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# PARP Inhibitors

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**Abstract** Poly (ADP-ribose) polymerase (PARP) is a novel therapeutic target in cancer. Preclinical studies demonstrate that PARP inhibitors selectively kill *BRCA*-deficient cells and potentiate the effects of DNA-damaging agents. There are several PARP inhibitors in clinical development, including olaparib, iniparib, veliparib, PF-01367338, and MK-4827. Phase II studies of single-agent olaparib demonstrate activity in *BRCA*-associated cancers. A randomized phase II trial showed that the addition of iniparib to gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer (TNBC) improved progression-free survival and overall survival. A phase III trial evaluating this combination in metastatic TNBC has completed accrual. Phase III studies of olaparib in *BRCA*-associated breast cancer and veliparib in breast cancer are being planned. This article reviews the clinical studies to date that have evaluated PARP inhibitors as a single agent or in combination with chemotherapy in patients with breast cancer, including *BRCA*-associated breast cancer and TNBC.

**Keywords** Poly (ADP-ribose) polymerase · PARP inhibitor · *BRCA*-associated breast cancer · Triple-negative breast cancer

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## Introduction

Breast cancer is the most common female malignancy, affecting one in eight women. Endocrine treatment and human epidermal growth factor receptor type 2 (HER2)-targeted therapies have led to significant improvements in overall survival in patients with hormone receptor–positive and HER2-positive breast cancers, respectively. Currently, there is no specific targeted treatment approach for patients with tumors that do not express estrogen receptor (ER), progesterone receptor (PR), and HER2, a condition referred to as triple-negative breast cancer (TNBC). In 2010, there were 207,090 cases of breast cancer diagnosed in the United States, of which approximately 10% to 15% were classified as TNBC, and about 5% were *BRCA*-associated breast cancer, the subgroup carrying genetic mutations in the *BRCA1* or *BRCA2* gene [1]. Reports of the effect of a *BRCA*-mutation on prognosis vary; however, Brekelmans et al. [2] and Rennert et al. [3] concluded that the overall prognosis in terms of 10-year survival was similar between carriers and non-carriers.

TNBC is characterized by an aggressive clinical course with a higher likelihood of early recurrence and death compared to ER-positive, PR-positive, or HER2-positive breast cancer [4–6]. Currently, chemotherapy is the mainstay of treatment for TNBC and *BRCA*-associated TNBC. Poly (ADP-ribose) polymerase (PARP) inhibitors appear to be among the most promising targeted therapy under investigation for these types of breast cancers. PARPs are a family of highly conserved enzymes in plants and animals. There are at least 18 members identified, with PARP-1 being the first one to be described and the most abundant, and PARP-2 being its close relative [7, 8]. PARP-1 accounts for greater than 90% of the ADP-ribosylation within the cells. PARP-1 is essential for a variety of

processes, including inflammation, ischemia, epigenetics, and DNA repair. The role of PARP-1 in DNA damage repair and maintenance of genomic stability makes it a suitable target for the treatment of cancer. PARP-1 is essential for the repair of DNA single-strand breaks (SSBs), predominantly through the base excision repair pathway [7, 9], whereas BRCA1 and BRCA2 proteins are essential for the repair of double-strand breaks (DSBs) and collapsed replication forks by the process of homologous recombination (HR) [10, 11]. Inhibition of PARP-1 leads to failure of SSB repair and accumulation of SSBs. During the S-phase of the cell cycle, the replication fork is arrested at the site of an SSB, resulting in degeneration into DSBs. In the cells that are HR-competent, such DSBs can be potentially repaired by the HR system, which is highly accurate, so genomic stability is subsequently maintained. In fact, PARP-1 knockout mice are viable and exhibit evidence of increased HR-directed repair [12]. This report describes the rationale for the use of PARP inhibitors in breast cancer and reviews the currently available clinical data of these compounds as a single agent and in combination with chemotherapy for the treatment of *BRCA*-associated breast cancer and TNBC.

## Rationale for the Use of PARP Inhibitors in Breast Cancer

There are two potential roles of PARP inhibitors as therapeutics in oncology (Fig. 1). The first scenario is the use of PARP inhibitors in tumors that are deficient in HR

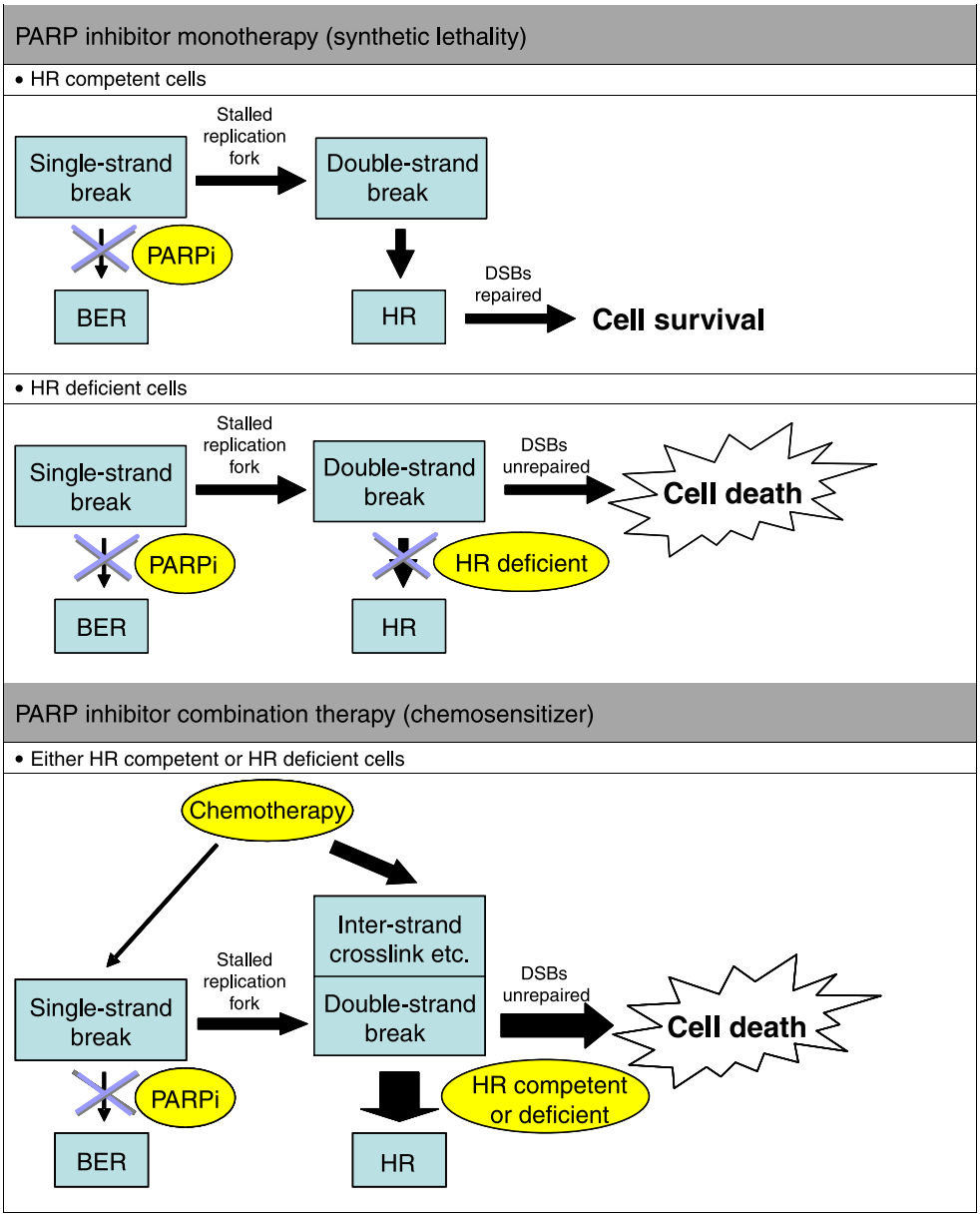


**Fig. 1** Schematic diagram of the rationales for the use of PARP inhibitors in oncology, either as monotherapy or combined with chemotherapy. *BER* base excision repair; *HR* homologous recombination; *PARPi* poly (ADP-ribose) polymerase inhibitor

repair or are suspected of having aberrations in the DNA repair pathway. This approach is referred to as "synthetic lethality," in which a mutation in either of the two genes individually has no effect, but combining the mutations leads to death [13]. In 2005, two landmark papers published in *Nature* independently demonstrate that *BRCA1*- and *BRCA2*-deficent cells were extremely sensitive to PARP inhibitors compared to heterozygous mutant or wild-type cells [14, 15]. In the absence of PARP-1, spontaneous SSBs collapse replication forks and degenerate into DSBs, triggering HR for repair. However, in *BRCA*-deficient cells, the accumulated DSBs overwhelm the less efficient mechanisms of DNA repair, such as nonhomologous end-joining (NHEJ). PARP-1 also contributes to the repair of DSBs through NHEJ, which is further impaired when PARP-1 activity is inhibited [16]. The resultant unrepaired DNA damage triggers apoptotic cell death, leading to "synthetic lethality." These observations led to the clinical investigation of PARP inhibitors in the treatment of *BRCA*-associated breast cancer and ovarian cancer, as well as sporadic TNBC, which share several pathologic and clinical features with the former. More than half of tumors in *BRCA1* carriers have a triple-negative phenotype [17, 18], whereas a subset of TNBC, although having intact *BRCA*, may have dysfunction of the *BRCA* gene product, termed "BRCAness." One study detected *BRCA1* promoter methylation in 11% of sporadic breast cancers, most of which are TNBC [19]. Other mechanisms include overexpression of HMG1 or the DNA-binding protein inhibitor ID4, which are negative regulators of *BRCA1* [19, 20], or overexpression of EMSY, which is a negative regulator of *BRCA2* [21].

There is also a role for PARP inhibitors in potentiating the cytotoxicity of DNA damaging agents, as they attenuate the repair of DNA damage [22–24]. Preclinical studies show that PARP inhibitors potentiate the effects of DNA-damaging agents, such as platinum compounds, topoisomerase inhibitors, and temozolomide (TMZ). The combination of a PARP inhibitor with DNA-damaging agents may be effective even in tumors without an HR defect by increasing the DSBs to the point of overwhelming a competent HR system. This has led to several clinical trials evaluating PARP inhibitors in combination with carboplatin, cisplatin, cyclophosphamide, or TMZ in sporadic TNBC, which may have an intact HR system.

## The Development of PARP Inhibitors

PARP has been the focus of medicinal chemistry programs for over 20 years, but only recently have PARP inhibitors entered clinical development. Currently, there are eight PARP inhibitors under investigation in oncology and include the following: olaparib (AZD-2281; AstraZeneca, KuDOS), iniparib (BSI-201, SAR240550; BiPar Sciences Inc., a subsidiary of Sanofi-Aventis), veliparib (ABT-888; Abbott Laboratories), PF-01367338 (AG-014699; Pfizer Inc.), MK-4827 (Merck & Co, Inc.), INO-1001 (Inotek Pharmaceuticals), CEP-9722 (Cephalon), and GPI 21016 (MGI Pharma) [25–27]. The five agents that are being evaluated in breast cancer trials include olaparib, iniparib, veliparib, PF-01367338, and MK-4827 (Table 1).

These PARP inhibitors are second-generation inhibitors that have high potency and specificity, and most inhibit PARP by competitive inhibition of the $NAD^+$ binding site of PARP-1. The 4-iodo-3-nitrosobenzamides are one class of PARP inhibitors and an example is iniparib, which utilizes a different mechanism that results in oxidation of the F1 zinc finger motif of the DNA-binding domain of PARP-1, leading to zinc ion rejection and inactivation of PARP-1 activity [28].

## PARP Inhibitors in *BRCA*-associated Breast Cancer

Olaparib is the first oral PARP inhibitor to be tested as a single agent in *BRCA*-associated cancers. The results of a phase I trial of olaparib monotherapy in advanced solid tumors with enrichment for *BRCA* carriers (NCT00516373) were published in the *New England Journal of Medicine* [29]. The trial enrolled 60 patients with advanced solid tumors; 22 were confirmed carriers of *BRCA1* or *BRCA2* mutations and one had a strong family history of *BRCA*-associated cancer but declined to undergo genetic testing. The maximum tolerated dose (MTD) of olaparib was 400 mg twice daily. Dose-limiting toxicities (DLT) consisted of grade 3 mood alteration and fatigue, grade 4 thrombocytopenia, and grade 3 somnolence. Other side effects were nausea, vomiting, taste alteration, anorexia, as well as a low incidence of anemia and thrombocytopenia. Clinical benefit, with radiologic or tumor marker responses or disease stabilization for more than 4 months, was experienced in 63% (12 of 19 patients) of the *BRCA* carriers. There were no responses in the patients without a *BRCA* mutation. Of the three patients with *BRCA*-associated breast cancer (all *BRCA2* in this study), one had a complete remission more than 60 weeks and another had stable disease (SD) for 7 months. The study also confirmed PARP inhibition and DNA DSB accumulation by examining the level of poly (ADP-ribose) (PAR) in peripheral blood mononuclear cells (PBMCs) and phosphorylated histone H2AX (γH2AX) foci, a marker of DNA DSBs, in plucked eyebrow-hair follicle samples. PARP inhibition by more than 90% was observed in PBMCs from patients treated with 60 mg or more of olaparib twice daily and γH2AX foci was induced at 6 hours after treatment with olaparib and sustained at all later time points [29].

**Table 1** Select clinical trials of PARP inhibitors in breast cancer

| Treatment regimen | Phase | Patient population | Identifier | Duration | Accrual goal | Primary outcome |
|---|---|---|---|---|---|---|
| **Olaparib** | | | | | | |
| Olaparib | II | Advanced *BRCA*-associated cancer, including breast, ovarian, prostate, and pancreatic cancer | NCT01078662 | February 2010–December 2011 | 300 | Efficacy |
| Olaparib and cediranib | I/II | Recurrent/metastatic TNBC and recurrent ovarian cancer | NCT01116648 | November 2009–October 2014 | 90 | Phase I: Safety and toxicity<br>Phase II: Efficacy |
| Olaparib and carboplatin | I | Metastatic TNBC, *BRCA*-associated breast or ovarian cancer, and sporadic ovarian cancer | NCT00647062 | December 2007–December 2009 | 101 | Safety and toxicity; PAR and γH2AX levels in PBMCs and tumor tissue |
| **Iniparib** | | | | | | |
| Iniparib with gemcitabine and carboplatin | IIIb | Metastatic TNBC—expanded access | NCT01130259 | May 2010–May 2011 | 1500 | Safety and toxicity |
| Iniparib and irinotecan | II | Metastatic TNBC with brain metastasis | NCT01173497 | July 2010–January 2013 | 40 | Efficacy (intra- or extra- cranial time to progression) |
| Iniparib twice-weekly with gemcitabine and carboplatin vs iniparib once-weekly with gemcitabine and carboplatin | II | Metastatic TNBC | NCT01045304 | February 2010–December 2011 | 160 | Objective response rate |
| Iniparib (twice-weekly or once-weekly) and weekly paclitaxel vs weekly paclitaxel | II | Stage II to IIIA TNBC—neoadjuvant | NCT01204125 | September 2010–January 2017 | 135 | Pathological complete response |
| Iniparib with gemcitabine and carboplatin | II | Stage I to IIIA TNBC and *BRCA*-associated breast cancer—neoadjuvant | NCT00813956 | December 2008–May 2012 | 36 | Pathological complete response |
| **Veliparib** | | | | | | |
| Veliparib and carboplatin vs veliparib | II | Stage III or IV *BRCA*-associated breast cancer | NCT01149083 | June 2010–May 2011 | 82 | Response rate |
| Veliparib and chemotherapy (paclitaxel± trastuzumab followed by doxorubicin and cyclophosphamide) vs chemotherapy | II | Stage II, III or regional stage IV breast cancer—neoadjuvant | NCT01042379 | March 2010–November 2014 | 800[a] | Pathologic complete response |
| Veliparib and temozolomide | II | Metastatic breast cancer with expansion cohort of *BRCA*-associated breast cancer | NCT01009788 | November 2009–October 2012 | 61 | Objective response rate; safety and efficacy in the expansion cohort |
| Veliparib with cisplatin and vinorelbine | I | Recurrent/metastatic breast cancer and *BRCA*-associated breast cancer | NCT01104259 | July 2010–May 2012 | 36 | Safety and toxicity |
| Veliparib and liposomal doxorubicin | I | Recurrent ovarian cancer and metastatic TNBC | NCT01145430 | February 2010–January 2012 | 72 | Safety and toxicity |
| Veliparib | I | Refractory *BRCA*-associated cancer, basal-like breast cancer, and platinum-refractory ovarian cancer | NCT00892736 | November 2008–February 2010 | 60 | Safety and toxicity |

**Table 1** (continued)

| Treatment regimen | Phase | Patient population | Identifier | Duration | Accrual goal | Primary outcome |
|---|---|---|---|---|---|---|
| **PF-01367338** | | | | | | |
| PF-01367338 and cisplatin vs cisplatin | II | Stage I-III TNBC or ER-positive, PR-positive, HER2-negative known *BRCA* carriers with significant residual disease at the time of surgery following preoperative chemotherapy | NCT01074970 | February 2010–February 2013 | 135 | 2-year disease-free survival |
| PF-01367338 | II | Locally advanced and metastatic *BRCA*-associated breast or metastatic *BRCA*-associated ovarian cancer | NCT00664781 | December 2007 – December 2009 | 56 | Response rate |
| **MK-4827** | | | | | | |
| MK-4827 | I | Advanced solid tumors enriched for *BRCA*-associated cancer | NCT00749502 | October 2008–August 2012 | 150 | Safety and toxicity; PAR level in PBMCs |

[a] Total accrual goal is 800 patients for the five arms that each contain a different investigational agent

*ER* estrogen receptor; *HER2* human epidermal growth factor receptor type 2; *PAR* poly(ADP-ribose), *PBMCs* peripheral blood mononuclear cells; *PR* progesterone receptor; *TNBC* triple-negative breast cancer

Based on encouraging activity in the phase I trial, the investigators conducted two separate phase II trials of olaparib monotherapy, one in *BRCA*-associated breast cancer and the other in *BRCA*-associated ovarian cancer [30••, 31]. The phase II multicenter trial of olaparib in *BRCA*-associated breast cancer (NCT00494234) enrolled metastatic breast cancer patients with a confirmed *BRCA1* or *BRCA2* mutation. Two sequential cohorts received olaparib continuously in 4-week cycles, initially at the MTD of 400 mg twice daily (cohort 1; $n$=27) and then at 100 mg twice daily (cohort 2; $n$=27). The median number of prior chemotherapy regimens was three. The majority of patients had previous exposure to taxanes and anthracyclines, and some to platinum. A significant portion of patients in both cohorts had triple-negative tumors (50% in cohort 1 and 64% in cohort 2). The majority of patients had *BRCA1* mutations (67% in cohort 1 and 56% in cohort 2). The primary endpoint was objective response rate (ORR) (complete response [CR] + partial response [CR]). Secondary endpoints were clinical benefit rate (CBR) (CR + PR + SD ≥ 23 weeks) and progression-free survival (PFS). The study reported an ORR of 41% (11 of 27) for cohort 1 and 22% (6 of 27) for cohort 2. CBR was 52% for cohort 1 and 26% for cohort 2. Median PFS was 5.7 months for cohort 1 and 3.8 months for cohort 2, suggesting a dose-response effect, with the caveat being that the trial design was not a randomized phase II. Treatment-related adverse events were mainly grade 1 or 2 and included fatigue (41% in cohort 1, 26% in cohort 2), nausea (41% in both groups), vomiting (11% in cohort 1, 15% in cohort 2), and anemia (4% in cohort 1, 7% in cohort 2) [30••].

MK-4827 is another oral PARP inhibitor that has been tested as monotherapy in a phase I trial (NCT00749502). In this two-part study, the dose escalation occurred in patients with advanced cancer ($n$=56) with enrichment for *BRCA* mutation carriers. The second part was an expansion cohort in sporadic platinum-resistant, high-grade serous ovarian cancer. The MTD was 300 mg once daily. Grade 1 or 2 nausea (45%), fatigue (34%), and anorexia (28%) were the most common adverse events. Three instances of grade 4 thrombocytopenia occurred at 400 mg once daily and were dose-limiting toxicities. Anti-tumor activity was observed and included PRs in five patients with ovarian cancer based on both Response Evaluation Criteria in Solid Tumors (RECIST) and Gynecologic Cancer InterGroup (GCIG) criteria, and all of whom were BRCA mutation carriers. There was one PR by RECIST only in a patient with BRCA-associated ovarian cancer, two PRs by RECIST only in patients with *BRCA*-associated breast cancer, and SD for more than 4 months in one patient with *BRCA*-associated ovarian cancer [32].

PF-01367338 (AG-014699), which is administered intravenously, was the first PARP inhibitor to undergo clinical investigation. A phase II trial of PF-01367338 intravenous (IV) at 12 mg/m$^2$ and TMZ at 200 mg/m$^2$ orally on days 1 to 5 of a 28-day cycle reported an ORR rate of 18% and an SD (≥6 months) rate of 18% in patients with chemotherapy-naïve metastatic melanoma. However, significant myelosuppression was observed [33]. There are ongoing trials of single-agent PF-01367338 in *BRCA*-associated breast cancer. A phase II study (NCT00664781) is evaluating PF-01367338 as monotherapy in locally advanced or metastatic breast cancer or metastatic ovarian cancer with known *BRCA1* or *2* mutations.

## PARP Inhibitors in Triple-Negative Breast Cancer

Iniparib is the first PARP inhibitor to be exclusively tested in metastatic TNBC. Phase I trials of iniparib as monotherapy (NCT00298675) or in combination with several chemotherapy regimens in advanced solid tumors (NCT00422682) did not identify a MTD. Notably, iniparib did not increase the frequency of known toxicities associated with these regimens, which included topotecan, TMZ, gemcitabine, and carboplatin/paclitaxel. At a dose of 2.8 mg/kg, PARP was inhibited in PBMCs by >50% after a single dose; this was increased to >80% after multiple doses [34, 35].

In a phase II multicenter trial (NCT00540358), patients with metastatic TNBC were randomized 1:1 to receive chemotherapy alone (gemcitabine 1000 mg/m$^2$ and carboplatin AUC=2 IV on days 1 and 8 of a 21-day cycle) or chemotherapy and iniparib (5.6 mg/kg IV on days 1, 4, 8, and 11 of a 21-day cycle) ($n$=123). Patients had received no more than two prior chemotherapy regimens for metastatic disease. Prior treatment with gemcitabine, carboplatin, cisplatin, or a PARP inhibitor was not allowed. Interim analysis in 86 patients demonstrated that the addition of iniparib to gemcitabine and carboplatin resulted in an improved CBR (62% vs 21%; $P$=0.0002) and ORR (48% vs 16%; $P$=0.002) compared with chemotherapy alone [36••]. Final efficacy and safety analysis was reported in the *New England Journal of Medicine*. In the intention-to-treat analysis, the addition of iniparib to gemcitabine and carboplatin resulted in an improved CBR (56% vs 34%; $P$=0.01) and ORR (52% vs 32%; $P$=0.02), despite the crossover of 51% of patients (30 of 59) from the chemotherapy-alone arm to the combination arm. The addition of iniparib also resulted in an improvement in PFS (5.9 vs 3.6 months; $P$=0.01) and OS (12.3 vs 7.7 months; $P$=0.01), although the study was not powered for an OS analysis. Grade 3 or 4 adverse events (mainly hematologic toxicity) were similar between the groups that were treated with chemotherapy alone versus chemotherapy and iniparib [37••].

A phase III trial of gemcitabine and carboplatin with or without iniparib completed enrollment in February 2010 with more than 500 patients accrued with metastatic TNBC. The primary endpoints were PFS and OS. The US Food and Drug Administration (FDA) granted Fast Track designation to iniparib for metastatic TNBC in December 2009 [38]. The results of this study are highly anticipated. An open-label, expanded access trial (NCT01130259) is recruiting patients with metastatic TNBC who have had no more than three prior chemotherapy regimens in the metastatic setting (prior gemcitabine and platinum agents are allowed).

There are several ongoing phase II trials of iniparib in TNBC. Because iniparib is highly lipophilic and crosses the blood-brain barrier, one trial (NCT01173497) is investigating iniparib in combination with irinotecan in TNBC patients with brain metastases. Given the convenience of a once-weekly infusion, a phase II trial (NCT01045304) is comparing a twice-weekly versus once-weekly dosing of iniparib in combination with gemcitabine and carboplatin in metastatic TNBC to determine if the schedules are comparable. Given the activity seen in the metastatic setting, the role of iniparib in patients with early stage breast cancer is being explored. One trial (NCT00813956) is evaluating the combination of gemcitabine, carboplatin, and iniparib for six cycles as neoadjuvant therapy in patients with stage I to IIIA TNBC. Enrollment has been expanded to include patients with a *BRCA1* or *BRCA2* mutation. A randomized phase II study (SOLTI NEOPARP, NCT01204125) is comparing weekly paclitaxel versus weekly paclitaxel and iniparib given twice weekly or once weekly as neoadjuvant therapy in patients with stage II to IIIA TNBC. The primary outcome of both neoadjuvant studies is pathologic complete response rate.

Other PARP inhibitors have been evaluated in phase I and II trials specifically for TNBC patients. Olaparib was studied in combination with weekly paclitaxel in patients with metastatic TNBC (NCT00707707). Olaparib at 200 mg orally twice daily was given with paclitaxel at 90 mg/m$^2$ on days 1, 8, and 15 of a 28-day cycle. No more than one prior chemotherapy regimen for metastatic disease was permitted. Two cohorts of patients were enrolled. The first cohort of patients did not receive G-CSF ($n$=9), but when grade 2 neutropenia occurred during the first two cycles of treatment in this group, granulocyte colony-stimulating factor (G-CSF) was added to the treatment of patients in cohort 2 ($n$=10). The ORR was 33.3% (3 of 9) and 40% (4 of 10) in cohorts 1 and 2, respectively, consisting of all partial responses. Higher than expected grade 3 and 4 hematologic toxicities were reported and included neutropenia (44%, 20%) and anemia (22%, 0%) in cohort 1 and cohort 2, respectively. This necessitated a dose modification (dose delay and/or reduction) of paclitaxel in 89% of patients in cohort 1 and 60% in cohort 2. The dose of olaparib was also reduced or interrupted in 44% of patients in cohort 1 and 30% in cohort 2 [39]. The higher than expected occurrence of neutropenia with the combination of chemotherapy with olaparib is in contrast to the experience that has been reported with iniparib and chemotherapy.

A phase II trial of single-agent olaparib given at 400 mg orally twice daily was evaluated in four cohorts of patients with the following diagnosis: advanced serous ovarian cancer ($n$=55), TNBC ($n$=15), *BRCA*-associated ovarian cancer ($n$=10), and *BRCA*-associated breast cancer ($n$=10). An ORR of 41.2% (7 of 17) was reported for ovarian cancer patients with known *BRCA* mutations and 23.9% (11

of 46) for non-*BRCA* advanced serous ovarian cancer. Notably, for patients with breast cancer, there were no confirmed objective responses in the *BRCA*-associated breast cancer (0 of 8) or TNBC (0 of 15). However, three of the four TNBC patients with known *BRCA* mutations experienced a reduction in the size of their target lesions compared to 13 of 14 patients with non-*BRCA* TNBC who had an increase in tumor volume [40]. Albeit a small study, this may be an indicator that the activity of single-agent PARP inhibitor in sporadic TNBC is low, and further supports the combination of a PARP inhibitor with chemotherapy in the treatment of these patients.

There are several ongoing trials of olaparib in combination with other agents for TNBC. A phase I/II trial (NCT01116648) is evaluating olaparib and cediranib (AZD2171), a potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, in patients with recurrent and/or metastatic TNBC. Another phase I trial (NCT00647062) is studying olaparib in combination with carboplatin in metastatic TNBC, *BRCA*-associated breast cancer or ovarian cancer, and sporadic ovarian cancer. PF-01367338 is undergoing a phase II evaluation (NCT01074970) in patients with stage I, II, or III TNBC who have residual disease following pre-operative chemotherapy. Patients are being randomized to four cycles of single-agent cisplatin or four cycles of PF-01367338 and cisplatin. The primary endpoint is 2-year DFS. Patients with ER-positive, PR-positive, and HER2-negative breast cancer are eligible if they are known *BRCA* mutation carriers.

## PARP Inhibitors in Sporadic Breast Cancer

Veliparib has been studied in combination with TMZ (NCT01009788) in patients with metastatic breast cancer ($n$=41), regardless of hormone receptor status, who have

**Table 2** Human DNA repair pathways and associated DNA repair-targeting agents in clinical development

| DNA repair pathways | DNA damage | Proteins involved | Hereditary syndromes | Agents (company; highest development status) |
|---|---|---|---|---|
| Direct repair | Base damage | $O^6$-alkylguanine-DNA alkyltransferase (MGMT, OGAT, ATase) | | MGMT inhibitors: $O^6$-benzylguanine (phase II), lomeguatrib (AstraZeneca/KuDos; discontinued) |
| Base excision repair | Single-strand break | PARP1, PARP2, APE1, XRCC1, ligase III, DNA pol β | | PARP inhibitors (see Table 1 for details)<br>APE1 inhibitors: TRC102 (Tracon; phase I) |
| Nucleotide excision repair | Bulky adduct | TFIIH, DNA pol δ, DNA pol ε, XPA, XPB, XPC, XPD, XPG, ERCC1/XPF, CSA, CSB | Xeroderma pigmentosum, Cockayne syndrome, trichothiodystrophy | CSA/CSB inhibitors: prodarsan (Pharming Group NV/DNage B.V.; phase II) |
| Homologous recombination | Double-strand break<br>Inter- and intra-strand crosslink | ATM, ATR, BRCA1, BRCA2, RAD51, RAD54, CHEK1, FANCA, DNA helicase, ERCC1, XRCC3 | Hereditary *BRCA*-associated breast or ovarian cancer, Fanconi anemia, ataxia telangiectasia, Bloom syndrome | ATM inhibitors: KU55933 (AstraZeneca/KuDos; preclinical), CP466722 (Pfizer; preclinical)<br>RAD51 inhibitor: MP470 (SuperGen/Montegen; phase I)<br>CHEK1 inhibitors: Chk1-A, B, C (Array Biopharma; preclinical), GNE900 (Genentech; preclinical) |
| Non-homologous end-joining | Double-strand break | Ku70/80, DNA-PK, XRCC4, ligase IV, DNA pol μ, DNA pol λ | | DNA-PK inhibitor: NU7441 (AstraZeneca/KuDos; suspended) |
| Mismatch repair | Mismatch insertion/deletion | MSH2, MSH6, MLH1, PMS1, PMS2 | Hereditary nonpolyposis colon cancer (Lynch syndrome) | |

*APE1* apurinic or apyrimidinic endonuclease 1; *ATM* ataxia telangiectasia mutated; *CHEK* cell cycle checkpoint kinase 1; *CSA* Cockayne syndrome type A; *CSB* Cockayne syndrome type B; *DNA-PK* DNA-dependent protein kinase; *MGMT* $O^6$-methylguanine-DNA-methyltransferase; *PARP* poly (ADP-ribose) polymerase

had at least one prior chemotherapy regimen for metastatic disease. Notably, 56% of patients had TNBC (23 of 41). *BRCA* mutation status was analyzed in 16 patients and eight were found to be *BRCA* mutation carriers. Veliparib was planned to be given at 40 mg orally twice daily on days 1 through 7 in combination with TMZ at 150 mg/m$^2$ orally on days 1 through 5 of a 28-day cycle. However, veliparib was reduced to 30 mg orally twice daily after grade 4 thrombocytopenia was observed during the first cycle of treatment. The study reported an ORR of 7% (3 of 41), which consisted of two partial responses and one complete response, and the CBR was 17% (7 of 41). However, the benefit was limited to the eight *BRCA* mutation carriers, which yielded an ORR of 37.5% (3 of 8) and a CBR of 62.5% (5 of 8). The mean PFS was 5.5 months in *BRCA* mutation carriers compared with 1.8 months in non-carriers. Dose modification of veliparib and TMZ was necessary due to the higher than expected incidence of grade 3 or 4 hematologic toxicity, which included thrombocytopenia (44%) and neutropenia (27%) [41]. The study incorporated further evaluation of this combination in an expansion cohort of 20 *BRCA* mutation carriers with metastatic disease. This trial, similar to the study of olaparib and paclitaxel, highlights the occurrence of increased toxicity when certain PARP inhibitors are combined with chemotherapy. It also shows preferential activity in BRCA-associated breast cancer.

There are several ongoing phase I/II trials of veliparib in sporadic breast cancer, either in the metastatic or neoadjuvant setting. One trial (NCT01104259) is examining veliparib in combination with cisplatin and vinorelbine in recurrent and/or metastatic breast cancer, as well as *BRCA*-associated breast cancer. In the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And Molecular Analysis 2 (I-SPY 2) trial (NCT01042379), veliparib is one of the five investigational agents being studied as part of a neoadjuvant regimen for stage II, III, or regional stage IV (supraclavicular lymph nodes as the only site of metastases) breast cancer. Veliparib is given in combination with paclitaxel ± trastuzumab followed by doxorubicin and cyclophosphamide, and compared to chemotherapy alone in an adaptive trial design.

## Future Directions

There are several issues that need to be addressed in the clinical development of PARP inhibitors for the treatment of breast cancer. First, not all patients with *BRCA*-associated breast cancer or TNBC respond to PARP inhibitors. Although most trials report an ORR of 30% to 40% with the use of a PARP inhibitor either as a single agent or in combination with a DNA-damaging agent, one study showed no objective response in sporadic TNBC [40]. Development of biomarkers that predict response to PARP inhibition is of critical importance. Does PARP-1 overexpression predict for clinical response? An analysis of PARP-1 expression in tumors from 97 patients in the phase II trial of iniparib in metastatic TNBC demonstrated that PARP-1 was significantly upregulated compared with normal breast tissue controls [42]. Correlating this overexpression with clinical responses in trials with PARP inhibitors will provide valuable information. Analysis of *BRCA* mutation status, *BRCA1* promoter methylation, and other genes integral to HR such as *RAD51*, *RAD54*, *ATM*, *CHEK1,* and *FANCA* in TNBC tumor samples may help further define the tumors that respond to PARP inhibitors [43–45]. For example, a 25-gene DNA repair signature was developed to identify *BRCA*-like sporadic TNBCs and was predictive of sensitivity to anthracycline treatment [46] (Table 2). In addition, γH2AX and RAD51 foci, as well as

**Table 3** Key points

- Base excision repair is a key pathway in the repair of single-strand breaks and is reliant on the enzyme poly (ADP-ribose) polymerase (PARP). BRCA1 and BRCA2 are essential for the repair of DNA double-strand breaks via homologous recombination.
- The potential roles of PARP inhibitors as therapeutics in oncology include 1) monotherapy in tumors that are deficient in homologous recombination, which is termed "synthetic lethality" and 2) in combination with DNA-damaging agents to potentiate their cytotoxicity.
- *BRCA*1-associated breast cancer and sporadic triple-negative breast cancer share several pathologic and clinical features. The majority of tumors arising in *BRCA*1 carriers have a triple-negative phenotype, and a subset of triple-negative breast cancer may have dysfunction of the *BRCA* gene product, termed "BRCAness."
- Olaparib is the first PARP inhibitor to be tested as a single agent in *BRCA*-associated cancers. The phase II trial of olaparib at 400 mg orally twice daily in *BRCA*-associated metastatic breast cancer showed an overall response rate of 41% and a clinical benefit rate of 52%.
- Iniparib is the first PARP inhibitor to be tested in combination with chemotherapy in metastatic triple-negative breast cancer. The randomized phase II trial of gemcitabine and carboplatin given with or without iniparib in patients with metastatic triple-negative breast cancer showed that the addition of iniparib to chemotherapy resulted in an improved clinical benefit rate (56% vs 34%; $P$=0.01) and overall response rate (52% vs 32%; $P$=0.02) as well as an improvement in progression-free survival (5.9 vs 3.6 months; $P$=0.01) and overall survival (12.3 vs 7.7 months; $P$=0.01).
- Several other PARP inhibitors, such as veliparib, PF-01367338, and MK-4827, are undergoing evaluation in phase I and II trials in breast cancer, either as single agent or in combination with chemotherapy.
- A phase III trial of gemcitabine and carboplatin with or without iniparib in metastatic triple-negative breast cancer completed accrual in February 2010. Phase III studies of olaparib in *BRCA*-associated breast cancer and veliparib in breast cancer are being planned.

PAR, have been proposed as pharmacodynamic markers of DNA damage and PARP inhibition [13, 29, 47, 48]. In the phase I trial of olaparib, examination of γH2AX foci in plucked eyebrow-hair follicle samples showed sustained induction of γH2AX foci, and the level of PAR in PBMCs was reduced by more than 90% after treatment with olaparib. Correlation of this type of pharmacodynamic data with clinical outcome in the trials where samples were obtained is an important aspect in the further development of PARP inhibitors.

The side effects of PARP inhibitors as monotherapy include fatigue, nausea, and vomiting. However, when combined with chemotherapy, there are higher than expected hematologic toxicities seen in the trials with olaparib and veliparib, which required dose modification of the PARP inhibitor and/or the chemotherapy agent. Additional phase I trials that carefully titrate the PARP inhibitor with chemotherapy are needed to determine the optimal PARP inhibitor–chemotherapy drug combination in order to maximize efficacy and minimize side effects. Notably, iniparib did not potentiate the known toxicities associated with chemotherapy. This may be partially explained by the selective lethal synthesis of the C-nitroso intermediates from the prodrug iniparib by the tumor cells, as well as other cellular killing mechanisms elicited by the C-nitroso compounds [49].

With the striking activity of single-agent olaparib in the treatment of *BRCA*-associated cancers, the use of a PARP inhibitor for possible chemoprevention in *BRCA*-associated cancers has been proposed [50, 51]. Long-term safety data are needed before such a strategy is feasible because PARP-1 plays an important role in the cardiovascular system and long-term memory [52, 53]. Chronic inhibition of PARP-1 could also potentially lead to enhanced mutagenesis and secondary malignancies as demonstrated in a mouse model [54].

Resistance to PARP inhibitors is likely to occur after prolonged use. Secondary *BRCA* mutations or intragenic deletion have been reported as mechanisms of resistance to platinum compounds [55, 56] and olaparib [57] in *BRCA*-associated cancers. Another study reported upregulation of *Abcb1a/b* genes encoding P-glycoprotein efflux pumps after long-term treatment with olaparib in a genetically engineered mouse model for *BRCA1*-associated breast cancer. Such resistance was reversed by co-administration of tariquidar, a P-glycoprotein inhibitor [58].

## Conclusions

Results from the phase III trial of iniparib in combination with gemcitabine and carboplatin in metastatic TNBC are eagerly awaited. Phase III trials of olaparib in *BRCA*-associated breast cancer and veliparib in the same population are being planned, with an expected initiation in 2011 [59, 60]. The collective data from these large trials will help better characterize the subtypes of breast cancer that best respond to PARP inhibitors, in addition to *BRCA*-associated breast cancer and TNBC. The available data to date demonstrate that PARP inhibitors have encouraging activity as a single agent or combined with chemotherapy in the treatment of *BRCA*-associated breast cancer as well as in combination with chemotherapy in metastatic TNBC (Table 3). If the efficacy of these compounds is confirmed in phase III trials, PARP inhibitors are the first example of successful exploitation of a "synthetic lethality" strategy in oncology. Further studies are needed to identify additional biomarkers that can predict response to PARP inhibitors.

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- • Of importance
- •• Of major importance

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