Development of Poly(ADP-Ribose) Polymerase Inhibitors in the Treatment of *BRCA*-Mutated Breast Cancer

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Abstract: The poly(ADP-ribose) polymerases (PARPs) 1 and 2 are DNA-binding enzymes that play a critical role in the repair of DNA. The use of PARP inhibitors is a rational therapeutic approach to selectively killing a subset of cancer cells with deficiencies in DNA repair pathways. PARP inhibitors that have undergone clinical investigation in the treatment of breast cancer include olaparib, talazoparib, veliparib, niraparib, and rucaparib. The antitumor activity of PARP inhibitors as single agents has been demonstrated in *BRCA*-associated metastatic breast cancer. In 2018, olaparib became the first oral PARP inhibitor to receive approval in the United States for the treatment of advanced *BRCA*-mutated breast cancer, an approval that represents a major change in the treatment paradigm for this subtype of breast cancer. PARP inhibition plus chemotherapy and PARP inhibition plus immunotherapy are novel approaches undergoing extensive study in breast cancer. This review focuses on the clinical development of PARP inhibitors administered singly or in combination with other agents for early-stage and metastatic *BRCA*-mutated breast cancer.

Introduction: *BRCA*-Mutated Breast Cancer

Mutations in the *BRCA1* or *BRCA2* gene account for approximately 5% to 10% of all breast cancers and approximately 15% to 20% of hereditary breast cancers.[1] Breast cancer develops in approximately 55% to 65% of patients harboring a *BRCA1* mutation and 45% of patients with a *BRCA2* mutation by the age of 70 years.[2] Germline *BRCA1* mutations are more frequently associated with triple-negative (ie, estrogen receptor–negative, progesterone receptor–negative, and human epidermal growth factor receptor type 2 [HER2]–negative) breast cancer; according to several studies, 60% to 80% of breast cancers in *BRCA1* mutation carriers are triple-negative, whereas *BRCA2* mutation carriers often have hormone receptor–positive breast tumors.[3,4] *BRCA* mutations are more likely to be found in younger patients and are suspected in individuals who have a personal history of bilateral breast cancer or ovarian cancer, are of Ashkenazi Jewish ancestry, or have a family history of early-onset breast

cancer, breast cancer in multiple relatives, male breast cancer, ovarian cancer, prostate cancer, or pancreatic cancer.[5] It has also been reported that *BRCA1* mutations are found in approximately 11% to 20% of patients with triple-negative breast cancer (TNBC) in the absence of a family history of cancer. Practice guidelines recommend a hereditary risk assessment in patients 60 years of age or younger in whom TNBC is diagnosed.[6,7]

Rationale for PARP Inhibition in *BRCA*-Mutated Breast Cancer

The poly(ADP-ribose) polymerase (PARP) enzyme plays a critical role in the repair of DNA single-strand breaks via the base-excision repair (BER) pathway. The PARP protein binds to sites of DNA damage and recruits other enzymes involved in DNA repair. In normal cells, BER and homologous recombination (repair of DNA double-strand breaks) are available to repair damaged DNA. In the cancer cells of *BRCA1* and *BRCA2* mutation carriers, in whom homologous recombination is not functioning, PARP inhibition leads to an accumulation of DNA single-strand breaks that degenerate into double-strand breaks; this process results in cell death because the cells are unable to repair DNA damage by either BER or homologous recombination.[8] Preclinical studies show that cells lacking the ability to repair DNA double-strand breaks by homologous recombination, such as cells lacking functional BRCA1 or BRCA2, are very sensitive to PARP inhibition.[9,10] The current model for the role of PARP in DNA damage and repair and the effect of PARP inhibitors in cells deficient in homologous recombination is described fully by Helleday.[11]

Clinical Trials of PARP Inhibitors in *BRCA*-Mutated Breast Cancer

Metastatic Setting: PARP Inhibitors as Monotherapy

Olaparib. Olaparib (Lynparza, AstraZeneca) was the first oral PARP inhibitor to be approved by the US Food and Drug Administration (FDA). It received approval in December 2014 as a single agent for the treatment of patients with deleterious or suspected deleterious germline *BRCA*-mutated advanced ovarian cancer treated with 3 or more prior lines of chemotherapy.[12] In August 2017, olaparib received an expanded indication for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a partial response (PR) or complete response (CR) to platinum-based chemotherapy, regardless of *BRCA* mutation status.[13,14]

In the setting of metastatic breast cancer (MBC), the antitumor activity of PARP inhibitors is evidenced in several trials (Table 1). The subtype of breast cancer with the most compelling evidence of benefit from PARP inhibitor monotherapy is *BRCA*-mutated breast cancer. Several phase 2 trials of olaparib as a single agent have been reported in patients with MBC. In the ICEBERG 1 study (Study to Assess the Efficacy and Safety of a PARP Inhibitor for the Treatment of BRCA-positive Advanced Breast Cancer), Tutt and colleagues evaluated olaparib in 54 patients who had MBC with germline *BRCA* mutations and had been treated previously with a median of 3 chemotherapy regimens.[15] The trial enrolled 2 groups of patients. Those in cohort 1, of whom 50% had triple-negative disease, received olaparib at 400 mg twice daily, and those in cohort 2 (64% with triple-negative disease) received olaparib at 100 mg twice daily. The overall response rate (ORR) in cohort 1 was 41% (95% CI, 26%-61%), with 10 PRs and 1 CR among 27 patients. The ORR in cohort 2 was 22% (95% CI, 11%-41%); PRs occurred in 6 of 27 patients. The rate of disease stabilization was 44% in both groups. Prominent grade 3 or 4 adverse effects in the higher-dose group included fatigue (15%), nausea (15%), vomiting (11%), and anemia (11%). This study showed that olaparib has single-agent activity in germline *BRCA* mutation–associated MBC previously treated with chemotherapy with a tolerable safety profile.

Gelmon and colleagues conducted a phase 2 multicenter, open-label, nonrandomized study of single-agent olaparib in patients with metastatic high-grade serous ovarian cancer, metastatic *BRCA*-mutated breast cancer, or TNBC.[16] A total of 91 patients (65 with ovarian cancer, 26 with breast cancer) were treated with olaparib at 400 mg twice daily. Of the 26 patients with breast cancer, 10 had a *BRCA1* (n=4) or *BRCA2* (n=6) mutation, and 5 of the 10 had TNBC. No confirmed objective responses were reported in the patients with breast cancer. Target lesion decreases of more than 30% appeared to occur in some of the patients with *BRCA*-mutated breast cancer, but these were not confirmed responses. The results suggest that single-agent PARP inhibition is not an effective treatment approach for sporadic TNBC without a germline *BRCA* mutation.

In an international, multicenter phase 2 study by Kaufman and colleagues, 298 patients who had metastatic cancer associated with a *BRCA1* or *BRCA2* mutation, including breast, ovarian, prostate, and pancreatic cancer, were treated with olaparib at 400 mg twice daily.[12] In the MBC cohort of 62 patients who had previously received a median number of 4.6 chemotherapy regimens for metastatic disease, the ORR was 12.9% (95% CI, 5.7%-23.9%) with 8 PRs. In the 30 patients with estrogen receptor–negative tumors, the response rate was 13.3% (95% CI, 3.8%-30.7%). This study

Table 1. Phase 2 and Phase 3 Studies of PARP Inhibitor Monotherapy in Metastatic Breast Cancer

Study	Patient Cohort	N	Treatment	Results
Phase 2 Studies				
Tutt, ICEBERG 1[15]	Metastatic *BRCA1/2*-mutated breast cancer	27 27	Olaparib	Cohort 1 (400 mg twice daily): ORR, 41% Cohort 2 (100 mg twice daily): ORR, 22%
Gelmon[16]	Metastatic *BRCA*-mutated breast cancer or triple-negative breast cancer	26	Olaparib	ORR, 0%
Kaufman[12]	Metastatic *BRCA1/2*-mutated breast cancer	62	Olaparib	ORR, 12.9%
Turner, ABRAZO[20]	Metastatic *BRCA1/2*-mutated breast cancer	48 35	Talazoparib	Cohort 1 (prior platinum): ORR, 21% Cohort 2 (platinum-naive): ORR, 37%
Phase 3 Studies				
Robson, OlympiAD[17]	Metastatic *BRCA1/2*-mutated HER2-negative breast cancer	205 vs 97	Olaparib vs chemotherapy	ORR, 59.9% vs 28.8% PFS, 7 vs 4.2 mo
Litton, EMBRACA[21]	Metastatic *BRCA1/2*-mutated HER2-negative breast cancer	287 vs 144	Talazoparib vs chemotherapy	ORR, 62.6% vs 27.2% PFS, 8.6 vs 5.6 mo

HER2, human epidermal growth factor receptor 2; mo, months; N, number of patients; ORR, overall response rate; PARP, poly(ADP-ribose) polymerase; PFS, progression free-survival.

provided further evidence of olaparib activity in advanced cancers with germline *BRCA1/2* mutations.

The first phase 3 trial to show an advantage of a PARP inhibitor over standard chemotherapy was presented at the plenary session of the 2017 annual meeting of the American Society of Clinical Oncology (ASCO) and published in the *New England Journal of Medicine* by Robson and colleagues.[17] This randomized, open-label study (OlympiAD; Assessment of the Efficacy and Safety of Olaparib Monotherapy Versus Physicians Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients With Germline BRCA1/2 Mutations) enrolled 302 patients with HER2-negative MBC who had received no more than 2 prior chemotherapy regimens for metastatic disease, had a germline *BRCA* mutation, and had received prior treatment with an anthracycline and a taxane. Patients were randomly assigned in a 2:1 ratio to either olaparib at 300 mg twice daily (n=205) or chemotherapy of the physician's choice (n=97), which was specified as capecitabine, vinorelbine, or eribulin (Halaven, Eisai). The primary endpoint was progression-free survival (PFS) by blinded independent central review. Secondary endpoints were overall survival (OS), ORR, safety, and health-related quality of life scores.

Because tablets were used in this study, the dosage of olaparib was 300 mg (two 150-mg tablets) twice daily with or without food. The tablet formulation is different from the 400-mg capsule formulation initially approved by the FDA in 2014, which is taken twice daily for the treatment of *BRCA*-mutated ovarian cancer. The tablet formulation was subsequently evaluated and found to be comparable, and was approved for use in August 2017.[18] More than 70% of the patients had received prior chemotherapy for metastatic disease, and 30% had received prior platinum in the neoadjuvant, adjuvant, or metastatic setting. In each arm, approximately 50% of patients had triple-negative tumors and 50% had hormone receptor–positive tumors. At a median follow-up of 14 months, median PFS was significantly greater in the olaparib arm than in the chemotherapy arm, at 7.0 months vs 4.2 months, respectively (hazard ratio [HR], 0.58; 95% CI, 0.43-0.80; $P<.001$). The ORR was 59.9% (95% CI, 52%-67.4%) in the olaparib arm and 28.8% (95% CI, 18.3%-41.3%) in the chemotherapy arm. The CR rate was 9% with olaparib and 1.5% with chemotherapy.

Treatment with olaparib was associated with a 7.5-point relative improvement (95% CI, 2.5-12.4; $P=.004$) in the health-related quality of life score derived from the 30-item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Grade 3 or higher toxicities occurred in 36.6% of those in the olaparib arm and 50.5% of those in the chemotherapy arm. The most common toxicities in the olaparib arm were grade 1 or grade 2 and included

anemia, neutropenia, leukopenia, nausea, vomiting, diarrhea, fatigue, headache, fever, and cough. The rate of discontinuation owing to adverse events was 4.9% in the olaparib arm and 7.7% with chemotherapy. Grade 3 or higher anemia was more frequent in the olaparib arm than in the chemotherapy arm (16.1% vs 4.4%). Grade 3 or higher neutropenia was more frequent in the patients receiving chemotherapy than in those receiving olaparib (26.4% vs 9.3%). No significant difference in OS was observed between the 2 groups (19.3 months for olaparib vs 19.6 months for chemotherapy), but the trial was not powered for this parameter. The benefit in ORR was not as great for the olaparib-treated patients with prior platinum exposure as it was for those with no prior platinum exposure (46% vs 65.8%). Another interesting observation was that a second progression event or death after first progression occurred after a longer time in the olaparib arm than in the chemotherapy arm (13.2 vs 9.3 months; HR, 0.57; 95% CI, 0.40-0.83; *P*=.003).

The results of the OlympiAD trial are noteworthy in several ways that go beyond the 2.8-month difference in PFS. In the TNBC subgroup, olaparib provided a targeted, noncytotoxic treatment option for patients with *BRCA*-mutated metastatic disease. In the triple-negative subgroup, the response rate was higher with olaparib than with chemotherapy (54.7% vs 21.2%), and the difference in PFS also was notable (HR, 0.43; 95% CI, 0.29-0.63). Patients with estrogen receptor–positive tumors also benefited from treatment with olaparib vs chemotherapy in terms of response rate (65.4% vs 36.4%). Overall, efficacy was improved, side effects were fewer, and quality of life was better with olaparib than with chemotherapy.

On the basis of results of the OlympiAD trial, the FDA approved olaparib on January 12, 2018, for patients with deleterious or suspected deleterious *BRCA*-mutated, HER2-negative MBC previously treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Additionally, patients who have *BRCA*-mutated MBC with hormone receptor–positive tumors are also candidates for olaparib if they have previously been treated with an endocrine therapy or if endocrine treatment is considered inappropriate. Patients must be selected for treatment according to the FDA-approved companion diagnostic BRCAnalysis CDx (Myriad Genetics).

Talazoparib. Talazoparib is an oral PARP inhibitor with phase 2 and phase 3 data in germline *BRCA1/2* mutation–associated MBC. It is a highly potent PARP inhibitor compared with olaparib, veliparib, niraparib (Zejula, Tesaro), and rucaparib (Rubraca, Clovis Oncology), and it traps PARP at the site of DNA damage.[19] The ABRAZO trial (A Phase 2, 2-Stage, 2-Cohort Study of Talazoparib in Locally Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation) was a multiple-center, open-label phase 2 study that investigated talazoparib in patients who had MBC with a germline *BRCA1/2* mutation.[20] Patients were enrolled into either of 2 cohorts. In cohort 1, patients were required to have had a PR or CR to the last platinum-containing regimen for metastatic disease and disease progression more than 8 weeks following the last dose of platinum. In cohort 2, patients had to have received 3 or more prior cytotoxic regimens for metastatic disease and no prior platinum for metastatic disease. The total of 84 patients enrolled in the study (cohort 1, n=49; cohort 2, n=35) received 1 mg of talazoparib daily. Approximately 40% of the patients had triple-negative tumors, 60% had estrogen receptor–positive tumors, and 7% had HER2-positive disease.

The ORR in cohort 1, with a prior response to platinum, was 21% (95% CI, 10%-35%), with 8 PRs and 2 CRs in 48 patients. The ORR in cohort 2, in which the 35 patients were pretreated and platinum-naive, was 37% (95% CI, 22%-55%); no CRs and 13 PRs occurred in this cohort. The rate of stable disease was 18% in both cohort 1 and cohort 2. Median PFS was 4.0 months in cohort 1 and 5.6 months in cohort 2. Median OS was 12.7 months in cohort 1 and 14.7 months in cohort 2. The ORR was 23% in patients with *BRCA1* mutations and 33% in patients with *BRCA2* mutations. The ORR in *BRCA1/2* mutation carriers was 26% in those with triple-negative disease and 29% in those with hormone receptor–positive disease (with any HER2 status). Of note, the patients in cohort 1 with the longest platinum-free interval (>6 months) exhibited the highest response rate (47%) and the longest PFS (6.9 months). As in other PARP inhibitor trials, myelosuppression was the predominant adverse event, and anemia was the most common reason for dose reduction. Similar response rates were observed in patients with *BRCA1* mutations and those with *BRCA2* mutations. Similar activity also was observed in patients with TNBC and those with non-TNBC. Activity was increased in platinum-naive patients and those with a longer platinum-free interval. The results of this trial show that single-agent PARP inhibition has clinical activity and a manageable toxicity profile in a population with germline *BRCA1/2* mutation–associated breast cancer.

In response to the promising antitumor activity of talazoparib observed in the ABRAZO trial, the phase 3 EMBRACA trial (A Study Evaluating Talazoparib, a PARP Inhibitor, in Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation; NCT01945775) was designed to evaluate talazoparib vs protocol-specific physician's choice of chemotherapy in patients who had HER2-negative MBC with a germline *BRCA1/2* mutation and had received 3 or fewer prior cytotoxic regimens for advanced disease.[21] This was an international, open-

label phase 3 study in which 431 patients were randomly assigned to either talazoparib at 1 mg daily (n=287) or capecitabine, eribulin, gemcitabine, or vinorelbine (n=144) in a 2:1 ratio. The primary endpoint was PFS by blinded independent central review, according to Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints were OS, ORR, and safety.

Approximately 62% of patients had received prior chemotherapy for metastatic disease, and 37% had received a prior platinum agent. In each arm, approximately 40% to 45% of patients had triple-negative tumors and approximately 55% to 60% of patients had hormone receptor–positive tumors. After a median of 11.2 months of follow-up, the median PFS was 8.6 months in the talazoparib arm and 5.6 months in the physician's choice arm (44% capecitabine, 40% eribulin, 10% gemcitabine, and 7% vinorelbine; HR, 0.542; *P*<.0001). ORR and clinical benefit rate at 6 months were better in the talazoparib arm than in the physician's choice arm (ORR, 62.6% vs 27.2%; odds ratio, 4.99; *P*<.0001; clinical benefit rate, 68.6% vs 36.1%; odds ratio, 4.28, *P*<.0001). Overall, 12 CRs occurred, all in patients treated with talazoparib. Interestingly, in the subgroup of patients with brain metastases, PFS was 4.1 months longer in the patients treated with talazoparib than in those treated with chemotherapy (HR, 0.32; 95% CI, 5.7 months vs 1.6 months; 0.15-0.68; *P*=.0016). Survival data from this trial are not mature and follow-up continues, but a preliminary analysis indicates a positive trend in favor of talazoparib, with a 24% reduction in the risk for death.

As in OlympiAD, a statistically significant difference was noted between estimated overall mean change from baseline in patient-reported global health status measured by the EORTC QLQ-C30 in the talazoparib-treated patients (3.0; 95% CI, 1.2-4.8) and that in the physician's choice–treated patients (–5.4; 95% CI, –8.8 to –2.0). Rates of grade 3 or 4 adverse events were similar in the talazoparib arm and the chemotherapy arm (25.5% and 25.4%). The main adverse event in the talazoparib arm was hematologic toxicity, mostly anemia (grade 3/4, 39.2% vs 4.8%), whereas in the chemotherapy arm it was neutropenia (grade 3/4, 34.9% vs 20.9%). The most common nonhematologic adverse events with talazoparib were fatigue, nausea, and headache, which led to permanent discontinuation in 7.7% of patients in the talazoparib group compared with 9.5% of patients in the physician's treatment of choice group. In summary, EMBRACA, which was larger than OlympiAD, is another phase 3 trial confirming an advantage of PARP inhibition compared with standard chemotherapy (improved PFS and ORR) in the treatment of patients who have MBC with germline *BRCA1* and *BRCA2* mutations.

Veliparib. Veliparib is an oral inhibitor of PARP1 and PARP2 enzymes. It crosses the blood-brain barrier and has been studied predominantly in combination with chemotherapy agents. The role of veliparib as a single agent was explored in a phase 1 dose escalation study in which 88 patients received doses ranging from 50 to 500 mg twice a day. The maximum tolerated dose was 400 mg twice a day.[22] The dose-limiting toxicities were grade 3 nausea and vomiting and grade 2 seizures. The 2 defined cohorts comprised patients who had advanced solid tumors with a *BRCA1/2* mutation and patients who had TNBC with wild-type *BRCA* or platinum-refractory ovarian, fallopian tube, or primary peritoneal cancer. A total of 35 patients who had MBC were treated with veliparib. The ORR was 29% (4/14) in the patients with a *BRCA* mutation and 5% (1/21) in the patients with wild-type *BRCA*; all responses were PRs. Antitumor activity was evident with veliparib monotherapy. The experience was similar to that reported with single-agent olaparib, in which activity in patients with sporadic TNBC was decreased compared with activity in *BRCA* mutation carriers. Further clinical development of veliparib in breast cancer is focused on combinations with platinum drugs, alkylating agents, and topoisomerase inhibitors.

Niraparib. Niraparib is a potent, orally active PARP1 and PARP2 inhibitor that was approved by the FDA in March 2017 as maintenance treatment in adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy.[23] The phase 1 study established a recommended phase 2 dose of 300 mg once daily and demonstrated clinical activity in patients with ovarian cancer or breast cancer.[24] Among the 13 patients with breast cancer in this dose escalation trial, 2 had a PR as best response (response rate, 15.4%; 95% CI, 1.9%-45.4%). Both patients were among the 4 with *BRCA* mutations (response rate in patients with *BRCA* mutations, 50.0%; 95% CI, 6.8%-93.2%).

Using the same design as OlympiAD and EMBRACA, a randomized, open-label, multicenter trial called BRAVO (A Phase III Trial of Niraparib Versus Physician's Choice in HER2 Negative, Germline BRCA Mutation-positive Breast Cancer Patients; NCT01905592) is comparing niraparib vs physician's choice single-agent chemotherapy with eribulin, vinorelbine, gemcitabine, or capecitabine in patients with HER2-negative *BRCA*-mutated MBC. The primary endpoint is PFS. Eligible patients are being randomly assigned in a 2:1 ratio to receive niraparib orally at a dose of 300 mg once daily on a continuous dosing regimen or physician's choice as previously described. On March 28, 2017, after an interim analysis of data by an independent data monitoring committee, the steering

committee for the BRAVO trial made a final determination to stop enrollment because many patients had dropped out of the chemotherapy arm and the trial could no longer support registration for the purported indication.

Rucaparib. Rucaparib is an oral PARP1/2 inhibitor that has activity against tankyrase 1 and 2.[25] In December 2016, the FDA granted accelerated approval to rucaparib for the treatment of advanced ovarian cancer in patients with a germline and/or somatic deleterious *BRCA* mutation who have been treated with 2 or more chemotherapy regimens. The dosage is 600 mg orally twice daily, with or without food.[26,27] The association between the "BRCAness" phenotype and response to rucaparib is currently being evaluated in breast cancer. This small phase 2 trial, referred to as RUBY (A Study to Assess the Efficacy of Rucaparib in Metastatic Breast Cancer Patients With a BRCAness Genomic Signature), is a single-arm, open-label, multiple-institution study evaluating the efficacy and safety of rucaparib in patients with HER2-negative MBC associated with a BRCAness phenotype as determined by a high tumor genomic loss-of-heterozygosity score and/or a somatic *BRCA* mutation.[28] Eligible patients must not harbor a germline *BRCA1/2* mutation. The targeted enrollment is 41 patients.

Metastatic Setting: PARP Inhibitors in Combination With Chemotherapy

The PARP inhibitors that were developed first, such as olaparib and veliparib, have been evaluated in combination with chemotherapy in a breast cancer–specific population. Most of these studies included enrollment of *BRCA1/2* mutation carriers. A phase 1 study used olaparib in combination with paclitaxel given intravenously (IV) weekly for the first- or second-line treatment of patients with metastatic TNBC.[29] *BRCA* mutation status was not reported. The 19 patients received olaparib at 200 mg twice a day continuously and paclitaxel at 90 mg/m^2 weekly for 3 weeks in a 4-week cycle. The study treatment was associated with a high rate of diarrhea and neutropenia even with secondary prophylaxis, although 37% (7/19) of the patients achieved a PR. Additional phase 1 studies have been conducted with olaparib and platinum agents and show activity, but the appropriate schedule of administration and the sequencing of olaparib in combination with the optimal chemotherapy partner needs further evaluation.[30,31]

Veliparib has also been extensively studied in breast cancer in combination with several chemotherapy drugs to potentiate cytotoxicity. Preclinical studies show that veliparib potentiates temozolomide and platinum drugs in xenograft models.[32] Several phase 1 trials have evaluated the antitumor activity of veliparib and platinum in advanced *BRCA*-associated breast cancer.[33,34] The BROCADE trial (The Study Evaluating Efficacy And Tolerability Of Veliparib in Combination With Temozolomide or In Combination With Carboplatin and Paclitaxel Versus Placebo in Subjects With BRCA1 and BRCA2 Mutation and Metastatic Breast Cancer) was a multicenter, 3-arm, partially blinded phase 2 study that compared placebo plus carboplatin/paclitaxel (PCP), veliparib plus carboplatin/paclitaxel (VCP), and veliparib plus temozolomide (VT) in patients who had MBC with a *BRCA1/2* mutation.[35] All patients were randomly assigned in a 1:1:1 ratio to receive PCP, VCP, or VT. The primary endpoint of this trial was PFS; secondary endpoints were OS, ORR, and clinical benefit rate, defined as the progression-free rate at week 18. A total of 284 patients with MBC had a centrally confirmed germline *BRCA1/2* mutation. The treatments consisted of the following: (1) placebo + carboplatin at area under the curve (AUC) 6 + paclitaxel at 175 mg/m^2 IV on day 3 of a 21-day cycle (PCP); (2) veliparib at 120 mg twice a day on days 1-7 + carboplatin at AUC 6 + paclitaxel at 175 mg/m^2 IV on day 3 of a 21-day cycle (VCP); and (3) veliparib at 40 mg twice a day on days 1-7 + temozolomide at 150 mg/m^2 daily on days 1-5, escalated to 200 mg/m^2 if tolerated during cycle 1, on a 28-day cycle (VT).

Median PFS was 14.1 months (95% CI, 11.5-16.2) for VCP and 12.3 months (95% CI, 9.3-14.5) for PCP (HR, 0.79; 95% CI, 0.54-1.16; *P*=.227). Median OS was 28.3 months for VCP and 25.9 months for PCP; the difference was not statistically significant (HR, 0.750; *P*=.1560.) The addition of veliparib to carboplatin/paclitaxel improved ORR (77.8% vs 61.3%; *P*=.027). In the all-oral VT arm, median PFS was 7.4 months, median OS was 19.1 months, and ORR was 28.6%, all of which were inferior to the results with PCP. The rates of neutropenia, thrombocytopenia, and nausea were similar in the PCP and VCP arms. Anemia, neutropenia, neuropathy, and alopecia occurred less frequently with VT than with PCP. This trial provides valuable data on the clinical activity and tolerability of the combination of a PARP inhibitor with DNA-damaging chemotherapies in *BRCA1*- or *BRCA2*-mutated MBC, demonstrating that VCP is an active regimen in this specific population and laying the foundation for a study with greater power.

An international phase 3 BROCADE 3 study (A Phase 3 Randomized, Placebo-controlled Trial of Carboplatin and Paclitaxel With or Without Veliparib in HER2-negative Metastatic or Locally Advanced Unresectable BRCA-associated Breast Cancer; NCT02163694) is randomly assigning to VCP or PCP in a 2:1 ratio patients with metastatic *BRCA*-associated breast cancer who

have received no more than 2 prior systemic treatments for metastatic disease. The primary outcome measure is PFS, and the accrual goal is 500 patients. The phase 2 and phase 3 BROCADE trials differ in some respects. In the phase 3 trial, the veliparib dose is the same (120 mg twice daily) but is given on a different schedule: days –2 through 5 on a 21-day cycle. Additionally, if patients discontinue paclitaxel/carboplatin because of toxicity, they can continue veliparib/placebo at 300 or 400 mg twice daily. This trial will help answer the question of whether there is an advantage to giving a PARP inhibitor with platinum-based chemotherapy.

PARP Inhibitors in Early Breast Cancer

Given the observed activity of PARP inhibitors in the metastatic studies, major phase 3 clinical trial efforts are under way to evaluate the benefit of PARP inhibitors in the adjuvant and neoadjuvant settings. Assessment of long-term toxicity will be important in patients with early-stage disease, however, given that myelodysplastic syndrome and acute myelogenous leukemia have been rarely reported (<2%) with PARP inhibitors. OlympiA (Olaparib as Adjuvant Treatment in Patients With Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer; NCT02032823) is a randomized, double-blinded, placebo-controlled phase 3 study to evaluate olaparib as adjuvant treatment in 1500 patients who have HER2-negative breast cancer with germline *BRCA1/2* mutations and have completed definitive local treatment (Table 2). The primary endpoint is invasive disease–free survival. Patient randomization is 1:1 to either olaparib at 300 mg twice daily for 12 months or matching placebo. Eligible patients with TNBC include the following: (1) those without a pathologic complete response (pCR, the absence of residual invasive cancer in the breast and lymph nodes) following at least 6 cycles of neoadjuvant chemotherapy followed by surgery, and (2) those with either axillary node–positive disease or axillary node–negative disease and a primary tumor larger than 2 cm who have undergone surgery and have completed at least 6 cycles of adjuvant chemotherapy. Eligible patients with hormone receptor–positive breast cancer must have at least 4 positive lymph nodes in the adjuvant setting and a non-pCR with a pretreatment clinical stage, post-treatment pathologic stage, estrogen receptor status, and tumor grade (CPS + EG) staging score of at least 3 in the neoadjuvant setting. This is a unique trial targeting a rare population, with the potential to change the current adjuvant standard of care of observation for high-risk TNBC with *BRCA* mutations, and to add to endocrine therapy for high-risk hormone receptor–positive breast cancer with *BRCA* mutations.

In the neoadjuvant setting, several studies have evaluated the combination of a PARP inhibitor and platinum-based chemotherapy in patients with TNBC, some of them with *BRCA1/2* mutations. As part of a multicenter, adaptively randomized phase 2 trial called I-SPY 2 (Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer), Rugo and colleagues examined the addition of veliparib combined with carboplatin to the standard weekly paclitaxel neoadjuvant backbone in HER2-negative breast cancer.[36] A total of 72 patients with stage 2 or stage 3 HER2-negative breast cancer were randomly assigned to receive either veliparib, carboplatin, and paclitaxel followed by doxorubicin and cyclophosphamide (AC) or standard therapy with weekly paclitaxel followed by AC. In the TNBC subset, the veliparib/carboplatin regimen yielded an estimated pCR rate of 51% (95% Bayesian probability interval [PI], 36%-66%), whereas the pCR rate with standard therapy was 26% (95% PI, 9% to 43%). This finding suggests that the predicted probability of success in a confirmatory randomized trial of this regimen in 300 patients with TNBC would be 88%. The benefit of veliparib/carboplatin was restricted to TNBC, as the estimated pCR rate among patients with hormone receptor–positive (and HER2-negative) breast cancer was 14% (95% PI, 3%-25%) in the veliparib/carboplatin arm and 19% (95% PI, 5%-33%) in the control arm. However, the pCR rates in relationship to *BRCA* mutation status were not reported. This was an innovative trial design to identify appropriate agents for further evaluation in a larger phase 3 setting.

The BrighTNess phase 3 trial (A Study Evaluating Safety and Efficacy of the Addition of ABT-888 Plus Carboplatin Versus the Addition of Carboplatin to Standard Chemotherapy Versus Standard Chemotherapy in Subjects With Early Stage Triple Negative Breast Cancer; NCT02032277) assessed the activity of veliparib in combination with carboplatin as neoadjuvant treatment in both mutant *BRCA*–associated and wild-type *BRCA* TNBC.[37] This was a multicenter, randomized, double-blinded, placebo-controlled trial that enrolled women who presented with clinical stage T2-4 N0-2 or T1 N1-2 triple-negative disease and were candidates for potentially curative surgery. A total of 634 patients were randomly assigned in a 2:1:1 ratio to 1 of 3 neoadjuvant treatment arms: (1) paclitaxel at 80 mg/m^2 × 12, carboplatin at AUC 6, and veliparib at 50 mg twice daily followed by doxorubicin and cyclophosphamide (AC); (2) paclitaxel at 80 mg/m^2 × 12, carboplatin at AUC 6, and placebo followed by AC; or (3) paclitaxel at 80 mg/m^2 × 12, placebo, and placebo followed by AC. All patients had to have undergone documented germline *BRCA* mutation testing. The primary endpoint was pCR in the breast and lymph nodes.

Table 2. Selected Ongoing Clinical Trials of PARP Inhibitors in Breast Cancer*

Study	Agents/Regimen	N	Phase	Start Date
Olaparib				
NCT02898207	Olaparib + onalespib	40	1	May 2017
NCT02227082	Olaparib + radiation	36	1	October 2013
NCT03109080	Olaparib + radiation	24	1	July 2017
PARTNER, NCT03150576	Comparator: carboplatin + paclitaxel Experimental arm 1: olaparib days –2 to 10 every 3 weeks + paclitaxel + carboplatin Experimental arm 2: olaparib days 3 to 14 every 3 weeks + paclitaxel + carboplatin	527	2/3	May 2016
NSABP B55/BIG 6-13/ OlympiA, NCT02032823	Olaparib or placebo for 1 year	1500	3	April 2014
Talazoparib				
NCT01989546	Talazoparib	24	Pilot	November 2013
NCT03330405	Talazoparib + avelumab	296	1b/2	October 2017
NCT02401347	Talazoparib	58	2	August 2015
Veliparib				
NCT01618357	Veliparib + radiation	44	Pilot	September 2012
NCT02849496	Arm 1: Veliparib Arm 2: Atezolizumab Arm 3: Veliparib + atezolizumab	90	2	November 2016
S1416 (SWOG), NCT02595905	Comparator: placebo + cisplatin Experimental arm: veliparib + cisplatin	333	2	July 2016
M12-914/BROCADE 3, NCT02163694	Comparator: placebo + carboplatin + paclitaxel Experimental arm: veliparib + carboplatin + paclitaxel	500	3	July 2014
Niraparib				
NCT03154281	Niraparib + everolimus	24	1	July 2017
Rucaparib				
NCT03101280	Rucaparib + atezolizumab	48	1b	May 2017
RUBY, NCT02505048	Rucaparib	41	2	March 2016

*As of January 20, 2018.

N, number of patients.

Initial results of the primary and safety analyses were reported at the ASCO meeting in 2017 and subsequently published in 2018. Although a significant improvement in pCR was observed in arm A compared with arm C (53% vs 31%; $P<.0001$), arm A did not show an improvement in pCR compared with arm B (53% vs 58%; $P=.36$), demonstrating that the improvement in pCR present in arm A was due to carboplatin, without an apparent contribution from veliparib. Prespecified analyses by stratification factors demonstrated no differences in pCR by germline *BRCA* status. In summary, veliparib did not improve the efficacy of platinum-based chemotherapy in the neoadjuvant setting in patients with TNBC.

An interesting approach to evaluating PARP inhibitor therapy was a trial with a preoperative window design, in which talazoparib was given for 2 months before neoadjuvant chemotherapy to patients who had breast cancer with a germline *BRCA* mutation and an HER2-negative tumor measuring 1 cm or more.[38] The main objectives of this pilot trial were feasibility and assessment of safety. In this small study, 13 patients, 10 of whom had *BRCA1* mutations and 9 of whom had triple-negative tumors, were accrued over 8 months and received talazoparib at 1 mg daily. A substantial clinical response was reported

in all patients, with a median decrease in tumor volume of 88% (range, 30%-98%), assessed by breast ultrasound after 2 months of single-agent PARP inhibitor therapy. None of the patients experienced any grade 4 adverse events. One patient required a dose reduction owing to grade 3 neutropenia. All patients received an anthracycline followed by a taxane with or without carboplatin. At surgery, all 10 patients with TNBC had a residual cancer burden of 0 or 1. The 2 patients with hormone receptor–positive tumors had a residual cancer burden of 3.

The study was subsequently modified to a phase 2 trial to assess pCR in an expansion cohort of 20 breast cancer patients with clinical stage I to III disease and a *BRCA* mutation after talazoparib treatment for 6 months before surgery.[39] Results were reported at the 2018 ASCO meeting. The primary endpoint was pCR. There were 15 patients with triple-negative disease. The pCR rate was 53% (10/19), with a residual cancer burden of 0. The most common grade 1 or 2 averse events were anemia, neutropenia, nausea, fatigue, and some alopecia. There was one case of grade 4 thrombocytopenia. Side effects were managed with dose reductions and blood transfusions. This experience is notable in that single-agent PARP inhibition in patients with early-stage *BRCA*-mutated breast cancer resulted in significant pCRs. A larger, phase 2, multicenter study is being conducted with talazoparib as neoadjuvant therapy in patients with germline *BRCA1/2*-mutated early-stage triple-negative breast cancer (NCT03499353).

A randomized, open-label, phase 2/3 trial called PARTNER (Platinum and Polyadenosine 5'Diphosphoribose Polymerisation Inhibitor for Neoadjuvant Treatment of Triple Negative Breast Cancer and/or Germline BRCA Positive Breast Cancer; NCT03150576) is evaluating the addition of olaparib to platinum-based neoadjuvant chemotherapy in patients with germline *BRCA*-mutated breast cancer or TNBC. Additional ongoing studies of PARP inhibitors in the treatment of breast cancer are summarized in Table 2.

Mechanisms of Resistance to PARP Inhibitors

Several mechanisms of resistance to PARP inhibitors have been described. A well-known one is the development of reversion mutations in *BRCA1* or *BRCA2* that partially restore BRCA functionality. Most of the earlier descriptions are associated with platinum agents in *BRCA1* or *BRCA2* carriers who have ovarian cancer.[40,41] Recently, reversion mutations in patients with breast cancer after treatment with a PARP inhibitor have been reported.[42,43] Reversion mutations can occur in the germline or somatic setting. The somatic reversion mutations that have been described are either a secondary mutation that restores the open reading frame or a direct reversion to the wild-type sequence. Either situation leads to PARP inhibitor resistance because the production of a functional BRCA1/2 protein is now restored. A hypothesized mechanism of resistance to PARP inhibition is loss of p53 binding protein 1 (53BP1), which is involved in DNA repair. Preclinical evidence shows that mutations resulting in loss of 53BP1 lead to a partial restoration of homologous recombination in *BRCA1/2*-mutant cells, which lessens sensitivity to PARP inhibitors.[44] Another purported mechanism is an upregulation of efflux drug transporters that is due to overexpression of P-glycoprotein.[45] Additional mechanisms involved in resistance to PARP inhibitors include increased activity of BRCA1/2 proteins due to increased stimulation of hypomorphic BRCA1/2 protein expression and decreased PARP expression due to epigenetic silencing of the gene or increased protein turnover.[46]

Important future directions of the clinical use of PARP inhibitors, given the emergence of resistance, include the exploration of combinations. Also, the potential benefit of PARP inhibitors in a patient population wider than *BRCA* carriers is of interest. Strategies include combining PARP inhibitors with other targeted agents, such as cyclin-dependent kinase (CDK) inhibitors, phosphatidylinositol 3-kinase (PI3K) inhibitors, and histone deacetylase (HDAC) inhibitors. Preclinical models show that inhibiting CDK, HDAC, or PI3K can sensitize *BRCA*-proficient cells to PARP inhibitors.[47-49]

A Novel Combination: PARP Inhibitors and Immunotherapy

An exciting combinatorial strategy is to use a PARP inhibitor plus immunotherapy. The addition of immune checkpoint blockade to PARP inhibitor therapy is an opportunity to improve therapeutic efficacy because it is hypothesized that PARP inhibitors possess immunomodulatory effects, which can promote a favorable microenvironment.[50,51] Additionally, this pairing avoids overlapping myelosuppression, which has been observed with PARP inhibitor and chemotherapy combinations. Several trials that are ongoing or completed in MBC focus on this combination; they include TOPACIO/KEYNOTE-162 (Niraparib in Combination With Pembrolizumab in Patients With Triple-negative Breast Cancer or Ovarian Cancer; NCT02657889) and MEDIOLA (A Phase I/II Study of MEDI4736 in Combination With Olaparib in Patients With Advanced Solid Tumors; NCT02734004). TOPACIO/KEYNOTE-162 is a phase 1/2 trial in which patients with metastatic TNBC or advanced ovarian cancer were treated with niraparib and pembrolizumab (Keytruda, Merck), an anti–programmed death 1 (PD-1) antibody.[52] In the phase 1 portion, 14 patients with

either ovarian cancer or TNBC were enrolled. Of the 14 patients, 5 had breast cancer. Pembrolizumab was administered at 200 mg IV every 3 weeks, and niraparib dosing ranged from 200 to 300 mg daily. The dose-limiting toxicity was thrombocytopenia. The recommended phase 2 dose was pembrolizumab at 200 mg IV every 3 weeks and niraparib at 200 mg once daily. One of the 5 patients with TNBC, who did not harbor a *BRCA* mutation, had stable disease for 10 cycles.

The open-label, phase 2 basket MEDIOLA trial combined olaparib and durvalumab (Imfinzi, AstraZeneca), a human monoclonal antibody of the immunoglobulin G1 kappa subclass that interferes with the interactions of programmed death ligand 1 (PD-L1), PD-1, and B7-1, molecules that are expressed on antigen-presenting cells and T cells.[53] One of the 4 arms recruited patients with advanced HER2-negative breast cancer and a *BRCA1/2* mutation, who received anthracycline and taxane therapy. Treatment consisted of olaparib at 300 mg twice daily for 4 weeks, then olaparib at 300 mg twice daily plus durvalumab at 1500 mg IV every 4 weeks until disease progression. The primary outcome measures were disease control rate at 12 weeks, safety, and tolerability. At the time of abstract reporting, 25 patients with MBC (11 with *BRCA1* and 14 with *BRCA2* mutations) were enrolled; 13 patients had hormone receptor–positive disease. The observed disease control rate at 12 weeks was 80% (20/25). Grade 3 or higher adverse events included anemia and neutropenia. Early results from these trials of combining a PARP inhibitor and immunotherapy show promise, and work in combining PARP and immune checkpoint inhibitors is ongoing.

Conclusion

PARP inhibitors are an active new form of therapy for *BRCA*-mutated MBC. A major milestone has been achieved with the approval of olaparib for the treatment of germline *BRCA*-mutated MBC, which has now become part of clinical practice. The availability of a specific treatment in the form of a PARP inhibitor targeting a cancer-specific molecular alteration for TNBC with a *BRCA* mutation is a clinical breakthrough, given that only chemotherapy was available before olaparib approval. PARP inhibitors offer an effective treatment alternative, improving quality of life compared with chemotherapy in patients who have mutant *BRCA1/2*-associated advanced breast cancer. It is encouraging to see several efforts directed at expanding the utility of PARP inhibitors to patients who have breast cancer that lack germline *BRCA1/2* mutations but may have somatic *BRCA* mutations or mutations in other genes involved in the homologous recombination repair pathway and may also benefit from treatment with these agents. Additionally, strategies to increase the antitumor activity of PARP inhibitors by combining them with chemotherapy or immunotherapy are being tested, and the hope is that these additional approaches will be included in future treatment algorithms for breast cancer.

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