts): 1 CR (3%), 6 PR (17%), 6 SD for ≥6 cycles (17%)—combination (34 pts): 1 CR (3%); 3 PR (9%), 5 SD for ≥6 cycles (15%) [88] In TNBC: cyclophosphamide alone (18 pts): 1 PR (6%), 1 SD for ≥6 cycles (6%); combination (21 pts): 2 PR (10%), 2 SD for ≥6 cycles (10%) [89]
NCT01042379 (I-SPY 2)	Stage II or III breast cancer (with a tumor ≥2.5 cm in diameter)	Veliparib	Carboplatin and paclitaxel	7 days (for 12 weeks)	Randomized, open-label paclitaxel (80 mg/m^2, weekly for 12 weeks) alone (control group) or combined with veliparib (50 mg BID for 12 weeks) + carboplatin (AUC 6 every 3 weeks)	Veliparib + carboplatin added to standard therapy resulted in higher rates of pCR in triple-negative patients: 51% pCR in the veliparib + carboplatin group; 26% pCR in the control group [90]

NCT01506609 (BROCADE)	Locally recurrent or metastatic *BRCA*-mutated breast cancer	Veliparib	Temozolomide or carboplatin and paclitaxel	28 days for TMZ arm; 21 days for other arms	Randomized, double-blind (48) veliparib (40 mg BID on days 1–7) + TMZ (150–200 mg/m^2 QD on days 1–5) OR veliparib (120 mg BID days 1–7) or placebo + carboplatin (AUC 6 on day 3) + paclitaxel (175 mg/m^2 on day 3)	Interim results demonstrated that differences in PFS and OS between the arms are not statistically significant [91]
NCT01116648	Platinum-sensitive, relapsed HGSOC or endometrioid ovarian, fallopian tube, or primary peritoneal cancer, or *BRCA*-mutated cancer	Olaparib	Cediranib	28 days	Randomized, open-label Olaparib (400 mg BID) alone or olaparib (200 mg BID) + cediranib (30 mg QD)	Not yet available; interim results demonstrated that cediranib plus olaparib improves PFS compared to olaparib monotherapy—9 months PFS in the olaparib arm—17.7 months PFS in the combination arm [92]
NCT number not available	Chemotherapy-naïve, metastatic melanoma	Rucaparib	Temozolomide	28 days	Single-arm rucaparib 12 mg/m^2 (IV) on days 1–5 + TMZ 150–200 mg/m^2 QD on days 1–5	Of 46 pts, 8 PR (17.4%) and 8 SD for ≥24 weeks (17.4%); median PFS of 3.5 months [93]

Abbreviations: BID, twice daily; CR, complete response; HGSOC, high-grade serous ovarian cancer; IV, intravenous; OS, overall survival; pCT, pathological complete response; PFS, progression-free survival; PR, partial response; Pts, patients; QD, once daily; RR, response rate; SD, stable disease; TMZ, temozolomide.

chemotherapies topotecan, doxorubicin, and gemcitabine, is the finding most suggestive of synergism between PARP inhibitors and chemotherapeutic agents. It is important to note, however, that not all chemotherapies carry this same risk; most PARP inhibitors, veliparib, in particular, do not yield increased incidence of myelosuppression when combined with platinum. The duration of therapy is an important factor when determining the PARP inhibitor dose that could be given without inducing severe toxicity—the longer the duration of the PARP inhibitor therapy, the greater is the potential for significant myelosuppression. One key unanswered question is the duration of DNA repair and when it is initiated. A better understanding of DNA repair temporal dynamics would be helpful in knowing when to start and how long to continue the administration of PARP inhibitor for optimal benefit and minimal toxicity.

11.5.1 Enhanced Toxicity

The first PARP inhibitor trial to indicate some synergism of this drug class with chemotherapy was a study of rucaparib given intravenously with temozolomide in melanoma patients [93]. Pharmacodynamic analysis showed PARP inhibition in PBMCs, and a clinical response rate of 17.4% was observed. The median OS was 9.9 months, and 36% of patients were progression-free at 6 months. This study predates the activity that has since been seen in melanoma with BRAF inhibitors and immunotherapy. Fifty-four percent of the patients in this trial required a dose reduction of the temozolomide due to myelosuppression. This was a single-arm study, and no subsequent trials were conducted to show the benefit of rucaparib in this combination.

More significant evidence of enhanced activity comes from the combination of PARP inhibition with topotecan. Based on preclinical data, veliparib's enhanced cytotoxicity with topotecan is thought to result from PARP trapping. In the phase I trial of topotecan given on a 5-day schedule, veliparib was only able to be administered at 10 mg BID on days 1–5 [27]. Also, the topotecan dose, 0.6 mg/m^2 on days 1–5, was 50% of the standard dose. This is the most significant compromise of the backbone chemotherapy in combination with PARP inhibitor. Interestingly, when veliparib was tested with topotecan given on a weekly schedule [78], veliparib was tolerable at close to the single-agent MTD. The veliparib MTD in this latter combination study is 300 mg BID given orally from 1 day before through 1 day after the topotecan dose; topotecan is given weekly at 3 mg/m^2 on days 2, 8, and 16, every 28 days. Similar to the previous topotecan–veliparib combination study, the DLT for this study is myelosuppression. Though veliparib is thought to be the weakest PARP trapper, results from the combination with topotecan given daily for 5 days indicate significant synergy. The increased cytotoxicity for this combination is not due to any pharmacokinetic interaction of the two agents. In the daily schedule, a >75% reduction in tumor PAR levels was observed in all three sets of paired biopsy samples, and a >50% reduction of PAR in PBMCs was also observed in 19 of 23 patients [27]. The circulating tumor cells and PBMCs collected also exhibited increased levels of γH2AX, a marker of apoptosis.

Olaparib also raised substantial toxicity issues in combination therapy. It was combined with gemcitabine and cisplatin in a phase I trial [81]. The initial starting dose was olaparib administered at 100 mg PO BID days 1–4, with cisplatin given at 60 mg/m^2 on day 3 and gemcitabine 500 mg/m^2 given on days 3 and 10. Significant neutropenia and thrombocytopenia were seen at this dose level. The trial was modified several times to try to improve

the marrow tolerance, including changing the days of cisplatin and gemcitabine administration to days 1 and 8, dosing only on day 1, and reducing cisplatin and gemcitabine dose. The final recommended phase II dose was olaparib 100 mg BID day 1, cisplatin 60 mg/m^2 day 1, and gemcitabine 500 mg/m^2 days 1 and 8. The increased myelosuppression observed was thought to be secondary to the pharmacokinetics of gemcitabine and olaparib. When administered together, gemcitabine seemed to increase the elimination half-life of olaparib. This, in the presence of cisplatin, may have increased the frequency of double-strand DNA breaks and therefore of myelosuppression. The timing of administration may also be relevant; in the single dosing studies, PAR values return to baseline 36 h after administration of the last olaparib dose, implying that a longer dosing schedule would be preferable. Two PRs were seen in this study despite the less-than-optimal dosing of cisplatin and gemcitabine [81].

Oral rucaparib has been tested in combination with carboplatin. With a dose of carboplatin AUC 5, 240 mg of oral rucaparib could be given daily for 14 days [87]. The DLTs were grade 4 neutropenia and grade 4 thrombocytopenia. No pharmacokinetic interaction was detected. The doses of carboplatin and rucaparib in this combination study are reduced relative to single-agent dosing of both agents. Despite the reduced dose, activity was seen in 3 out of 33 patients. The toxicity and activity imply potential synergy between the two agents.

The Pediatric Preclinical Testing Program compared the combination of talazoparib with temozolomide or topotecan *in vitro* and *in vivo* [94], and temozolomide showed great synergy with talazoparib, especially in Ewing sarcoma cell lines. This synergy was not lost despite the low dose of temozolomide used. This study was the basis for the development of a clinical trial (NCT02116777). Given concerns of potential myelosuppression, as the single-agent DLT is thrombocytopenia, the phase I trial was designed to start with low-dose temozolomide, representing a change in paradigm.

11.5.2 Clinical Benefits

Despite the extensive clinical research that has been performed with PARP inhibitors, there are few trials comparing the effects of chemotherapy with or without combination PARP inhibitor treatment. These types of studies are needed to more clearly define the beneficial role PARP inhibition plays, but a major obstacle has been the fact that, due to myelosuppression, most combination regimens require a reduction in the chemotherapy dose to make PARP inhibition tolerable [95]. While most of the available data on combination treatment are from studies with veliparib, the first agent to have undergone testing of chemotherapy with or without a PARP inhibitor is iniparib. The initial phase II results suggested a role for iniparib, but the phase III data did not support this finding [50,96], and this agent was subsequently reported not to be a PARP inhibitor [97,98]. The most common chemotherapeutic agents that have shown promising preclinical activity in combination with PARP inhibition are temozolomide, platinum, and topoisomerase inhibitors, likely due to the impact of these agents on DNA repair mechanisms.

Temozolomide has been tested in combination with veliparib, rucaparib, and talazoparib in various cancers, including metastatic melanoma and SCLC. In melanoma, although the results were encouraging, the timing of introduction into the clinic was poor in that it

coincided with the release of BRAF inhibitors. A phase II double-blind, placebo-controlled, randomized trial evaluated veliparib 20 or 40 mg BID for 7 days given with temozolomide 150–200 mg/m^2 QD for days 1–5 in patients with metastatic melanoma. The median PFS was 3.7 and 3.6 months in the veliparib 20 and 40 mg combination arms, respectively, compared to PFS of 2 months in the temozolomide plus placebo group. While the PFS nearly doubled with the PARP inhibitor, the duration of PFS was very short, and these differences did not reach statistical significance [68]. However, in the exploratory subgroup analysis, patients with low expression of ERCC1 treated with veliparib had PFS of 5.6 months, compared to 1.9 months in the group treated with placebo [68]. Another interesting finding was that patients with detectable p16 had doubled PFS with veliparib treatment (3.8 months vs 1.8 months with placebo). This finding is suggestive of synthetic lethality, i.e., impairment of BER enhancing the effects of the interference of other pathways [99].

Temozolomide (150–200 mg/m^2/day) was combined with 40 mg veliparib vs placebo in relapsed SCLC as well; a randomized, double-blind phase II trial demonstrated a significantly higher response rate with veliparib–temozolomide compared to temozolomide alone, although an improvement in PFS was not observed [100]. Similarly, a single-arm phase II study evaluating rucaparib and temozolomide in patients with metastatic melanoma showed an improvement in the response rate and PFS compared with historical controls [93].

The BROCADE trial evaluates the concept of PARP inhibition vs PARP trapping [48]. Though PARP trapping has not been demonstrated in humans due to the lack of a clinical assay, preclinical studies suggest that platinum is not affected by PARP trapping, while temozolomide is an ideal candidate for synergy with a PARP trapper. The trial population is patients with *BRCA*-associated breast cancer, so a positive response demonstrating the benefit of adding veliparib is anticipated. Interestingly, in preclinical studies, veliparib is the weakest PARP trapper [17]. This trial is ongoing and will help elucidate possible mechanism of action for PARP inhibitors.

The dose of veliparib is heavily dependent on whether inhibition or trapping is the predominant mechanism; as noted, the tolerable dose of veliparib with platinum is greater than two times the dose used when veliparib is combined with alkylating agents or topoisomerase inhibitors. The major side effect of the combination for PARP trapping-based synergy is increased frequency and severity of myelosuppression. When myelosuppression has not been used to define DLT, the dose of veliparib used in combination has been significantly higher. In a phase I trial of veliparib with temozolomide in acute myeloid leukemia, for example, 150 mg of veliparib was given in combination with 200 mg/m^2 of temozolomide for 7 days [37]. The DLT was gastrointestinal, and greater doses of temozolomide and veliparib were administered.

The I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2; NCT01042379) trial also suggested significant benefits for a PARP inhibitor being administered in combination with chemotherapy treatments. I-SPY 2 is the second phase of a neoadjuvant breast cancer trial testing various investigative combinations, with a primary endpoint of pathological complete response (pCR). Ten relevant biomarker classifications were used to define groups based on HER-2 status, hormone receptor status, and risk within each arm: all, hormone-receptor-positive, hormone-receptor-negative, HER2-positive, HER2-negative, high-risk category 2 on the

70-gene MammaPrint assay, HER2-positive and hormone-receptor-positive, HER2-positive and hormone-receptor-negative, HER2-negative and hormone-receptor-positive, and triple-negative (HER2-negative, estrogen-receptor-negative, and progesterone-receptor-negative). The patient population that has shown benefit from the addition of veliparib–carboplatin to standard chemotherapy is the TNBC group, with a pCR rate of almost double that of the group that received the control treatment [90]. However, this is the same group that had shown benefit from carboplatin in the neoadjuvant setting in the GeparSixto and CALGB 40603 trials [101,102]. The other tumor types in which the veliparib–carboplatin regimen was evaluated, HER2-negative and hormone-receptor-positive/HER2-negative, did not demonstrate the same improvement. The I-SPY 2 trial was not designed to show the isolated benefit of veliparib alone, but despite this lack of evidence regarding single-agent veliparib, the advantage of the combination in the triple-negative population is an important finding.

11.6 NONCHEMOTHERAPY COMBINATIONS

In addition to the evidence supporting the combination of PARP inhibitors with chemotherapy, there are preclinical data to indicate a possible synergy with nonchemotherapy agents as well. Antiangiogenic drugs, for example, may enhance the effects of PARP inhibition. Hypoxia and VEGFR3 inhibition downregulate homologous recombination repair genes, such as *BRCA* and *RAD51*, creating a favorable environment for PARP inhibitor activity [103–105]. Based on these data, a phase I trial of olaparib and cediranib was completed, with activity observed in HGSOC patients. Interestingly, responses were seen in *BRCA* wild-type patients and in cisplatin-resistant patients [86]. No response was seen in the TNBC group. A phase II randomized trial was initiated in cisplatin-sensitive recurrent high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer, comparing olaparib vs olaparib and cediranib [92]. The trial was not restricted to *BRCA* mutation patients. In a post hoc analysis, the *BRCA* wild-type patient group benefited most from the combination vs olaparib alone, with PFS 16.5 months vs 5.7 months, respectively. Though this trial was designed to evaluate the addition of cediranib rather than to demonstrate the benefit of adding olaparib, it did broaden the activity of PARP inhibitor into *BRCA* wild-type patients.

Another interesting combination is the administration of a PARP inhibitor with trabectedin. Both agents are involved in the BER and nucleotide excision repair DNA damage repair pathways. In studies of rucaparib, synergy was observed in soft-tissue sarcoma cell lines, and *in vivo* tumor growth inhibition in a mouse model of liposarcoma was greater with the combination than with either of the single agents [106].

In addition to the prototypical synthetic lethality induction approach that has been demonstrated (cell death from loss of *PARP-1* in cells with *BRCA1* and *BRCA2* mutations), PARP inhibitors may also be combined with compounds that inactivate HR repair through other mechanisms. Inhibition of the proteasome by bortezomib or genetic inactivation of the proteasome inhibited DNA repair complex recruitment and led to suppression of HR in mammalian cells [107]. Furthermore, Neri et al. [108] used bortezomib to induce “BRCAness” to sensitize multiple myeloma cells to PARP inhibitors. The veliparib and bortezomib combination

resulted in sustained levels of H2AX and enhanced cell kill, further suggesting that the proteasome is involved in HR repair.

Because radiation induces DNA strand breaks and replication stress, PARP inhibitors, especially veliparib, have been studied in combination with radiation. However, determination of the appropriate dosing and schedule for such combinations is complex; because PARP inhibitors alone may not have single-agent activity in non-HR-defective cells, any decrease in radiation dose or duration may have detrimental effects, especially in very radiosensitive tumors. As previously discussed, the combination of veliparib and radiation has been evaluated in several trials. In one such study, low-dose, fractionated whole-abdominal radiation was paired with veliparib. Fatigue and myelosuppression were the major toxicities, and veliparib was tolerable at a reasonable dose of 250 mg BID [109]. In a study of locally advanced rectal cancer, veliparib was given with capecitabine and radiation, and the MTD was 400 mg BID, identical to the single-agent dose. After treatment, patients underwent surgery, and 29% of patients exhibited a pathological CR [110]. The treatment of primary or secondary brain tumors with veliparib and radiation has also been studied, with mixed results. For example, in NSCLC patients with brain metastases, veliparib (50 and 200 mg) was tested in combination with whole-brain radiation; no significant difference in OS, relative to the whole-brain radiation plus placebo arm, was observed [111]. In glioblastoma multiforme (GBM), veliparib was given at 10 mg BID with radiation and temozolomide. This was hindered by myelosuppression, suggestive of an additive effect, according to the authors [112].

Lastly, no area of investigation is complete today without considering the addition of immunotherapy. Immune checkpoint inhibitors represent a new class of anticancer therapy that has had promising results in various solid tumor types. These agents block signaling through immune checkpoints, regulatory pathways that typically act to downregulate cytotoxic T-cell function and can be co-opted by malignant cells to evade immune destruction. Immune checkpoint inhibitor therapies, such as those targeting PD-1 or CTLA-4, allow T-cells to become activated and mount an immune response against the tumor [113,114]. Preclinical evidence in a *BRCA1*-deficient ovarian cancer model suggests that combining CTLA-4 blockade therapy with a PARP inhibitor may have clinical benefit [115], as PARP may, in addition to mediating DNA repair, play a role in immunomodulation [116,117]. There are also preclinical data that suggest an association between *BRCA1/2* mutational status and neoantigen load, tumor-infiltrating lymphocytes, and the expression of immune checkpoint inhibitors. Specifically, *BRCA1/2*-mutated cancers may express higher levels of neoantigens and therefore be more immunogenic [118]. Several clinical trials evaluating the combination of PARP inhibitors with immune checkpoint blockade agents in various BRCA-deficient reproductive system cancers are ongoing [15].

11.7 CONCLUSION

Several PARP inhibitors are currently available in the clinic, and some of them have received regulatory approval in specific diseases and indications. Recently, PARP trapping was identified as an additional mechanism of action of PARP inhibitors. The effect of PARP binding directly to DNA causes DNA DSBs, and this activity seems to correlate with myeloid

and platelet suppression effects *in vivo*. This strong myelosuppression effect makes it difficult to combine PARP inhibitors with chemotherapies without compromising the dose of either component. Veliparib is a potent PARP enzyme catalytic inhibitor but a weak PARP trapper, which seems to allow combination with chemotherapy agents to achieve enhanced clinical activity. However, the veliparib dose in these combinations is less than 50% of the single-agent MTD in several combinations, especially with topoisomerase inhibitors. On the other hand, in cases where PARP trapping is not an important component of synergism, as with platinum, PARP inhibitor combinations may provide an improved therapeutic window. This combination window is associated with a broad range of tumor types and combinations and may yield activity outside of HR-deficient patients. Another promising area outside of HR deficiencies is hematologic malignancies; for example, in AML, both veliparib with temozolomide and veliparib with carboplatin/topotecan seem to be well tolerated and have shown promise in phase I trials. However, the most significant advances with the PARP inhibitors have focused on the HR-deficient setting, with continued widening of the beneficial population beyond *BRCA*-mutated patients.

PARP inhibitors are only just starting to become extremely useful tools in the treatment of cancer. In the area of HR deficiency, continued work in defining the optimal population is ongoing, both in terms of genomic testing as well as using other agents to induce tumor "BRCAness". In the realm of chemotherapy combinations, the chemotherapy backbone of interest and its area of activity should define the population that will potentially benefit most from each combination, as in the case of carboplatin and ovarian cancer. Meanwhile, PARP inhibitor combinations with other targeted therapies and immunotherapy are still in the early stages of exploration. PARP inhibitors are infants in their journey to becoming powerful oncologic therapeutic tools.

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