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Breast Cancer (ML Telli, Section Editor)

Update on PARP Inhibitors in Breast Cancer

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Opinion statement

The single agent activity of PARP inhibitors (PARPi) in germline *BRCA* mutated (gBRCAm) breast and ovarian cancer suggests untapped potential for this new class of drug in breast cancer. The US Food and Drug Administration has approved three PARPi (olaparib, rucaparib, and niraparib) so far to treat certain ovarian cancers, including those with gBRCAm and olaparib for treatment of gBRCAm breast cancers. Several PARPi are now under clinical development for breast cancer in the various treatment settings. Recently, two phase III trials of olaparib (OlympiaD) and talazoparib (EMBRACA) demonstrated 3-month progression-free survival improvement with PARPi compared to physician's choice single agent chemotherapy in metastatic gBRCAm breast cancer. To date, PARPi seems less efficacious in metastatic breast cancer patients than those with *BRCA* mutated platinum-sensitive recurrent ovarian cancer, perhaps reflecting the biologic heterogeneity and low somatic *BRCA* mutation rate in breast cancer. The use of PARPi is gradually evolving, including combination strategies with chemotherapy, targeted agents, radiotherapy, or immunotherapy in women with and without gBRCAm. The role of predictive biomarkers, including molecular signatures and homologous recombination repair deficiency scores based on loss of heterozygosity and other structural genomic aberrations, will be crucial to identify a subgroup of patients who may have benefit from PARPi. An improved understanding of the mechanisms underlying PARPi clinical resistance will also be important to enable the development of new approaches to increase efficacy. This is a field rich in opportunity, and the coming years should

see a better understanding of which breast cancer patients we should treat with PARPi and where these agents should come in over the course of treatment.

Introduction

Over the past few decades, significant advances have been made in understanding the genetic causes of familial breast cancers, including cloning of the *BRCA1* and *BRCA2* genes in the mid-1990s [1]. The essential role of BRCA1 and BRCA2 proteins in homologous recombination repair (HRR), a high-fidelity DNA double-strand break (DSB) repair mechanism, has been extensively documented [2]. Loss of function of the BRCA proteins is thought to contribute to genetic instability, potentially leading to malignancy [3••]. *BRCA1* and *BRCA2* mutations account for about 10% of all breast cancers and about 30% of hereditary breast cancers [1]. Individuals who harbor germline *BRCA1* or *BRCA2* mutation (gBRCAm) are at much greater risk of developing breast and/or ovarian cancer over their lifetime: 45–65 and 15–40% for breast and ovarian cancer, respectively [4, 5]. A majority of patients with gBRCA1m that develop breast cancer have tumors that lack estrogen receptor (ER), progesterone receptor (PR), and do not have amplification of human epidermal growth factor 2 (HER2), so called triple negative breast cancer (TNBC). By contrast, only ~ 15% of sporadic breast cancers are TNBC [6•]. Most patients with gBRCA2m who develop breast cancer have tumors that express ER and/or PR in proportions similar to sporadic breast cancer [7, 8].

The seminal advance since the cloning and recognition of the relationship between gBRCAm and breast and ovarian cancers is the identification and application of new important molecular targets, poly-(ADP ribose) polymerase (PARP) family members, and other proteins involved in HRR [9, 10]. Of the 17 PARP family proteins, PARP1 and/or PARP2 are required to repair DNA single-strand breaks (SSBs) and PARP1 also is involved in repair of DSBs and replication fork injury [11]. The PARP-1 enzyme has been implicated in signaling DNA damage through its ability to recognize and rapidly bind to DNA SSBs; it mediates base excision repair by recruiting the scaffolding proteins, e.g., XRCC1, DNA ligase III, and DNA polymerase ß [12]. DNA-bound activated PARP-1 uses nicotinamide adenine dinucleotide (NAD+) to poly-ADPribosylate nuclear target proteins, at the site of DNA damage, including topoisomerases, histones, and PARP-1 itself, to signal the need for both DNA SSB and DSB repair. This observation suggests that inhibition of PARP-1 activity where HRR is compromised would lead to adverse consequences for the tumor cells. PARP inhibitor (PARPi) also traps PARP1 and PARP2 while in complex with damaged DNA, and trapped PARP prevents its participation in DNA repair, resulting in cytotoxic consequences for the cells [13]. This mechanism of action may be important to the clinical activity and toxicity of the PARPi class [13].

The clinical use of PARPi identified the integral role of *BRCA1* and *BRCA2* in maintaining functional high-fidelity DNA repair through HRR. The single agent PARPi activity in *BRCA* mutant ovarian cancer treatment suggests untapped potential for this new class in gBRCAm breast cancer. Additionally, there is a potential therapeutic role for PARPi in a wider subgroup of breast cancer that may have defective DNA repair, e.g., mutations in *ATM*, *ATR*, *PALB2*, or *CHEK2* [14]. Accumulating evidence suggests that further clinical exploration of PARPi as monotherapy or combinations is warranted in patients not only with gBRCAm-associated breast cancer, but also in breast cancer with HRR dysfunction [14]. Here, we briefly review the preclinical data and clinical development of PARPi and discuss its future development in breast cancer.

PARPi in breast cancer: preclinical evidence

The clinical utility of PARPi as monotherapy in gBRCAm-associated tumors is based on the concept of synthetic lethality, where neither PARP inhibition alone nor BRCA deficiency alone is lethal but the combination is [15]. In a series of

pivotal preclinical studies, PARPis were noted to cause selective cytotoxicity for in vitro and in vivo models of BRCA-deficient cells [16, 17]. Bryant et al. were the first to document this finding, showing that the PARPi NU1025 and AG14361 were profoundly cytotoxic in V-C8 (*BRCA2*-deficient) cells but did not affect V79 (*BRCA2*-expressing) cells [17]. They observed similar cytotoxic effects of NU1025 in the MCF7 and MDA-MB-231 breast cancer cell lines following siRNA-induced BRCA2 depletion in these cells [17]. Farmer and colleagues also reported that PARPi KU0058684 and KU0058948 exhibited particularly cytotoxic effects in mouse embryonic stem cell lines deficient in either BRCA1 or BRCA2 [16].

The concept of using PARPi as single agents to induce cell death through synthetic lethality represented a novel approach to cancer treatment but may not be the only mechanism by which PARPi could improve cancer therapy. When used in combination therapy, PARPi enhanced the effectiveness of conventional treatments by impairing the repair of damage caused by those agents (e.g., impeding repair of SSB induced by radiotherapy or platinum agents) [18–23]. Donawho et al. showed that the PARPi ABT-888 (veliparib) potentiated cytotoxicity of cisplatin and carboplatin and led to tumor regression in *BRCA1* and *BRCA2* mutated MX-1 breast xenograft model [21]. Other groups have reported similar findings supporting the efficacy of PARPi/platinum therapy in *BRCA1* and *BRCA2* deficient mammary tumors and in TNBC cell lines [18, 22, 23]. Additionally, other chemotherapeutics such as gemcitabine, temozolomide, and topoisomerase-1 inhibitors have been investigated in combination with PARPis in *BRCA*-mutated TNBC cell lines, yielding significant reduction in tumor cell replication and increased DNA damage [23–25]. Taken together, these preclinical studies have helped the development of clinical trials investigating the benefit of PARPi and platinum agents or other cytotoxic agents.

Recently, targeted agents, e.g., phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) inhibitors or cell cycle checkpoint regulators, have been explored preclinically and clinically in combination with PARPi [26, 27]. Combining a PARPi (olaparib or veliparib) with a PI3K inhibitor (NVP-BKM120) has shown synergistic cytotoxicity in both *BRCA1*-mutated and *BRCA* wild-type TNBC models [27, 28]. Proteins involved in cell cycle checkpoint pathways, particularly cell cycle checkpoint kinase (CHK)1 or WEE1, also emerged as therapeutic targets as the loss of cell cycle checkpoint control leads to the accumulation of DNA damage and ultimately cell death [29–31]. Booth et al. showed that combining any one of four different PARPis (olaparib, veliparib, rucaparib, NU1025) with a CHK1 inhibitor (CHK1i; AZD7762, LY2603618, UCN-01) increased SSBs and DSBs in both *BRCA* wild-type and *BRCA*-mutated breast cancer cell lines [24, 31]. Thus, utilizing a PARPi/CHKi strategy may have a broader clinical applicability in breast cancer, independent of gBRCAm status.

Targeting growth factor receptors is also under preclinical and clinical investigation [24]. The epidermal growth factor receptor (EGFR) is mutated in a variety of different cancers, including various subtypes of breast cancer [32]. EGFR-activating mutations often result in receptor amplification, which is targetable via monoclonal antibodies or small molecule tyrosine inhibitors [33, 34]. Sui et al. reported a markedly enhanced antitumor effect of PARPi/EGFR inhibitor therapy (olaparib and erlotinib) compared to each treatment alone in *BRCA* wild-type EGFR-overexpressing ovarian cancer xenograft models (A2780 cells). These results encourage the expanded use of this therapy to a subgroup of

breast cancer containing *EGFR* amplifications [35]. Furthermore, the insulin-like growth factor type 1 receptor (IGF-1R) is involved in tumorigenesis and shown to exhibit hyper-activation in *BRCA1*-mutation-associated breast cancers [36–38]. Preclinical studies have shown *BRCA1*-deficient breast and ovarian cancer cell lines to be particularly vulnerable to IGF-1R inhibitors (IGF-1Ri), and PARPi/IGF-1Ri combination therapy resulted in a synergistic cytotoxic effect on these cells [39]. However, despite these promising preclinical results, this approach has yet to be implemented in a clinical setting.

Many of the most significant advances in cancer therapy have recently aimed at stimulating the immune system to participate in tumor cell killing [40]. These approaches have expanded the fundamental role of PARPi in the treatment of cancer, as PARPi has immunomodulatory activity. Huang et al. showed that BMN 673 (talazoparib) significantly increased the number of CD8+ T cells and NK cells in the microenvironment and the production of IFN-gamma and TNF-alpha by lymphocytes in *BRCA1*-deficient ovarian cancer murine models (BR5FVB1-Akt) [41]. PARPi (olaparib, talazoparib or rucaparib) upregulated PD-L1 expression in breast cancer in vitro and in vivo models, partly due to inactivation of GSK3β [42]. Subsequent blockade of PD-L1 resensitized PARPi-treated cancer cells to T cell killing, yielding greater tumor regression with the combination therapy in breast cancer mouse models [42]. Taken together, these findings highlight the role of PARPi in cellular processes unrelated to DNA damage repair and emphasize the need for further investigation into the immunoregulatory effects of PARPi therapy in breast cancer.

Clinical development of PARPi in breast cancer

Five PARPis are in clinical development, olaparib, rucaparib, niraparib, talazoparib, and veliparib. The first three listed are the United States (US) Food and Drug Administration (FDA)-approved PARPis for specific indications in ovarian cancer. Several of PARPis are now under clinical development for breast cancer, with some showing clinical activity in gBRCAm breast cancer, and olaparib has recently been approved by the FDA for use in gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting. Overall, PARPis have been less efficacious in *BRCA* wild-type patients with breast cancer than in those with ovarian cancer, perhaps reflecting the biological heterogeneity and low somatic *BRCA* mutantion rate in breast cancer [43]. In gBRCAm recurrent ovarian cancer, PARPi activity correlates with platinum sensitivity [44]; higher response rates (RRs) were reported in platinum-sensitive recurrent gBRCAm ovarian cancer compared with platinum-resistant disease (approximately 48 vs. 28% overall RR) [45]. It is unclear whether platinum sensitivity plays the similar role in breast cancer setting.

PARPi therapy in breast cancer: clinical experiences

A number of clinical trials have reported partial or complete results of PARPi treatment in breast cancer patients, which are summarized in Table 1. PARPis have been studied in monotherapy and in combination with radiotherapy or cytotoxic chemotherapy [24]. The clinical benefit of combining PARPi with

Table 1. PARPi clinical trials with results

PARPi monotherapy trials	Phase	Patients	Dose and schedule	Common (> 10%) adverse events	Response in BC
Olaparib [46••] Fong 2009	I	Solid tumors ($n = 60$) BC ($n = 9$) with 3 gBRCAm carriers	Olaparib capsule 400 mg BID	G1/2: nausea, fatigue, vomiting, anemia G3/4: fatigue, thrombocytopenia	1 CR, 1 SD 7 mo in gBRCAm, 1 PR with unknown gBRCAm status
Olaparib [47] Tutt 2010	II	gBRCAm BC ($n = 27$)	Olaparib capsule 400 mg BID	G1/2: nausea, fatigue, vomiting G3/4: nausea, fatigue, vomiting, anemia	ORR 41% 1 CR, 10 PR
Olaparib [48] Gelmon 2011	II	OC and TNBC ($n = 91$) BC ($n = 26$); 10 gBRCAm carriers	Olaparib capsule 400 mg BID	G1/2: nausea, fatigue, vomiting, anorexia G3/4: none	ORR 0 PFS 1.8 mo PFS 3.6 mo in gBRCAm carriers
Olaparib [49] Kaufman 2015	II	gBRCAm solid tumors ($n = 298$) gBRCAm BC ($n = 62$)	Olaparib capsule 400 mg BID	G1/2: nausea, fatigue, vomiting, anorexia, anemia, headache, diarrhea, dyspepsia G3/4: anemia	ORR 12.9% SD ≥ 8 weeks 47% PFS 3.7 mo
Olaparib [50••] Robson 2017	III (OlympiaD)	gBRCAm HER2 negative BC: olaparib ($n = 205$) vs. chemotherapy ($n = 97$)	Olaparib tablet300 mg BID vs. chemotherapy[a]	G1/2: anemia, nausea, vomiting, fatigue, headache, cough G3/4: anemia	ORR 59.9% vs. 28.8% PFS 7 mo vs. 4.2 mo ($p < 0.001$)
Rucaparib [51] Drew 2016	II	gBRCAm OC ($n = 54$) and BC ($n = 23$)	Rucaparib IV and PO (92 mg/day to 600 mg BID)	G1/2: nausea, fatigue, headache, diarrhea G3/4: none	IV – SD 44% (8/18 BC) PO – SD ≥ 12 weeks 2% (1/5 BC)
Talazoparib [52] Litton 2016	II	gBRCAm BC ($n = 13$)	Talazoparib 1 mg/day for 2 mo followed by neoadjuvant chemotherapy	G1/2: neutropenia, anemia, nausea, fatigue G3/4: neutropenia	Tumor volume decrease in all 13 patients
Talazoparib [53] Turner 2017	II	gBRCAm BC ($n = 84$) Cohort 1: 49 pts. after platinum based therapy Cohort 2: 35 pts. after ≥ 3 non-platinum cytotoxic regimen	Talazoparib 1 mg/day	G1/2: anemia, fatigue, nausea, diarrhea, thrombocytopenia, neutropenia G3/4: anemia, thrombocytopenia, neutropenia	Cohort 1: 21% ORR Cohort 2: 37% ORR
Talazoparib [54] De Bono 2017	I	Solid tumors ($n = 110$) BC ($n = 22$) and 14pts were treated with RP2D	Talazoparib (0.025 mg–1 mg/day)	G1/2: fatigue, anemia, náusea, thrombocytopenia, alopecia, neutropenia G3/4: anemia, thrombocytopenia, neutropenia	ORR for pts. treated with RP2D: 50% (1 CR, 6 PR), 5 SD ≥ 24 weeks) All pts. had gBRCAm
Talazoparib [55] Litton 2017	III (EMBRACA)	gBRCAm HER2 negative BC talazoparib ($n = 287$) vs. chemotherapy ($n = 144$)	Talazoparib 1 mg daily vs. chemotherapy	G1/2: anemia, fatigue, neutropenia, nausea, headache, thrombocytopenia G3/4: anemia, neutropenia, thrombocytopenia	ORR 62.2% vs 27.2% PFS 8.6 mo vs 5.6 mo ($p < 0.001$)
Niraparib [56] Sandhu 2013	I		Niraparib 300 mg daily	G1/2: nausea, anemia, fatigue, thrombocytopenia,	2 PR in 4 gBRCAm carriers

Table 1. (Continued)

PARPi Combination trials	Phase	Patients	Schedule	Toxicity (>10%)	Response in BC
		Solid tumors ($n = 100$) BC ($n = 12$), with 4 gBRCAm carriers		constipation G3/4: anemia, thrombocytopenia	
Olaparib plus Paclitaxel [57] Dent 2013	I	TNBC ($n = 19$) unknown gBRCAm status	Olaparib capsules 200 mg BID and paclitaxel weekly 90 mg/m^2 Olaparib maintenance 400 mg BID (Cohort 2: G-CSF prophylaxis)	G1/2: diarrhea, fatigue, nausea G3/4: neutropenia, anemia	ORR 37%
Olaparib capsules plus Carboplatin [58] Lee 2014	I/Ib	gBRCAm ($n = 45$) with OC ($n = 37$) or BC ($n = 8$)	Olaparib capsules 400 mg BID (days 1–7) and carboplatin followed by olaparib maintenance	G1/2: nausea, fatigue, headache, GERD G3/4: neutropenia, thrombocytopenia, anemia	ORR 87.5% (1 CR, 6 PR)
Olaparib tablets plus Carboplatin [59] Lee 2017	I/Ib	OC ($n = 60$), UT ($n = 4$) and BC ($n = 14$) – 11 TNBC, 2 hormone receptor negative HER2[b] and 1 hormone receptor positive/HER2[b]	Olaparib tablets 100-200 mg BID (days 1–7) and carboplain followed by olaparib maintenance	G1/2:anemia, thrombocytopenia, nausea, fatigue, headache G3/4:lymphopenia, thrombocytopenia, neutropenia	N/A
Olaparib plus Cisplatin [60] Balmana 2014	I	Solid tumors ($n = 54$) BC ($n = 42$), with 17 gBRCAm carriers	Olaparib capsule 50–200 mg BID and cisplatin 60–75 mg/m^2 followed by olaparib maintenance	G1/2: nausea, fatigue, vomiting G3/4: neutropenia, anemia, lymphopenia	ORR 71% in gBRCAm group
Olaparib plus AZD5363 (AKTi) [61] Michalarea 2016	I	Solid tumors ($n = 53$) BC ($n = 16$), with 8 gBRCAm carriers	Olaparib tablets 300 mg BID and AZD 4/7 or 2/7 days	G1/2: nausea, anemia, fatigue, diarrhea, anorexia, mucositis G3/4: rash, anemia, diarrhea, vomiting, proteinuria	ORR 50% (4/8) gBRCAm and 1 sporadic TNBC
Rucaparib plus Cisplatin [62] Miller 2015	II (Hoosier Oncology BRE09–146)	gBRCAm or TNBC, residual tumor post neoadjuvant anthracycline and/or taxane ($n = 128$)	Cisplatin 75 mg/m^2 ± rucaparib IV 25-30 mg Days 1,2,3–4 cycles Rucaparib IV 30 mg or PO 100 mg weekly, 24 weeks	G1/2: nausea, neutropenia, fatigue, anorexia, anemia G3/4: neutropenia, fatigue	2-yr DFS Cisplatin 58.3% vs. Cisplatin [b]Rucaparib 63.1% ($p = 0.43$)
Rucaparib plus Carboplatin [63] Wilson 2017	I	Solid tumors ($n = 85$) BC ($n = 22$), with 7 gBRCAm	Rucaparib IV 12-24 mg then PO 80-360 mg and chemotherapy[c]	G1/2: nausea, fatigue, anemia, constipation, vomiting, diarrhea, neutropenia G3/4: thrombocytopenia, neutropenia, nausea, vomiting, anemia	1 CR; 1 PR in gBRCAm carriers for 3 mo; and SD unknown
Veliparib alone, or plus Carboplatin post PD [64] Somlo 2017	I/II	gBRCAm BC ($n = 71$) Phase I ($n = 27$), Phase II ($n = 44$)	Veliparib 400 mg BID (single agent); 150 mg BID (with carboplatin)	Monotherapy - G1/2: nausea, fatigue, vomiting, lymphopenia. G3/4: none G1/2: anemia, fatigue, lymphopenia, neutropenia, thrombocytopenia G3/4:	ORR Phase I 56% Phase II 14% in gBRCA1m ($n = 22$) and 36% in gBRCA2m ($n = 22$).

Table 1. (Continued)

				thrombocytopenia, anemia, neutropenia, lymphopenia	
Veliparib plus Carboplatin/Paclitaxel [65] Han 2018	II	gBRCAm BC ($n = 290$)	Veliparib 120 mg BID Days 1–7 or placebo, plus C/P or temozolomide	G1/2: neutropenia, thrombocytopenia, nausea G3/4: neutropenia, thrombocytopenia	PFS Veliparib 14.1 mo vs. 12.3 mo ($p = 0.227$) ORR Veliparib 77.8% vs. Placebo 61.3%; ($p = 0.027$)[d]
Veliparib plus Carboplatin/Paclitaxel [66] Rugo 2016	II	HER2negative BC ($n = 116$) Veliparib[b] C/P ($n = 72$) vs. C/P ($n = 44$)	Veliparib 50 mg BID plus C/P	G1/2: nausea, fatigue, neutropenia, anemia, thrombocytopenia, neuropathy G3/4: neutropenia, thrombocytopenia, anemia	In TNBC, pCR Veliparib[b] C/P 51% vs. C/P 26%

[a]Physicians choice single-agent (capecitabine, eribulin, or vinorelbine in 21-day cycles)
[b]Physicians choice single agent (capecitabine, eribulin, gemcitabine, or vinorelbine in 21-day cycle)
[c]Carboplatin, paclitaxel + carboplatin, pemetrexed + cisplatin, epirubicin + cyclophosphamide
[d] Arm with veliparib + temozolomide was inferior, PFS 7.4 mo and ORR 28.6%
"≥" greater than or equal
C/P carboplatin and paclitaxel, *gBRCAm* germline *BRCA* mutation, *OC* ovarian cancer, *BC* breast cancer, *UT* uterine cancer, *ORR* overall response rate, *PFS* progression-free survival, *CR* complete response, *PR* partial response, SD = stable disease, *RP2D* recommended phase 2 dose, *pCR* pathologic CR, *G* grade, *mo* months, *yr* year, *BID* twice daily, *pt* patients

cytotoxic chemotherapy or radiotherapy yielded improved efficacy; however, increased adverse events have been a challenge for further development [57, 58, 60]. In phase I/Ib studies of olaparib and carboplatin [58, 59], olaparib schedules had to be changed to interrupted use of the PARPi with carboplatin every 3 weeks, with resumption of continuous daily use of olaparib in the maintenance phase after stopping carboplatin. All other PARPi combination trials showed the increased hematological toxicity in the combination therapies, as well as fatigue and gastrointestinal toxicities [61–64, 66, 67].

Olaparib

Olaparib is the first US FDA and European Medicines Agency (EMA)-approved PARPi for use in gBRCAm ovarian cancer and now FDA approved for gBRCAm breast cancer [68, 69]. Olaparib was also granted breakthrough therapy designation by the US FDA for treatment of gBRCAm or *ATM*-mutated metastatic castration-resistant prostate cancer [68]. Olaparib is available in two types of formulations, capsule and tablets [70]. Comparative bioavailability studies demonstrated that 400 mg twice daily capsule formulation is equivalent to 200–250 mg twice daily tablet formulation [59, 71, 72]. Olaparib is rapidly absorbed, with peak plasma concentration of 1–3 h post-ingestion and mean half-life of 6.1 h [46••]. Good reviews have been published recently describing its biology and clinical development in ovarian cancer; therefore, it will not be summarized here [73–75]. In earlier studies, the clinical benefit of olaparib was observed in advanced breast cancer patients with gBRCAm [46••]. Olaparib activity was shown to be dose-dependent, with a reported RR of 41% with 400 mg twice daily vs. RR 22% with 100 mg twice daily in gBRCAm carriers with advanced/recurrent triple negative or hormone receptor positive breast cancer [47]. Recently, Robson et al. reported the findings of the randomized, open-label, phase III OlympiAD trial in which they compared olaparib alone with standard chemotherapy in patients with gBRCAm, HER2-negative, metastatic breast cancer [50••]. Two thirds of patients received one or two prior lines of chemotherapy for metastatic disease. They received olaparib (300 mg tablets twice daily) or standard 'physician's choice' chemotherapy (capecitabine, eribulin, or vinorelbine) with 2:1 randomization. Olaparib was clinically superior to the standard therapy with median progression-free survival (PFS; 7.0 vs. 4.2 months; $p < 0.001$) and RR (59.9 vs. 28.8%) [72]. The impact of prior exposure to platinum agents, whether PARPi induce cross-resistance to the subsequent chemotherapy such as other DNA damaging agents, and the long-term risks and benefits are unclear.

There are limited data on combination trials of PARPi and targeted therapies. Michalarea et al. reported preliminary data on the phase I trial of olaparib and an oral AKT inhibitor, AZD5363, in which 16 breast cancer patients were enrolled [61]. Four of eight gBRCAm breast cancer and one of eight sporadic TNBC had RECIST response to the combination therapy. Another phase I study of the PI3K inhibitor BKM120 and olaparib (300 mg tablets twice daily) was reported, in which 24 breast cancer patients (13 TNBC and 11 hormone receptor positive and HER2-negative) were enrolled, including 15 gBRCAm carriers [76]. Of the 18 evaluable patients, five (28%) had partial response and eight (44%) had stable disease. Among 12 gBRCAm carriers of these 18 evaluable patients, four had partial response and five had stable disease. More

recently, preliminary results of phase II MEDIOLA study were reported at the 40th San Antonio Breast Cancer Symposium. This single arm, phase II trial evaluated the combination of olaparib and durvalumab, a PD-L1 inhibitor in gBRCAm HER2-negative metastatic breast cancer patients. The combination therapy resulted in 80% (20/25) of disease control rate (defined by CR + partial response + stable disease) at 12 weeks, and 48% (12/25) maintained disease control rate at 28 weeks, with unconfirmed ORR 52% (13/25) [77]. It is unclear how much clinical activity is from PARPi and how much activity is from immune checkpoint inhibition. Future use and clinical trials should take into consideration that immunotherapies may elicit a better immune response if used while the patient is still immunocompetent at earlier stages of the disease course [78].

Talazoparib

Talazoparib is an oral PARPi with a greater PARP-DNA trapping activity compared to other PARPis in preclinical settings [79, 80]. Median peak plasma concentration is 1–2 h post-dose, with mean half-life of 50 h and steady state reached around 2 weeks in most patients taking a recommended phase 2 dose (RP2D) of 1 mg/daily [81]. Early findings from a pilot study of talazoparib demonstrated decrease in tumor volume (median – 78% [range – 30 to – 98%] in all early-stage gBRCAm breast cancer patients ($n = 13$), treated with talazoparib for 2 months followed by standard neoadjuvant chemotherapy [52]. This study is currently ongoing with a target accrual of 20 patients. More recently, the results of the phase III trial of talazoparib in breast cancer (EMBRACA) were presented at the 40th San Antonio Breast Cancer Symposium. This is the second of four-ongoing phase III clinical trials of PARPis in advanced breast cancer to report findings. gBRCAm carriers with HER2-negative metastatic disease were randomized 2:1 to talazoparib ($n = 287$) vs. physician's choice chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine; $n = 144$). The median PFS was 8.6 months for talazoparib arm vs. 5.6 months for chemotherapy arm (HR = 0.542, $p < 0.0001$). Overall RR (ORR) was also better in talazoparib arm, with 62.6 vs. 27.2% (HR = 4.99, $p < 0.0001$) [55]. About 55% of patients in the talazoparib arm experienced grade 3 or 4 hematologic adverse events vs. 38% of those in the physician's choice chemotherapy arm. It appears that equitoxic doses of high trapping PARPi may result in relatively similar clinical activity to those with less trapping activity [82] and DNA-PARP trapping may also be associated with enhanced toxicity, most often hematologic adverse events.

Veliparib

Veliparib is an oral PARPi-1/2 with a RP2D of 400 mg twice daily when used as single agent [83]. Median peak plasma concentration is 0.5–1.5 h post-dose, with a short half-life, mean of 5 h [84]. Clinical trials of veliparib, either single agent or combinations, are now ongoing for breast cancer in various settings (Table 2). The I-SPY2 trial is a multicenter, phase II trial using Bayesian adaptive randomization as a platform for high-risk patients with stage II/III breast cancer. The patients receive a backbone of standard neoadjuvant therapy, and investigational regimens are added to evaluate pathological complete response (pCR) as a primary endpoint [66]. One of the experimental arms included PARPi, veliparib; patients were randomized to the combination of veliparib and

Table 2. Ongoing PARPi trials

Drug company	Year opened	Phase	Name	NCT number	Status
Olaparib AztraZeneca	2016	II-III	Randomized, Phase II/III, 3 Stage Trial to Evaluate the Safety and Efficacy of the Addition of Olaparib to Platinum-based Neoadjuvant Chemotherapy in Breast Cancer Patients with TNBC and/or gBRCA. (PARTNER)	NCT03150576	recruiting
	2014	III	Olaparib as Adjuvant Treatment in Patients with Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer. (OlympiA)	NCT02032823	recruiting
	2012	I	Phase I Study of the Oral PI3kinase Inhibitor BKM120 or BYL719 and the Oral PARP Inhibitor Olaparib in Patients with Recurrent Triple Negative Breast Cancer or High Grade Serous Ovarian Cancer	NCT01623349	active, not recruiting
	2014	Ib	A Phase Ib Study of the Oral PARP Inhibitor Olaparib With the Oral mTORC1/2 Inhibitor AZD2014 or the Oral AKT Inhibitor AZD5363 for Recurrent Endometrial, Triple Negative Breast, and Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	NCT02208375	active, not recruiting
	2013	I	Olaparib Dose Escalation in Combination With High Dose Radiotherapy to the Breast And regional Lymph Nodes in Patients With Breast Cancer	NCT02227082	recruiting
	2010	I-II	Phase I/II Study of Cediranib and Olaparib in Combination for Treatment of Recurrent Papillary-Serous Ovarian, Fallopian Tube, or Peritoneal Cancer or for Treatment of Recurrent Triple-Negative Breast Cancer	NCT01116648	active, not recruiting
	2016	II	A Phase 2 Study of Cediranib in Combination With Olaparib in Advanced Solid Tumors	NCT02498613	recruiting
	2015	I-II	Phase I/II Study of the Anti-Programmed Death Ligand-1 Antibody MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers	NCT02484404	recruiting
	2016	I-II	A Phase I/II Study of MEDI4736 (Anti-PD-L1 Antibody) in Combination With Olaparib (PARP Inhibitor) in Patients With Advanced Solid Tumors	NCT02734004	active, not recruiting
	2017	II		NCT03167619	open, not yet recruiting

Table 2. (Continued)

Drug company	Year opened	Phase	Name	NCT number	Status
			Phase II Multicenter Study of Durvalumab and Olaparib in Platinum tReated Advanced Triple Negative Breast Cancer (DORA)		
Rucaparib Clovis Oncology	2016	II	A Single Arm, Open-label, Phase II Study to Assess the Efficacy of Rucaparib in Metastatic Breast Cancer Patients With a BRCAness Genomic Signature (RUBY)	NCT02505048	recruiting
	2016	II	Window study of the PARP inhibitor rucaparib in patients with primary triple negative or BRCA1/2 related breast cancer (RIO)	Open in UK (ISRCTN 92154110 CRUK/12/034)	recruiting
Veliparib AbbVie	2016	II	Phase II Multiple-Arm, Open-Label, Randomized Study of PARP Inhibition (Veliparib; ABT-888) and Anti-PD-L1 Therapy (Atezolizumab; MPDL3280A) Either Alone or in Combination in Homologous DNA Repair (HDR) Deficient Triple Negative Breast Cancer (TNBC)	NCT02849496	recruiting
	2016	II	Phase II Randomized Placebo-Controlled Trial of Cisplatin With or Without ABT-888 (Veliparib) in Metastatic Triple-Negative Breast Cancer and/or BRCA Mutation-Associated Breast Cancer	NCT02595905	recruiting
	2014	III	A Phase 3 Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the PARP Inhibitor Veliparib (ABT-888) in HER2 Negative Metastatic or Locally Advanced Unresectable BRCA-Associated Breast Cancer	NCT02163694	recruiting
	2009	II	A Phase 2 Study of ABT-888 and Temozolomide for Metastatic Breast Cancer and an Expansion Cohort in BRCA1/2 Mutation Carriers	NCT01009788	active, not recruiting
	2012	II	A Randomized, Phase 2 Study of the Efficacy and Tolerability of Veliparib in Combination With Temozolomide or Veliparib in Combination With Carboplatin and Paclitaxel Versus Placebo Plus Carboplatin and Paclitaxel in Subjects With BRCA1 or BRCA2 Mutation and Metastatic Breast Cancer	NCT01506609	active, not recruiting
Niraparib Tesaro	2016	I-II	Phase 1/2 Clinical Study of Niraparib in Combination With Pembrolizumab (MK-3475) in Patients With Advanced or Metastatic Triple-Negative Breast	NCT02657889	recruiting

Table 2. (Continued)

Drug company	Year opened	Phase	Name	NCT number	Status
			Cancer and in Patients With Recurrent Ovarian Cancer (TOPACIO)		
	2013	III	A Phase III, Randomized, Open Label, Multicenter, Controlled Trial of Niraparib Versus Physician's Choice in Previously-treated, HER2 Negative, Germline BRCA Mutation-positive Breast Cancer Patients (BRAVO)	NCT01905592	active, not recruiting
	2017	II	A Feasibility Study of Niraparib for Advanced, BRCA1-like, HER2-negative Breast Cancer Patients: the ABC Study	NCT02826512	open, not yet recruiting
Talazoparib Pfizer	2017	I-Ib	A Phase 1b/2 Study To Evaluate Safety And Anti Tumor Activity Of Avelumab In Combination With The Poly(Adenosine Diphosphate [Adp]-Ribose) Polymerase (Parp) Inhibitor Talazoparib In Patients With Locally Advanced Or Metastatic Solid Tumors	NCT03330405	recruiting
	2013	III	A Phase 3, Open-label, Randomized Parallel,2-arm, Multi-center Study Of Talazoparib(Bmn 673) Versus Physician's Choice In Germline Brca Mutation Subjects With Locally Advanced And/or Metastatic Breast Cancer, Who Have Received Prior Chemotherapy Regimens For Metastatic Disease	NCT01945775	active, not recruiting
	2015	II	A Pilot Study of Talazoparib as a Neoadjuvant Study in Patients With a Diagnosis of Invasive Breast Cancer and a Deleterious BRCA Mutation	NCT02282345	recruiting

chemotherapy (carboplatin and paclitaxel, followed by doxorubicin plus cyclophosphamide) or standard chemotherapy (paclitaxel alone, followed doxorubicin plus cyclophosphamide) [66]. Patients with HER2-negative breast cancer, with either hormone receptor positive or negative, were enrolled in this part of the I-SPY trial. pCR rates were 51% in veliparib and carboplatin arm, as opposed to 26% in the standard chemotherapy arm in which 17% of patients had deleterious gBRCAm in the experimental arm vs. 5% in the control arm [66]. In a similar way, the phase III BrighTNess study evaluated the addition of carboplatin with and without veliparib to the standard neoadjuvant combination of paclitaxel followed by doxorubicin and cyclophosphamide in 634 TNBC patients. pCR rates increased significantly with the use of carboplatin (53 and 58% in the two arms offering carboplatin vs. 31% without carboplatin), while veliparib added no further benefit to chemotherapy [54].

A phase II trial also enrolled 290 gBRCAm patients with locally advanced or metastatic breast cancer for treatment with the combination of carboplatin and paclitaxel with and without veliparib or a third arm with veliparib and temozolomide [65]. The primary endpoint of PFS was similar between the arms offering carboplatin and paclitaxel (14.1 months with veliparib vs. 12.3 months with placebo, $p = 0.227$). The ORR was increased by veliparib compared to placebo (77.8 vs. 61.3%, respectively, $p = 0.027$), without impacting the OS (28.3 vs 25.9 months, respectively, $p = 0.156$) [65]. Veliparib and temozolomide alone were inferior to the carboplatin and paclitaxel containing arms in ORR, PFS, and OS.

Rucaparib

Rucaparib is a second FDA-approved oral PARPi for use in gBRCAm and somatic *BRCA*-mutated advanced ovarian cancer [85]. The median peak plasma concentration is reached in 1.9 h and mean half-life is 17–19 h after a RP2D of 600 mg twice daily [86]. Additionally, an intravenous (IV) formulation of rucaparib was investigated in breast cancer patients. Drew et al. reported stable disease only in 44% (8/18) of metastatic breast cancer patients with gBRCAm, treated with IV rucaparib at dose of 18 mg/m^2 [51]. The phase I trial of IV rucaparib in combination with chemotherapy (carboplatin, paclitaxel and carboplatin, pemetrexed and cisplatin, or epirubicin and cyclophosphamide) resulted in one CR and one partial response out of seven gBRCAm carriers, in a total of 22 metastatic breast cancer patients enrolled. No further details on clinical or histological characteristics were described in this trial which included other solid tumor patients [63]. The single arm, phase II window of opportunity RIO trial also assesses rucaparib efficacy and biomarkers in sporadic TNBC and gBRCAm breast cancer patients prior to commencing primary neoadjuvant treatment. The primary endpoint is Ki67 response defined as ≥ 50% fall from baseline to end of rucaparib treatment [87] and results are awaited.

The Hoosier Oncology BRE09-146 phase II trial randomized 128 TNBC or known gBRCAm patients with residual disease post-neoadjuvant therapy with anthracycline or taxane to cisplatin alone or cisplatin combined with rucaparib [62]. The primary endpoint of 2-year disease-free survival (DFS) was similar between the two arms (58.3% with cisplatin and 63.1% with cisplatin and rucaparib, $p = 0.43$). The presence of gBRCAm had no impact in those findings which was partly due to the lower dose used than RP2D of rucaparib and the

small sample number ($n = 22$) of gBRCAm patients enrolled in the trial [62].

Niraparib

Niraparib is a recently FDA-approved PARPi for unselected platinum-sensitive recurrent ovarian cancer patients, with a RP2D of 300 mg daily [88]. Median peak plasma concentration is reached around 3 h post-dosage. The mean elimination half-life of niraparib is 36 h, after daily 300-mg doses [88]. In the phase I study evaluating niraparib in solid tumors, 22 of the 100 patients had metastatic breast cancer, and 2 partial responses were seen in 4 breast cancer patients with gBRCAm, no details of histological subtypes were reported for these 22 breast cancer patients [56].

Initial results from phase I part of TOPACIO trial were recently presented, with good tolerability and RP2D for niraparib in combination with pembrolizumab for treatment of patients with metastatic TNBC and ovarian carcinoma [89]. From the 14 patients enrolled in the phase I, 5 had TNBC and the best response in this group was seen in one *BRCA* wild-type patient with stable disease for 10 months.

Table 2 summarizes ongoing clinical trials using PARPi.

Safety of single agent PARPi

The side effect profile of PARPi monotherapy presents quite uniformly as gastrointestinal (nausea, vomiting, anorexia, diarrhea), hematological (anemia, thrombocytopenia, neutropenia) adverse events and fatigue. Notably, some adverse events are more commonly observed (> 10%) with certain PARPi, e.g., rucaparib (hepatotoxicity) and niraparib (thrombocytopenia) [90, 91]. It is possible that some differences in the "off-target" profile of different PARPis might contribute to adverse side effects [92]. The potential long-term increased risk of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) has been observed in < 1% of patients enrolled in clinical trials so far [46••, 49, 88]. Most patients in those trials were heavily pretreated, making the exact contribution of PARPi in the development of MDS or AML difficult to assess although it is possible that DSBs caused by PARPi may be accumulated in normal tissues, e.g., bone marrow. Careful hematological evaluation and monitoring for second hematological malignancies are warranted.

Future directions

The marked benefit of PARPi in patients with gBRCAm has validated gBRCAm as a predictive biomarker for PARPi response in breast cancer patients. At present, it remains unclear how to best identify breast cancer patients who will respond better to PARPi beyond gBRCAm status. Although tumor phenotypes can provide some predictions, as evidenced by responses of sporadic TNBC to PARPi monotherapy, the RRs are lower than those with gBRCAm breast or ovarian cancer [43, 93]. Other forms of HRR dysfunction, such as mutations in *ATM*, *ATR*, *PALB2*, or *CHEK2*, also need further clinical investigations for PARPi in breast cancer treatment settings. Another opportunity for PARPi is the treatment of breast cancer patients with brain metastasis. PARPis (olaparib, veliparib, niraparib) have been described as potentially penetrating the blood-brain barrier [94–96], which increases their possible clinical utility in brain

metastases-prone TNBC.

To date, many studies have been reported describing the mechanisms of action of PARPi, as well as mechanisms of clinical resistance of PARPi, which were not described in detail here. Some of resistance mechanisms are associated with reversion mutations in *BRCA1* or *BRCA2* gene, as well as inactivation of DNA repair proteins, e.g., 53BP1 and REV7, or increased activity of RAD51, all known to restore HRR function [2, 97, 98]. The combination therapies would be the appropriate next steps to mitigate the resistance by using two distinct treatments and also to potentiate PARPi activity. Among many PARPi combination trials, our phase 2 basket trial of durvalumab and olaparib is now enrolling TNBC patients with and without gBRCAm to examine the role of neoantigen expression and changes in immune microenvironment induced by PARPi (NCT02484404).

Lastly, it would be critical to design and interpret clinical trials based on the biological hypothesis and robust preclinical data. Understanding more about the molecular abnormalities involved in HRR-deficient tumors, exploring novel therapeutic trial strategies and drug combinations, and defining potential predictive biomarkers, is necessary to rapidly advancing the field of PARPi therapy for breast cancer. This is a field rich in opportunity, and the coming years should see a better understanding of which breast cancer patients we should treat with PARPi and where these agents should come in over the course of treatment.

Compliance with Ethical Standards

Conflict of Interest

Alexandra S. Zimmer, Mitchell Gillard, Stanley Lipkowitz, and Jung-Min Lee declare they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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