Role of PARP in DNA Damage Repair

Cellular function is dependent on the maintenance of genomic integrity. Endogenous and exogenous insults may induce damage to DNA and result in the formation of single-strand DNA breaks (SSBs). PARP enzymes 1 and 2 are key to the repair of these SSBs. PARP1 binds to the SSBs, which activates its catalytic function and results in PARylation of PARP1. This in turn stimulates the recruitment of DNA repair effectors to the site of DNA damage. AutoPARylation of PARP1 releases PARP1 from the repaired DNA, and cell cycle replication recommences.

If PARP activity is inhibited, the enzyme appears to be physically “trapped” on the DNA, physically obstructing the progress of replication and introducing significant replication stress. Replication fork stalling occurs with subsequent collapse and the formation of double-strand breaks (DSBs). Homologous recombination-directed repair is a highly accurate process for repairing DSBs. Both BRCA1 and BRCA2 are critical to the process of homologous recombination-directed DNA repair. If homologous recombination repair is impaired by the loss of BRCA1 or BRCA2 function, then other DNA repair pathways may be engaged, such as nonhomologous end joining (NHEJ). NHEJ is less accurate, leading to genomic instability, which may be sufficient to result in cell death (Figure 1).

In classical genetics, synthetic lethality describes a situation whereby a defect in either of 2 genes has a limited effect on a cell, but defects in both genes leads to cell death. In 2005, Bryant et al and Farmer et al demonstrated synthetic lethality proof-of-concept with the PARP inhibitor (PARPi) olaparib in BRCA-mutated cells. This seminal preclinical work paved the way for the subsequent clinical studies of PARPi in homologous recombination-deficient cancers, particularly those arising in BRCA mutation carriers.

Although this model is used to explain the mechanism of PARPi cytotoxicity in the setting of germline BRCA (gBRCA) mutations, PARP1 appears to be involved in other aspects of DNA repair, including repair of DSBs. Inhibition of these functions may also contribute to cell death. In addition, PARPi has been shown to induce mitophagy (degradation of mitochondria by autophagy) and cell apoptosis.

Abstract

PARP enzymes are essential for DNA damage repair. Cancers with defective homologous recombination DNA repair, such as BRCA1 and BRCA2-mutated breast cancers, are targets for PARP inhibitors (PARPi) through the exploitation of synthetic lethality. A number of PARPi are currently undergoing clinical evaluation in breast cancer, with olaparib and talazoparib having demonstrated superior efficacy compared with standard chemotherapy in advanced germline BRCA-mutated cancer. This review describes the biological rationale for PARPi and presents the accumulating data on PARPi use in breast cancer.
Evolution of PARP Targeting in Breast Cancer

There are currently a number of PARPi in clinical development, including olaparib, veliparib, niraparib, rucaparib, and talazoparib. These PARPi are similar in that they all inhibit PARP1 and PARP2 catalytic activity but have differing potency in PARP trapping. Greater PARP trapping has been associated with enhanced preclinical efficacy, but no clinical studies have directly compared different PARPi in patients.

Three PARPi agents are currently FDA-approved for use in ovarian cancer (olaparib, niraparib, and rucaparib), and on January 12, 2018, olaparib received FDA approval for use in patients with gBRCA-mutated, HER2-negative, advanced breast cancer previously treated with chemotherapy and/or endocrine therapy. Several trials are also studying the benefit of PARPi in other diseases, including prostate and pancreas cancers (Figure 2, Table 1). To date, there have been 2 general therapeutic approaches when targeting PARP in breast cancer: patients with a gBRCA mutation and unselected patients with triple-negative breast cancer (TNBC). The following sections will discuss the most relevant data with respect to the evolution of PARPi for the treatment of advanced or metastatic breast cancer.

Olaparib

The first-in-human study of olaparib monotherapy in patients with solid tumors identified the maximum tolerated dose to be 400 mg twice daily. In this study, 19 evaluable patients with gBRCA1/2 mutations were enrolled in an expansion cohort, and 47% (8 ovarian and 1 breast cancer) achieved a complete or partial response. Tutt et al. subsequently conducted a proof-of-concept phase II study in 54 patients with breast cancer with gBRCA mutations, which described an objective response rate (ORR) of 41% (95% CI, 25–59) in 27 patients receiving olaparib capsules at 400 mg twice daily and 22% (95% CI, 11–41) in patients receiving 100 mg twice daily. Another phase II study by Kaufman et al. described an ORR of 12.9% (95% CI, 5.7–23.9) in 62 heavily pretreated patients with gBRCA-mutated breast cancer, further supporting the clinical activity of the compound.

Most breast cancers in BRCA1 mutation carriers are hormone receptor–negative and do not overexpress HER2 (ie, TNBC). Because of this, there was early hope that TNBC in women without BRCA mu-
tations would also harbor defects in homologous recombination that would render it sensitive to PARPi in a manner similar to that observed in BRCA-deficient cells. However, Gelmon et al.\textsuperscript{13} conducted a small phase II study of olaparib in unselected TNBC that casted doubt on this hypothesis. In this study, 23 patients with unselected TNBC were enrolled: 15 were BRCA wild-type and 8 had a gBRCA mutation. The primary end point was ORR, with no confirmed responses in 15 patients with TNBC but without BRCA mutations.

A positive phase II randomized study of another purported PARPi, iniparib, in combination with gemcitabine and carboplatin in patients with metastatic TNBC unselected for BRCA mutations\textsuperscript{14} led to a strategic reevaluation of the gBRCA-directed approach for compounds other than iniparib and to a temporary pause in development in BRCA-mutated breast cancer pending the results of a confirmatory phase III study, which failed to meet its primary end point.\textsuperscript{15} Indeed, 2 groups showed that iniparib failed to inhibit PARP.\textsuperscript{16,17} PARPi development in breast cancer stalled and focus turned toward development

### Table 1. PARP Inhibitors in Phase III Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial Identifier</th>
<th>Setting</th>
<th>Design</th>
<th>Population</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>OlympiAD\textsuperscript{10} NCT02000622</td>
<td>Advanced/Metastatic</td>
<td>Olaparib vs PCT</td>
<td>Advanced/Metastatic gBRCA, ≤2 prior lines</td>
<td>Resulted</td>
</tr>
<tr>
<td></td>
<td>Olympia NCT02032823</td>
<td>Adjuvant</td>
<td>Olaparib vs placebo</td>
<td>Early-stage gBRCA, post completion SOC adjuvant therapy</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Veliparib</td>
<td>BROCADE 3 NCT02163694</td>
<td>Advanced/Metastatic</td>
<td>C + P + veliparib vs C + P + placebo</td>
<td>Metastatic gBRCA, ≤2 lines of prior therapy</td>
<td>Recruiting</td>
</tr>
<tr>
<td></td>
<td>BrighTNess\textsuperscript{9} NCT02032277</td>
<td>Neoadjuvant</td>
<td>C + P + veliparib → AC vs C + P + placebo → AC vs Placebo + placebo + P → AC</td>
<td>Neoadjuvant TNBC</td>
<td>Resulted</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>EMBRACA\textsuperscript{12} NCT01945775</td>
<td>Advanced/Metastatic</td>
<td>Talazoparib vs PCT</td>
<td>Advanced/Metastatic gBRCA, ≤3 prior lines</td>
<td>Resulted</td>
</tr>
<tr>
<td>Niraparib</td>
<td>BRAVO NCT01905592</td>
<td>Advanced/Metastatic</td>
<td>Niraparib vs PCT</td>
<td>Advanced/Metastatic gBRCA, ≤2 prior lines</td>
<td>Not recruiting</td>
</tr>
</tbody>
</table>

Abbreviations: AC, doxorubicin + cyclophosphamide; C, carboplatin; gBRCA, germline BRCA; P, paclitaxel; PCT, physician’s choice chemotherapy; SOC, standard of care; TNBC, triple-negative breast cancer.
PARP Inhibitors in Breast Cancer

in ovarian cancer. Fortunately, the benefits of PARPi in BRCA-deficient ovarian cancers were sufficient to rekindle interest in the breast cancer arena\textsuperscript{18,19} and the phase III OlympiAD study of olaparib compared with physician’s choice of chemotherapy (PCT) was launched in patients with BRCA mutations and metastatic HER2 non-overexpressing breast cancer.\textsuperscript{20} OlympiAD was a randomized, open-label, phase III trial evaluating olaparib monotherapy (300-mg tablets twice daily) compared with conventional chemotherapy.\textsuperscript{20} A total of 302 patients who had received ≤2 prior therapies in the advanced setting were randomized 2:1 to the study arms. After a median follow-up of 14.5 months, progression-free survival (PFS), the primary end point, was significantly prolonged with olaparib versus standard therapy (7.0 vs 4.2 months; hazard ratio [HR], 0.58; 95% CI, 0.43–0.8; \textit{P}<.001); response rate in the olaparib group was also increased (59.9% vs 28.8%). At planned interim analysis, there was no difference in overall survival between the 2 groups. No new safety signals were observed. Any-grade nausea and vomiting were increased with olaparib compared with standard chemotherapy (58% vs 35.2%, respectively, and 29.8% vs 15.4%, respectively). Olaparib was associated with fewer overall grade 3/4 toxicities, with anemia the only grade 3/4 adverse event seen more frequently in this group (16.1% vs 4.4%). Olaparib was the first PARPi to demonstrate superior efficacy and better tolerability compared with standard chemotherapy in gBRCA-mutated advanced breast cancer, resulting in its FDA approval for treatment of this patient subgroup.

**Talazoparib**

Talazoparib is another PARPi undergoing evaluation in breast cancer. A phase I trial in patients with gBRCA-mutated breast cancer determined that 1 mg/d was the recommended phase II dose.\textsuperscript{21} ORR in patients with breast cancer was 50%, with 7 of 14 patients experiencing a response (1 complete and 6 partial responses). The clinical benefit rate at ≥24 weeks was 85.7%. Additionally, results of the phase II ABRAZO trial have been presented in abstract form.\textsuperscript{20} The 2 cohorts in this study included patients with gBRCA-mutated breast cancer with previous exposure to platinum (cohort 1) and those with no prior platinum exposure but who received ≥3 lines of therapy (cohort 2). The ORR was 21% in cohort 1 and 37% in cohort 2, and the ORRs by BRCA mutation and subtype of breast cancer were 24% for BRCA1, 34% for BRCA2, and 26% for TNBC. The most frequently reported adverse events were anemia (52%), fatigue (45%), and nausea (42%).

The EMBRACA study is evaluating talazoparib as monotherapy in patients with gBRCA-mutated breast cancer compared with PCT, with a similar design to the OlympiAD trial. In this open-label phase III study, 287 patients were randomized to talazoparib at 1 mg and 144 patients to PCT.\textsuperscript{21} All patients had gBRCA-mutated, HER2-negative, advanced breast cancer and could have received no more than 3 prior lines of chemotherapy in the advanced setting. Median PFS, which was the primary end point, was significantly improved with talazoparib compared with PCT (8.6 vs 5.6 months; HR, 0.542; \textit{P}<.0001), and the ORR was superior (62.6% vs 27.2%; HR, 4.99; \textit{P}<.0001). An interim analysis of overall survival seemed to show a positive trend in favor of talazoparib, although these data are immature. Any hematologic adverse event of grade 3 or 4 were more frequent in patients treated with talazoparib versus PCT (54.9% vs 38.1%), including grade 3 or 4 anemia (39.2% vs 4.8%) and thrombocytopenia (14.7% vs 1.6%); however, grade 3 or 4 neutropenia was less frequent with talazoparib (20.9% vs 34.9%).

**Veliparib**

Veliparib has been evaluated as both a monotherapy and in combination with chemotherapy in patients with breast cancer. Phase I studies in TNBC established 400 mg twice daily as the monotherapy dose, with an ORR of 60% in patients with gBRCA-mutated breast cancer versus 5% in those with wild-type disease.\textsuperscript{21} A subsequent phase II study of single-agent veliparib showed a PFS of 5.2 months, with a response rate of 14% and 36% for patients with BRCA1 and BRCA2 mutations, respectively.\textsuperscript{21} Results of combining veliparib with carboplatin and paclitaxel in the randomized phase II BROCADE study in patients with gBRCA-mutated breast cancer have been published in abstract form.\textsuperscript{21} The combination resulted in a significantly improved ORR compared with carboplatin/paclitaxel and placebo (77.8% vs 61.3%; \textit{P}=.027). PFS was 14.1 months for the veliparib arm versus 12.3 months for placebo, which was not statistically significant. No increase in toxicity was reported in either arm. A confirmatory phase III
BROCADE 3 study is currently ongoing (ClinicalTrials.gov identifier: NCT02163694).

**Niraparib**
Other PARPi have been more difficult to combine with cytotoxic chemotherapy due to myelosuppression, and development has been proceeding largely as single agents in gBRCA breast cancer. Niraparib was recently approved for use as postchemotherapy maintenance in patients with platinum-sensitive relapsed ovarian cancer. The open-label randomized phase III BRAVO trial (ClinicalTrials.gov identifier: NCT01905592) was evaluating niraparib compared with PCT in patients with gBRCA-mutated breast cancer in a similar design to the OlympiAD study, but was closed early and has not been reported.

**PARPi in Early-Stage Breast Cancer**
The long established paradigm in breast cancer has been the transition of a therapy to the adjuvant setting once it has been proven to be both tolerable and efficacious in advanced disease. The transition of PARPi has been no different, with a number of agents being evaluated at an earlier disease stage.

OlympiA is a phase III randomized study evaluating olaparib at 300 mg twice daily for 1 year in patients with gBRCA1/2 mutation with residual disease after neoadjuvant chemotherapy; those with node-positive TNBC or node-negative TNBC with a tumor measuring ≥2 cm following adjuvant chemotherapy; or those with estrogen receptor–positive disease with ≥4 nodes following surgery and adjuvant chemotherapy (ClinicalTrials.gov identifier: NCT02032823).

Veliparib was evaluated in patients with TNBC as part of the I-SPY 2 study. Patients received weekly paclitaxel with or without carboplatin and veliparib, followed by standard doxorubicin and cyclophosphamide in the neoadjuvant setting. The predicted pathologic complete response (pCR) rate was 51% versus 26% in the control arm. These results revealed an 88% projected probability of success in a phase III study, leading to graduation of this combination from the I-SPY 2 platform. However, results of the 3-arm, randomized, placebo-controlled phase III BrighTNess study (ClinicalTrials.gov identifier: NCT02032277), which evaluated the addition of veliparib to carboplatin versus carboplatin alone versus placebo followed by standard chemotherapy given neoadjuvantly in patients with TNBC, failed to show an improvement in pCR for the combination of veliparib and carboplatin versus carboplatin alone (53.2% vs 57.5%, respectively).29

Lastly, talazoparib is being tested as monotherapy for a 4- to 6-month duration in the neoadjuvant setting for patients with a gBRCA mutation (ClinicalTrials.gov identifier: NCT02282345). A pilot study by the same group investigated single-agent talazoparib for 2 months in a similar patient cohort, followed by standard chemotherapy, and results showed that all 13 patients enrolled had a decrease in tumor volume, with an average reduction of 78% (range, 30%-98%).30

**Combining PARPi With Other Therapies**
The strategy for combining PARPi with other therapeutic agents aims to increase response rates, prevent or delay resistance, and improve clinical outcomes. Cytotoxic chemotherapy is the obvious companion to pair with a PARPi, and numerous studies with differing agents have attempted this strategy but have been limited by toxicity, especially myelosuppression.31–33 Approaches to overcoming the toxicity have included reducing the PARPi dose, abbreviating the PARPi dosing schedule, or using a lower dose of the chemotherapeutic agent (ClinicalTrials.gov identifiers: NCT02561832, NCT02264678, NCT02358200). However, whether any of these strategies will lead to improved outcomes compared with using maximal doses of either agent is unclear.

Combining immunotherapy with PARPi is a promising approach with limited expected cross-toxicity. Sound clinical rationale exists for combining a checkpoint inhibitor with PARPi in BRCA-mutated cancers, because these cancers are more genomically unstable due to the defect in homologous recombination, and therefore may be more immunogenic. Data show that tumors with a defect in mismatch repair, which is another DNA repair pathway, are responsive to the PD-1 inhibitor pembrolizumab.34 As of May 2017, pembrolizumab is FDA-approved for adults and pediatric patients with advanced mismatch repair–deficient solid tumors that have progressed on prior therapy.

The MEDIOLA trial is a phase I/II open-label basket study of olaparib and durvalumab in patients
PARP Inhibitors in Breast Cancer

with advanced solid tumors. Results were recently presented for the cohort with HER2-negative and gBRCA mutation–positive advanced breast cancer. Patients could not have received a PARPi or immunotherapy, prior anthracycline and taxane was required, and prior platinum therapy was allowed. Patients received single-agent olaparib, 300 mg orally twice daily for 4 weeks, after which durvalumab, 1.5 g intravenously was added every 4 weeks. A total of 25 patients were enrolled, 12 (48%) having estrogen receptor–positive disease and 13 (52%) having TNBC. The ORR was 67% in patients with no prior therapy (6 of 9), 67% in patients with 1 prior therapy (6 of 9), 20% in patients with 2 prior therapies (1 of 5), and 0% in patients with ≥3 prior therapies (0 of 2). Median PFS had not been reached, with data cut-off at 6 months. The combination was generally well tolerated, with no unexpected toxicity observed. Grade ≥3 events included anemia (8%), neutropenia (8%), and fatigue (4%), and were all attributed to olaparib. A single case of grade ≥3 of both hemolysis and pancreatitis was reported and thought to be related to durvalumab therapy.

Niraparib is also being investigated in combination with the PD-1 inhibitor pembrolizumab in a phase I/II study in TNBC and ovarian cancer (ClinicalTrials.gov identifier: NCT02657889). Additional immunotherapy and PARPi combination studies are also in development.

Early-phase studies are investigating the combination of PARPi with inhibitors of cell cycle checkpoints and DNA repair. The biological rationale for combining PARPi with other compounds (eg, ATR, WEE1, and CHEK1/2 inhibitors) that also inhibit DNA repair pathways is that by inhibiting 2 repair pathways simultaneously, cancer cells have fewer ways to repair damaged DNA, leading to apoptosis. These approaches are being evaluated in a number of different cancer types, including breast cancer. For example, the ATR inhibitor AZD6738 is being evaluated in a phase I study in combination with olaparib in patients with breast cancer with a germline or somatic BRCA mutation. This study also includes a cohort of patients with non–BRCA-mutated TNBC (ClinicalTrials.gov identifier: NCT02264678). An open-label, randomized, multicenter phase II study will assess the efficacy and safety of olaparib monotherapy versus olaparib in combination with AZD6738 and in combination with the WEE1 inhibitor AZD1775 in patients with TNBC (NCT03330847). And the CHEK1/2 inhibitor (LY2606368) is being investigated in a phase II study in BRCA1/2 mutation–associated breast cancer, TNBC, ovarian cancer, and prostate cancer (NCT02203513).

Conclusions

PARP is now a proven target, with its inhibition showing significant clinical benefit in a phase III study in patients with gBRCA mutation–positive breast cancer. However, the road traveled by PARPi has not been without its obstacles. Despite early signals of activity of PARPi in breast cancer, the failure of iniparib interrupted further development of these drugs for this cancer type. Fortunately, compelling clinical data, particularly in ovarian cancer, led to a recommitment to the evaluation of these agents. Olaparib was the first PARPi to demonstrate superior efficacy compared with standard chemotherapy in patients with gBRCA-mutated advanced breast cancer, resulting in its regulatory approval. This milestone marks the end of the beginning for PARP targeting in breast cancer. Ongoing and future studies are required to better define which patients to treat with PARPi and whether the target population can be extended beyond those with gBRCA mutations. It will also be important to assess when to treat these patients; how to sequence these drugs with currently established therapies, particularly platinum agents; how to combine PARPi with other novel therapies; and how to overcome resistance. The hope is that these trials will incorporate informative correlative components that will further our understanding of the biology of targeting PARP in breast cancer and add to the arsenal of therapies available, ultimately improving patient outcomes.

References


© JNCCN—Journal of the National Comprehensive Cancer Network  |  Volume 16  Number 9  |  September 2018
26. Han HS, Sook DH, Robson ME, et al. Efficacy and tolerability of veliparib (V; ABT-888) in combination with carboplatin (C) and paclitaxel (P) vs placebo (Pc)+CP in patients (pts) with BRCA1 or BRCA2 mutations and metastatic breast cancer: a randomized, phase 2 study [abstract]. Presented at the 2016 San Antonio Breast Cancer Symposium; December 6–10, 2016; San Antonio, Texas. Abstract S2-05.

© JNCCN—Journal of the National Comprehensive Cancer Network | Volume 16 Number 9 | September 2018