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PARP Inhibitors for Breast Cancer Treatment
A Review

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IMPORTANCE Poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors have revolutionized the treatment of patients with germline *BRCA1/2*-associated breast cancer, representing the first targeted therapy capable of improving outcomes in patients with hereditary tumors. However, resistance to PARP inhibitors occurs in almost all patients.

OBSERVATIONS This narrative review summarizes the biological rationale behind the use of PARP inhibitors in breast cancer, as well as the available evidence, recent progress, and potential future applications of these agents. Recent studies have shown that the benefit of PARP inhibitors extends beyond patients with germline *BRCA1/2*-associated metastatic breast cancer to patients with somatic *BRCA1/2* variants and to those with germline *PALB2* alterations. Moreover, these agents proved to be effective both in the metastatic and adjuvant settings. However, patients with metastatic breast cancer usually do not achieve the long-term benefit from PARP inhibitors observed in other tumor types. Mechanisms of resistance have been identified, but how to effectively target them is largely unknown. Ongoing research is investigating both novel therapeutics and new combination strategies to overcome resistance. PARP1-selective inhibitors, by sparing the hematological toxic effects induced by the PARP2 blockade, are promising agents to be combined with chemotherapy, antibody-drug conjugates, and other targeted therapies.

CONCLUSIONS AND RELEVANCE Although the efficacy of PARP inhibitors is well established, many questions persist. Future research should focus on identifying predictive biomarkers and therapeutic strategies to overcome resistance. Integrating well-designed translational efforts into all clinical studies is thereby crucial to laying the groundwork for future insights from ongoing research.

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Familial breast cancer has been known since the 19th century,[1] though the *BRCA1* gene was only discovered in 1990.[2,3] In 1994, both *BRCA1* and *BRCA2* genes were cloned.[4] Remarkably, this happened when almost nothing was known about the human genome, at the very dawning of genomics technologies.

The discovery of *BRCA1* and *BRCA2* opened several lines of research to unveil how to prevent and treat *BRCA*-associated tumors. For more than 20 years, however, the identification of a germline *BRCA1/2 (gBRCA1/2)* pathogenic variant (hereafter, *gBRCA* variant) has affected mostly screening and surgical procedures to manage the risk of subsequent tumors, while systemic therapies for already diagnosed *BRCA*-associated tumors were not different from those for sporadic tumors.

Agents targeting poly(adenosine diphosphate–ribose) polymerase (PARP) were first investigated in combination with chemotherapy and radiation therapy following preclinical data that showed synergistic activity, but these agents were soon abandoned due to unfavorable toxic effects.[5] In 2014, olaparib, a PARP inhibitor, was approved for patients with advanced ovarian cancer, becoming the first drug available specifically for a hereditary form of cancer. Since then, 3 additional PARP inhibitors (ie, talazoparib, rucaparib, and niraparib) have been approved across different cancer types, and olaparib has recently entered the adjuvant space for patients with *gBRCA1/2*–associated high-risk breast cancer. However, the population of patients with breast cancer who derive a substantial benefit from PARP inhibitors is still limited. To date, several lines of research are ongoing to understand how to expand the efficacy of PARP inhibitors beyond tumors harboring *gBRCA1/2* variants, how to develop effective combination strategies, and how to reduce toxic effects (**Figure 1**).

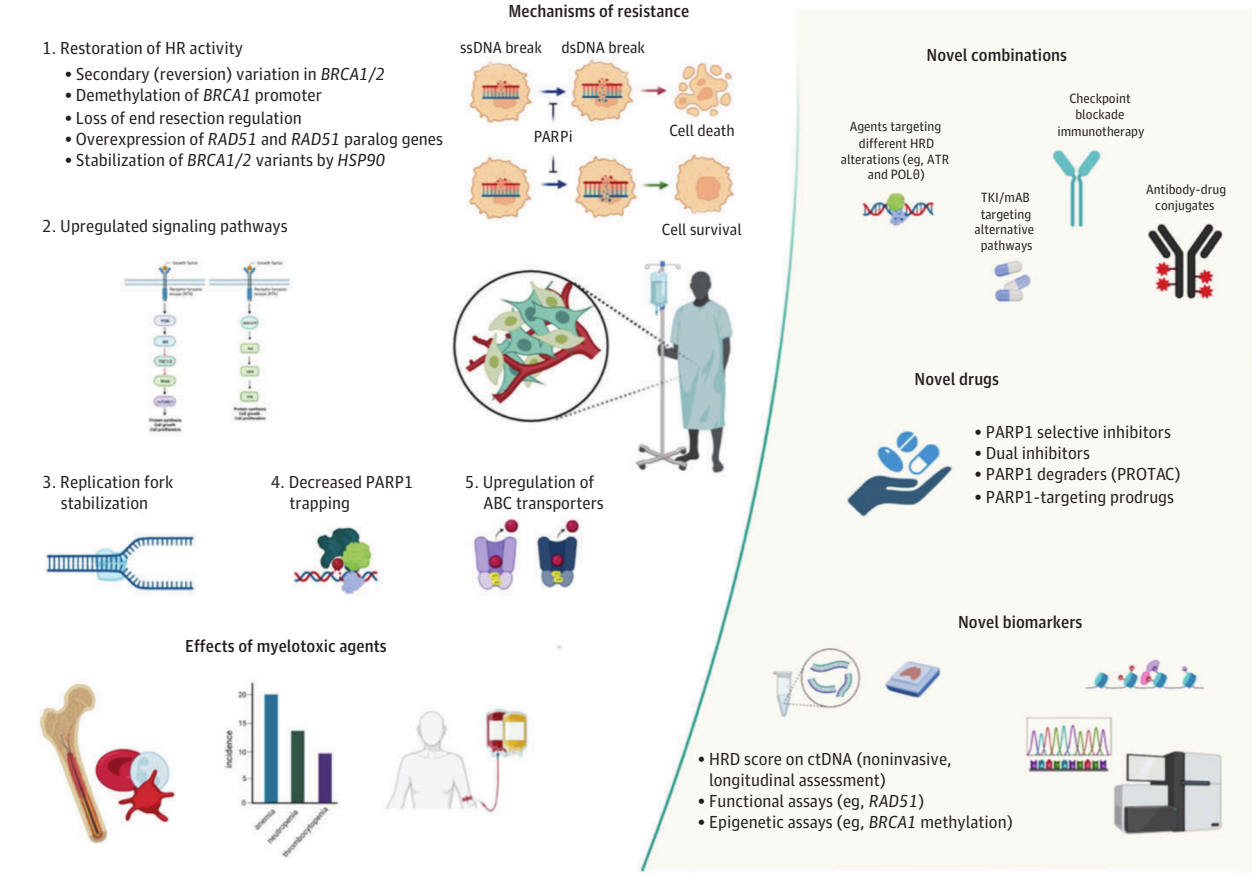
Discussion

Mechanism of Action of PARP Inhibitors

The Role of PARP in Tumors with Germline *BRCA1* and *BRCA2* Variants

DNA damage repair (DDR) mechanisms are essential pathways to fix DNA breaks. As multiple exogenous and endogenous factors con-

Figure 1. Limitations and Future Directions of PARP Inhibitors for Breast Cancer



The efficacy of PARP inhibitors in patients with breast cancer is limited by the development of mechanisms of resistance and by the frequent occurrence of adverse effects. Many mechanisms of resistance have been characterized, including restoration of homologous recombination activity through a variety of potential processes, upregulation of alternative signaling pathways (eg, RAS or PI3K/AKT/mTOR pathway), mitigation of the replication stress via replication fork stabilization, decreased PARP1 trapping, and upregulation of ABC transporters. Novel strategies are under investigation to both overcome resistance to PARP inhibitors and reduce toxic effects, such as new drug combinations and innovative medications with better tolerability. Ongoing research efforts are also uncovering novel biomarkers to identify additional patients who may benefit from these agents. ctDNA indicates circulating tumor DNA; dsDNA, double-strand DNA; HR, homologous recombination; HRD, homologous recombination deficiency; mAB, monoclonal antibody; PROTAC, proteolysis-targeting chimera; TKI, tyrosine kinase inhibitor; ssDNA, single-strand DNA.

stantly induce tens of thousands of DNA breaks every day, these complex machineries are key checkpoints to guarantee cell integrity and prevent the initiation of malignant neoplasm. Many DDR pathways have been characterized, and they are involved in different types of DNA damage, such as single-strand or double-strand breaks, base damage, bulky adducts, crosslinks, or replication lesions.[6]

BRCA1 and *BRCA2* are tumor suppressor genes encoding 2 key proteins involved in the homologous recombination repair (HRR) pathway that rely on the undamaged chromosome as the template for error-free damage reversal and have a crucial role in repairing double-strand breaks. A single copy of the *BRCA1* or *BRCA2* gene is sufficient to repair DNA breaks, and a second loss or double hit is needed to impair this pathway. When this happens, the repair of double-strand breaks shifts toward the more error-prone nonhomologous end-joining repair pathway that, unlike HRR, links the break ends without the need for a homologous template.[7]

PARP proteins are a family of nuclear enzymes involved in multiple DDR processes. PARP1 and PARP2 are the most abundant in human cells, and PARP1 is the most involved in DNA repair. After detecting single-strand or double-strand breaks, PARP binds to DNA breaks, recruits DDR components that cooperate to stabilize the replication fork, and allows for DNA repair.[8]

In 2005, 2 back-to-back articles showed how this defect may be exploited therapeutically through a mechanism called *synthetic lethality*, which refers to tumor-specific cell death induced by the simultaneous impairment of alternative DDR pathways.[9,10] In individuals with *gBRCA1/2* alterations, PARP inhibition leads to the impairment of alternative DDR pathways and thus to irreparable genomic damage and cell death.[9,10] Two major mechanisms of action have been described for PARP inhibitors: catalytic inhibition, by competing with NAD+ binding, and PARP trapping, by generating PARP-DNA complexes that block the replication fork and cause its collapse.[8]

PARP Inhibition Beyond *gBRCA1/2* Variants: Homologous Recombination Deficiency

Homologous recombination is a multifactorial process involving many different proteins beyond BRCA1 and BRCA2. Genomic alterations affecting genes encoding for these proteins may impair HRR and become a target of synthetic lethality for PARP inhibitors as well as other DDR-targeting agents.[11] Analogously, epigenetic alterations, such as *BRCA1* gene promoter methylation, may affect these genes and lead to similar HRR misfunctioning.[12,13] Altogether, these alterations are responsible for a phenotype called *BRCAness* or homologous recombination deficiency (HRD), which identifies sporadic cancers with genomic, transcriptomic, or epigenetic alterations that impair the homologous recombination pathway similar to tumors from carriers of *gBRCA1/2* variants.[14] As for *BRCA1/2*, a double hit or biallelic inactivation is required to impair this pathway. A pan-cancer analysis of the Cancer Genome Atlas identified this biallelic inactivation in homologous recombination–related genes in approximately 5% of all tumors, which was found more often in breast (10%) and ovarian (25%) cancers.[15] Somatic *BRCA1* and *BRCA2* genetic alterations are estimated in approximately 2.5% of sporadic tumors, whereas *BRCA1* promoter methylation is reported in 11% to 14% of sporadic tumors.[12,13]

However, it is known that HRD tumors may acquire genomic alterations that lead to the restoration of homologous recombination function, such as secondary *BRCA1* or *BRCA2* mutations (reverse mutations)[16] or demethylation of the *BRCA1* promoter.[17] In this dynamic situation, the role of HRD may be questioned by the static nature of modern assays used to measure it, as most of them measure the consequences of HRD, in terms of genomic scars.[18] Assays capturing the functional status of HRR may thus better predict response to PARP inhibitors. For instance, a novel assay measuring *RAD51* foci via immunofluorescence has proved to identify homologous recombination–proficient tumors misclassified as HRD by mutation signatures and to better correlate with PARP-inhibitor sensitivity.[19]

PARP Inhibition and Breast Cancer: Clinical Evidence

Deleterious germline alterations in *BRCA1/2* genes are detected in approximately 5% of unselected patients with breast cancer.[20,21] Higher frequency has been reported in patients with triple-negative breast cancer (TNBC), family history of breast or ovarian cancer, younger age, and Ashkenazi Jewish ancestry.[22] Patients carrying *gBRCA1* variants have a higher incidence of TNBC, while carriers of *gBRCA2* variants tend to develop estrogen receptor–positive (ER-positive) breast cancer.[23] Several PARP inhibitors have been developed and investigated in patients with breast cancer. Results from major trials are summarized in **Table 1**,[24-31] whereas the most frequent toxic effects caused by these agents are outlined in **Figure 2**.

Advanced Setting

In the phase 3 OlympiAD trial, olaparib improved progression-free survival (PFS) (hazard ratio [HR], 0.58 [95% CI, 0.43-0.80]; $P < .001$), doubled the objective response rate (ORR) (59.9% vs 28.8%) and had a more favorable safety profile compared with the treatment of physician's choice in patients with *gBRCA1/2* variants pretreated with up to 2 lines of chemotherapy for metastatic breast cancer.[25] Although there was no survival difference between the 2 treatment arms (HR, 0.90 [95% CI, 0.66-1.23]; $P = .51$),[24] an exploratory analysis showed a benefit favoring olaparib when administered as first-line therapy.[42] In the phase 3 EMBRACA trial, talazoparib improved PFS (HR, 0.54 [95% CI, 0.41-0.71]; $P < .001$) and ORR (62.6% vs 27.2%) compared with the treatment of physician's choice in carriers of *gBRCA1/2* variants pretreated with up to 3 chemotherapy regimens.[26] Also, talazoparib did not improve overall survival (HR, 0.85 [95% CI, 0.67-1.07]; $P = .17$).[27] In both trials, a significant improvement in health-related quality of life and a delay in time to deterioration was observed for patients receiving PARP inhibitors.[43,44]

The combination of PARP inhibitors and chemotherapy has synergistic activity in preclinical models.[45] Although this was also verified in clinical studies, most of them closed early because of intolerable toxic effects, particularly hematological.[5] The only exception among first-generation PARP inhibitors was veliparib, which, likely due to the lower trapping power and better tolerability, proved to be safe and active when combined with carboplatin and paclitaxel in the phase 2 BROCADE study.[46] In the confirmatory phase 3 BROCADE3 trial, the same triplet improved PFS compared with chemotherapy (HR, 0.71 [95% CI, 0.57-0.88]; $P = .002$).[28] Mature survival data are awaited, although preliminary results showed a numerical advantage for the veliparib arm.[28] Continuation of single-agent veliparib/placebo in patients who discontinued chemotherapy without progression was allowed, and veliparib maintenance was superior to placebo in a post hoc exploratory analysis.[47]

As the activity of PARP inhibitors relies on synthetic lethality in the context of an impaired HRR pathway, these agents have been also investigated in HRD or BRCAness tumors without *gBRCA1/2* alterations. The evidence accumulated so far failed to show a benefit, suggesting a biological difference between tumors driven by *gBRCA1/2* alterations and most other HRR alterations, with the exception of germline *PALB2* (*gPALB2*) and possibly somatic *BRCA1/2* (*sBRCA1/2*) alterations. In the TBCRC 048 study, olaparib led to a high ORR in patients with *gPALB2* (82%) or *sBRCA1/2* (50%) alterations, but no responses among patients with *ATM*-associated or *CHEK2*-associated tumors.[27] Similarly, no activity was observed with single-agent talazoparib beyond *gBRCA1/2* except for carriers of *gPALB2* in a phase 2 study.[30] In the RUBY trial,[48] only 5 of 40 patients (13.5%) with s*BRCA1/2* alterations or *HRD*-positive metastatic breast cancer derived a clinical benefit from rucaparib. Further investigation is needed to identify predictive biomarkers among patients who may benefit from PARP inhibitors beyond *gBRCA1/2* and *gPALB2* status.

Early Setting

In the phase 2 NEOTALA trial, 24-week neoadjuvant talazoparib led to a pathologic complete response (pCR) rate of 53% in carriers of *gBRCA1/2* variants with TNBC.[35] This is similar to what was achieved with anthracycline-taxane–based neoadjuvant regimens, prior to the use of immune checkpoint inhibitors. Similarly, neoadjuvant niraparib led to a 40% pCR rate in a small pilot study including both ER-positive and TNBC.[49] Additional phase 2 studies testing single-agent neoadjuvant PARP inhibitors are ongoing (NCT05498155[50] and NCT05582499[51]).

Following reassuring safety data seen in the advanced setting, the combination of veliparib plus chemotherapy has been tested also in the early-stage setting. However, a similar pCR rate and event-

Table 1. Key Completed Clinical Trials Investigating PARP Inhibitors in Patients With Breast Cancer

Study	Phase	Primary end point	Population	Treatment arms (No. patients)	Results	Comments
Metastatic setting, single agents						
OlympiAD[24,25]	3	PFS	Carriers of *gBRCA1/2* variants with ERBB2-negative tumors; ≤2 prior CT lines for MBC	Olaparib (205) vs treatment of physician's choice (97) (capecitabine, eribulin, vinorelbine)	Median PFS, 7.0 vs 4.2 mo (HR, 0.58 [95% CI, 0.43-0.80]; *P* < .001) ORR, 59.9% vs 28.8% Median OS, 19.3 vs 17.1 mo (HR, 0.90 [95% CI, 0.66-1.23]; *P* = .51) Median OS (first-line setting), 22.6 vs 14.7 mo	Led to regulatory approval
EMBRACA[26,27]	3	PFS	Carriers of *gBRCA1/2* variants with ERBB2-negative tumors; ≤2 prior CT lines for MBC	Talazoparib (287) vs treatment of physician's choice (144) (capecitabine, eribulin, gemcitabine, or vinorelbine)	Median PFS, 8.6 vs 5.6 mo (HR, 0.54 [95% CI, 0.41-0.71]; *P* < .001) ORR, 62.6% vs 27.2% Median OS, 19.3 vs 19.5 mo (HR, 0.85 [95% CI, 0.67-1.07]; *P* = .17)	Led to regulatory approval
BROCADE3[28]	3	PFS	Carriers of *gBRCA1/2* variants with ERBB2-negative tumors; ≤2 prior CT lines for MBC	Carboplatin + paclitaxel plus veliparib (337) vs carboplatin + paclitaxel (172)	Median PFS, 14.5 vs 12.6 mo (HR, 0.71 [95% CI, 0.57-0.88]; *P* = .002) Median OS (preplanned interim analysis), 33.5 vs 28.2 mo (HR, 0.95 [95% CI, 0.73-1.23]; *P* = .67)	Maintenance veliparib allowed if CT stopped due to toxic effects
Olaparib Expanded (TBCRC048)[29]	2	ORR	Non-*BRCA1/2* germline variant in HRD gene (cohort 1) or somatic variant in HRD gene or *sBRCA1/2* (cohort 2); ≤2 prior CT lines for MBC	Olaparib (27 in cohort 1; 27 in cohort 2)	Cohort 1: ORR, 33% (*gPALB2* variant 82%) Cohort 2: ORR, 31% (*sBRCA1/2* variant 50%) Median PFS, 13.3 mo for *gPALB2* variant Median PFS, 6.3 mo for *sBRCA1/2* variant	Confirmed responses only in *gPALB2* and *sBRCA1/2*; primary end point met
Talazoparib Beyond BRCA[30]	2	ORR	ERBB2-negative disease with variants in HRD-related genes other than *gBRCA*1 and *gBRCA*2	Talazoparib in *g/sBRCA1/2*-wild type with other variants in HRD-related pathway genes (13)	ORR, 31% CBR, 54%	Primary end point met
Metastatic setting, combination therapy						
TOPACIO[31]	1/2	Safety, ORR	TNBC, ≤2 prior CT lines for MBC, no prior PARP inhibitors or ICIs	Niraparib + pembrolizumab (55; 15 *gBRCA*1/2 variant)	ORR, 21% (*gBRCA* variant, 47%; PD-L1-positive, 32%) Median PFS, 2.3 mo (8.3 mo in *gBRCA1/2* variant)	Primary end point not met
MEDIOLA[32]	1/2	Safety, 12-wk DCR	Carriers of *gBRCA1/2* variants with ERBB2-negative tumors; ≤2 prior CT lines for MBC	Olaparib + durvalumab (34)	ORR, 63% 12-wk DCR, 80% Median PFS, 8.2 mo	NA
VIOLETTE[33]	2	PFS	TNBC, stratified by *gBRCA1/2* variant status and HRD, 1-2 prior lines for MBC	Olaparib + ceralasertib (112) vs olaparib + adavosertib (47) vs olaparib (114)	Median PFS, 5.3 vs 3.6 mo (HR, 0.79 [95% CI, 0.59-1.04]; *P* = .18) ORR, 28.6% vs 21.1%	Olaparib + adavosertib arm closed early for safety
Metastatic setting, maintenance therapy						
DORA[34]	2	PFS	TNBC with clinical benefit from 1-2 line platinum-based CT	Maintenance olaparib + durvalumab (23) or olaparib alone (22)	Median PFS, 4 mo and 6.1 mo In carriers of *gBRCA1/2* variants, 8.2 mo	Noncomparative design

(continued)

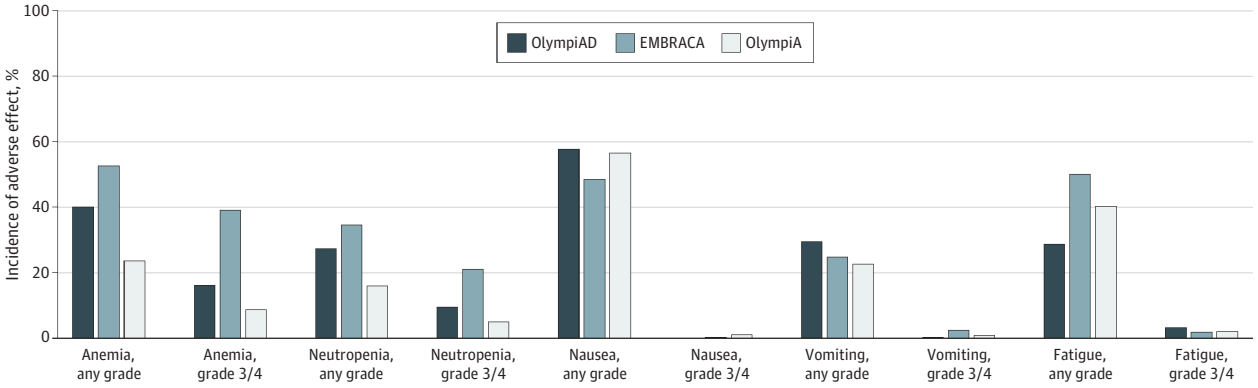
Table 1. Key Completed Clinical Trials Investigating PARP Inhibitors in Patients With Breast Cancer (continued)

Study	Phase	Primary end point	Population	Treatment arms (No. patients)	Results	Comments
Neoadjuvant setting						
NEOTALA[35]	2	RCB	Carriers of *gBRCA1/2* variants; ERBB2-negative tumors ≥1 cm	Neoadjuvant talazoparib for 24 wk (20)	pCR, 53% RCB-0/I, 63%	Primary end point met
BrighTNess[36,37]	3	pCR	Carriers of *gBRCA1/2* variants with stage 2-3 TNBC	Veliparib + paclitaxel + carboplatin (316) vs carboplatin + paclitaxel (160) vs paclitaxel (158)	pCR, 53% vs 58% vs 31% 4-y Event-free survival, 78.2% vs 79.3% vs 68.5% (HR, 1.12 [95% CI, 0.72-1.72]; *P* = .62 for carboplatin + veliparib + paclitaxel vs carboplatin + paclitaxel)	NA
GeparOLA[38,39]	2	pCR with olaparib-paclitaxel	cT2-T4 or cT1cN+ or TNBC or Ki-67 > 20%; *g/sBRCA1/2* variant and/or high HRD score	Olaparib 100 mg + paclitaxel (69) and carboplatin + paclitaxel (37); both followed by EC	pCR, 55.1% (52.6% in hormone receptor-positive) and 48.6% (20% in hormone receptor-positive) 4-y iDFS, 76% and 88.5%	Noncomparative design
Adjuvant setting						
OlympiA[40,41]	3	iDFS	ERBB2-negative, high-risk EBC after primary CT[a]	Olaparib for 1 y vs placebo	4-y iDFS, 83% vs 75% (HR, 0.63 [95% CI, 0.50-0.78]; *P* < .001) 4-y OS, 90% vs 86% (HR, 0.68 [95% CI, 0.47-0.97]; *P* = .01)	Led to regulatory approval

Abbreviations: CBR, clinical benefit rate; CT, chemotherapy; DCR, disease control rate; EBC, early breast cancer; EC, epirubicin/cyclophosphamide; ICI, immune-checkpoint inhibitor; *gBRCA1/2*, germline *BRCA1/2*; HR, hazard ratio; HRD, homologous recombination deficiency; iDFS, invasive disease-free survival; MBC, metastatic breast cancer; NA, not applicable; ORR, objective response rate; OS, overall survival; PARP, poly(adenosine diphosphate–ribose) polymerase; pCR, pathologic complete response; PFS, progression-free survival; RCB, residual cancer burden; *sBRCA1/2*, somatic *BRCA1/2*; TNBC, triple-negative breast cancer.

[a] Inclusion criteria differed for hormone receptor–positive and TNBC and according to neoadjuvant vs adjuvant CT (see text and reference for details).

Figure 2. Most Frequent Adverse Effects From Single-Agent PARP Inhibitors Observed in the Phase 3 OlympiAD, EMBRACA, and OlympiA Registration Trials



free survival were observed for neoadjuvant veliparib-paclitaxel-carboplatin and paclitaxel-carboplatin in patients with stage II to III TNBC in the phase 3 BrighTNess trial.[36,37] In the subgroup of 70 carriers of *gBRCA1/2* variants, the pCR rates were 57% and 50% in the veliparib/carboplatin/paclitaxel and carboplatin/paclitaxel arms, respectively, questioning the additional role of PARP inhibitors. Neoadjuvant low-dose olaparib (100 mg twice daily)–paclitaxel and carboplatin-paclitaxel, both followed by epirubicin/cyclophosphamide, had similar pCR rates (55.1% and 48.6%, respectively) and long-term outcomes (4-year invasive disease-free survival: 76% and 88.5%, respectively) in the phase 2, noncomparative GeparOLA trial, which enrolled patients with ER-positive or TNBC and a high HRD score.[38,39] Olaparib-paclitaxel was significantly better tolerated and led to a remarkable pCR rate of 52.6% (10 of 19 patients) in the ER-positive subgroup.[38] In the ongoing phase 2/3 PARTNER trial, a novel schedule of olaparib (150 mg twice daily, days 3 to 14) combined with carboplatin-paclitaxel is under investigation (NCT03150576).[52]

In the adjuvant setting, the phase 3 OlympiA trial evaluated 1 year of olaparib vs placebo in patients with high-risk ERBB2-negative breast cancer harboring *gBRCA1/2* variants after chemotherapy.[40] Olaparib reduced the risk of recurrence (4-year invasive disease-free survival, 83% vs 75%; HR, 0.63 [95% CI, 0.50-0.78]; $P < .001$) and demonstrated a 32% reduction in risk of death (4-year overall survival, 90% vs 86%; HR, 0.68 [95% CI, 0.47-0.97]; $P = .01$).[41] Ongoing key clinical trials investigating PARP inhibitors in this setting are outlined in **Table 2**.[50,51,53-59]

Future Therapeutic Strategies

Despite the benefit of PARP inhibitors for patients with *gBRCA1/2*-associated breast cancer, resistance often occurs, and the long-term responses observed in other tumor types, such as ovarian cancer, are rarely seen. Several mechanisms of resistance have been described, including restoration of HRR activity, impairment of PARP trapping, stabilization of the replication fork, increased drug efflux, or hyperactivation of alternative pathways, but effective strategies to overcome resistance are lacking.[60] Preclinical data showed that novel regimens and drugs may be effective in tumors that develop resistance to single-agent PARP inhibitors, and clinical studies are ongoing (**Table 3**).[61-85]

Novel Combination Regimens

Unrepaired DNA damage due to PARP inhibition modulates the tumor immune microenvironment by diverse mechanisms, including the formation of neoantigens and the induction of interferon-related genes (eg, programmed cell death ligand-1).[86] In preclinical models, PARP inhibitors combined with immunotherapy have been shown to enhance immune response and to synergistically inhibit tumor growth.[87] In the TOPACIO trial, niraparib plus pembrolizumab yielded an ORR of 21% in unselected patients with metastatic TNBC, with numerically higher response rates in patients with *sBRCA1/2* variants (ORR, 47%) and in those with programmed cell death ligand-1–positive tumors (ORR, 32%).[31] In the phase I/II MEDIOLA trial, olaparib plus durvalumab led to a 28-week disease control rate of 50% in patients with *gBRCA1/2* variants and metastatic breast cancer with favorable tolerability.[32] However, the first randomized study adding immunotherapy (atezolizumab) to a PARP inhibitor (olaparib) among carriers of *gBRCA*1/2 variants with advanced breast cancer did not show a significant PFS benefit for the combination.[88]

In the maintenance setting, the phase 2 DORA trial evaluated olaparib with or without durvalumab in patients with advanced TNBC and prior benefit from platinum chemotherapy.[34] Median PFS was 4.0 months in the olaparib and 6.1 months in the olaparib plus durvalumab arms, respectively. Patients without *gBRCA1/2*-altered tumors had durable disease control with olaparib maintenance with or without durvalumab, suggesting the potential value of prior platinum response as a biomarker to select patients for maintenance PARP inhibition.

The combination of chemotherapy and PARP inhibition has been historically hindered by the overlapping toxic effects. However, the improved therapeutic index of antibody-drug conjugates (ADCs) makes them an appealing combination partner for PARP inhibitors. Combining PARP inhibitors and ADCs carrying a topoisomerase 1 (TOP1) inhibitor payload, such as sacituzumab govitecan or trastuzumab deruxtecan, is particularly intriguing given the synergism between TOP1 inhibitors and PARP inhibitors and the potential synthetic lethality[89]: TOP1 inhibitors induce the trapping of TOP1 on DNA and the formation of single-strand breaks, which need a functional PARP1 to be repaired. Trials combining TOP1-ADCs and PARP inhibitors are ongoing.

Table 2. Key Ongoing Studies Investigating PARP Inhibitors in Patients With Early Breast Cancer

Registration identifier	Phase	Primary end point	Disease	Variant status	Prior PARP inhibitor use	No. enrolled	Class	Interventional cohort drug
NCT05582499[51]	1/2	pCR rate	BC	NR	NS	716	PARP inhibitor + CDK inhibitor	Fluzoparib + dalpiciclib/ fluzoparib + chemotherapy
NCT05332561 (COGNITION-GUIDE)[53]	2	iDFS	BC (TNBC cohort)	s/g*BRCA1/2*, g*PALB2*	NS	240	PARP inhibitor	Olaparib
NCT05761470[54]	2	pCR rate	*ERBB2*-negative BC	HRD	NS	66	PARP inhibitor + IO	Fluzoparib + camrelizumab + chemotherapy
NCT02849496[55]	2	PFS	*ERBB2*-negative BC	*BRCA1/2*	Not allowed	81	PARP inhibitor + IO	Olaparib + atezolizumab
NCT04481113[56]	1	MTD	Hormone receptor–positive/ *ERBB2*-negative BC	NR	Not allowed	8	PARP inhibitor + CDK inhibitor	Niraparib + abemaciclib
NCT05834582[57]	2	pCR rate	TNBC	g*BRCA* 1/2	Not allowed	60	PARP inhibitor	Fluzoparib + chemotherapy
NCT03911453[58]	1	PD-L1 expression	TNBC	NR	Not allowed	20	PARP inhibitor	Rucaparib
NCT05498155[50]	2	pCR rate	TNBC	s/g*BRCA1/2*	Not allowed	50	PARP inhibitor + IO	Olaparib ± durvalumab
NCT04582255[59]	2	pCR rate TILs change	*ERBB2*-negative BC	g*BRCA1/2*, g*PALB2*	Not allowed	62	PARP inhibitor + IO	Niraparib + dostarlimab

Abbreviations: BC, breast cancer; CDK, cyclin-dependent kinase; *gBRCA*, germline *BRCA*; HRD, homologous recombination deficiency; iDFS, invasive disease-free survival; IO, immunotherapy; MTD, maximum tolerated dose; NR, not required; NS, not specified; PARP, poly(adenosine diphosphate–ribose) polymerase; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; *sBRCA*, somatic *BRCA*; TILS, tumor-infiltrating lymphocytes; TNBC, triple-negative breast cancer.

Preclinical data in TNBC models showed synergistic antitumor effects from the coinhibition of PARP and DDR regulators, such as the ataxia telangiectasia and Rad3-related (ATR) and WEE1 kinases.[90] WEE1 regulates cell cycle progression, whereas ATR intervenes in the DNA damage response. In 2 phase 1 studies, the combination of the ATR inhibitor camonsertib and low-dose PARP inhibitors (talazoparib, niraparib, or olaparib) showed an ORR of 13% in heavily pretreated patients with DDR-aberrant solid tumors, although only 1 of 17 patients with breast cancer achieved an objective response.[91] The phase 2 VIOLETTE trial investigated olaparib alone, in combination with the ATR inhibitor ceralasertib or the WEE1 inhibitor adavosertib as second-line or third-line treatment for patients with unselected metastatic TNBC. Similar ORR and PFS were observed between the 3 treatment arms, irrespective of the presence of genetic alterations in homologous recombination pathway genes.[33]

In wild-type *BRCA1/2* preclinical models, coinhibition of bromodomain and extraterminal (BET) proteins and PARP led to enhanced antitumor activity.[92] BET proteins are key regulators of transcriptional outputs that regulate HRR gene expression. When combined with olaparib in an ovarian cancer model, BET inhibitors showed a synergistic increase in DNA damage and checkpoint defects, which ultimately led to cell death by mitotic catastrophe. In a phase 1/2 study, the BET inhibitor ZEN-3694 plus talazoparib showed promising activity in pretreated patients with TNBC and without *gBRCA1/2* variants.[93] The safety profile of the combination was manageable with thrombocytopenia as the most common adverse event. Key clinical trials investigating novel combinations are reported in Table 3.

New-Generation PARP Inhibitors

The development of resistance and the nonnegligible rate of off-target toxic effects have hindered the use of PARP inhibitors in combination therapy and in a broader population of patients with cancer, but novel agents are trying to overcome these limitations (Table 3). Studies have demonstrated that the hematological toxic effects of PARP inhibitors are mainly due to the inhibition of PARP2,[94] while the synthetic lethality with BRCA deficiency is driven by the interaction with PARP1.[95] Therefore, selective inhibition of PARP1 has become an appealing therapeutic strategy, and PARP1-selective inhibitors are under development. Among them, AZD5305 has demonstrated remarkable pharmacokinetics, pharmacodynamics, and safety pharmacology profiles in preclinical models.[96] This agent has higher selectivity for PARP1 compared with PARP2, leading to highly stable PARP1 trapping, and a strong antiproliferative effect limited to HRD cells.[97] Similar results were obtained on in vivo models of HRD TNBC and ovarian cancer.[98] Following these encouraging preclinical results, the phase 1/2 PETRA trial (NCT04644068) is evaluating AZD5305 in patients with metastatic tumors carrying pathogenic alterations of HRR genes.[71] In a preliminary analysis of 40 patients harboring germline/somatic alterations of *BRCA1/2*, *PALB2*, or *RAD51C/D*, AZD5305 proved to be safe and active, with an ORR of 25% and a disease control rate of 53%. Overall, 4 of 10 responses were seen among patients who progressed on prior PARP inhibitors.[99] In the expansion phase, AZD5305 is investigated as monotherapy or in combination with chemotherapy, ADCs, or endocrine therapy.

In addition to PARP1-selective inhibitors, novel agents acting as dual inhibitors of PARP1 and intracellular molecules (eg, histone deacetylases, DNA topoisomerases, PI3K pathway effectors), PARP1 degraders based on proteolysis targeting chimera technology and PARP1-targeting prodrugs are under development.

Table 3. Key Ongoing Clinical Trials Investigating Novel PARP Inhibitors or New Combinations in Patients With Advanced Breast Cancer

Registration identifier	Phase	Primary end point	Disease	Variant status	Prior PARP inhibitor use	No. enrolled	Class	Interventional cohort drug
NCT04090567[61]	2	ORR	BC	*gBRCA1/2*	Mandatory	60	PARP inhibitor + ATR inhibitor + VEGFR inhibitor	Olaparib + cediranib/ceralasertib
NCT05759546[62]	2	PFS	Hormone receptor-positive/*ERBB2*-negative BC	NR	NS	200	PARP inhibitor + CDK inhibitor	Fluzoparib + dalpiciclib
NCT05594095[63]	2	ORR	Hormone receptor-positive/*ERBB2*-negative BC	*s/gBRCA1/2*, *PALB2*	NS	140	PARP inhibitor + CDK inhibitor	Fluzoparib + dalpiciclib
NCT04174716 (VASTUS)[64]	1/2	ORR	Solid tumors	HRD	Not allowed	310	PARP inhibitor	Venadaparib (IDX-1197)
NCT04586335[65]	1	DLT, ORR	Solid tumors	HRD	Allowed	350	PARP inhibitor + PIK3CA inhibitor	Olaparib + risovalisib
NCT04503265[66]	1/2	MTD	Solid tumors	HRD	NS	122	MP inhibitor + PARP inhibitor	AMXI-5001
NCT03162627[67]	1	MTD	Solid tumors	NR	Allowed	90	PARP inhibitor + MEK inhibitor	Olaparib + selumetinib
NCT04991480[68]	1/2	DLT, PFS	Solid tumors	NR	Allowed	330	Pol-θ inhibitor + PARP inhibitor	ART4215 ± talazoparib/niraparib
NCT05564377 (ComboMATCH)[69]	2	Accrual rate	Solid tumors	NR	NS	2900	PARP inhibitor + PIK3CA inhibitor	Olaparib + alpelisib
NCT05700669[70]	1/2	DLT, ORR	Solid tumors	NR	Allowed	115	dsDNA fragment + PARP inhibitor	AsiDNA + olaparib
NCT04644068 (PETRA)[71]	1/2	DLT	Solid tumors	*s/gBRCA1/2*, *PALB2*, *RAD51*	Allowed	604	PARP1-selective inhibitor	AZD5305 monotherapy or with ADC or chemotherapy or camizestrant
NCT04053672[72]	1	MTD	Solid tumors	PARP7 amplification	NS	130	PARP inhibitor	RBN-2397
NCT04585958[73]	1	DLT	Solid tumors (dose escalation)	NR	NS	55	PARP inhibitor + ADC	Olaparib + trastuzumab deruxtecan
NCT05740956[74]	1	MTD, ORR	Solid tumors (including *ERBB2*-negative BC)	HRD	Allowed	318	PARP inhibitor	(HS)-10502
NCT05898399[75]	1/2	DLT, PFS	Solid tumors (including *ERBB2*-negative BC)	*s/gBRCA1/2*	Allowed	250	Pol-θ inhibitor + PARP inhibitor	ART6043 ± olaparib/talazoparib
NCT05417594[76]	1/2	DLT	Solid tumors (including *ERBB2*-negative BC)	*s/gBRCA1/2*, *PALB2*, *RAD51*	Not allowed	270	PARP inhibitor	AZD9574 ± temozolomide
NCT02484404[77]	1/2	ORR, RP2D	Solid tumors (including TNBC)	*gBRCA1/2*	Not allowed	384	PARP inhibitor + IO + VEGFR inhibitor	Durvalumab + olaparib ± cediranib
NCT02419495[78]	1	Safety profile	Solid tumors (including TNBC)	NR	NS	221	PARP inhibitor + XPO1 inhibitor	Olaparib + selinexor
NCT05252390[79]	1/2	DLT, ORR	Solid tumors (including TNBC)	NR	NS	657	PARP inhibitor + BD2 inhibitor	NUV-868 + olaparib
NCT02208375[80]	1/2	MTD	Solid tumors (including TNBC)	NR	Allowed	159	PARP inhibitor + mTOR inhibitor/AKT inhibitor	Olaparib + vistusertib/capivasertib
NCT02498613[81]	2	ORR, safety	Solid tumors (including TNBC)	NR	Allowed	126	PARP inhibitor + VEGFR inhibitor	Olaparib + cediranib
NCT04837209 (NADiR)[82]	2	ORR	TNBC	NR	Allowed	32	PARP inhibitor + IO	Niraparib + dostarlimab + radiation therapy
NCT03801369[83]	2	ORR	TNBC	NR	Not allowed	132	PARP inhibitor + IO/MEK inhibitor/AKT inhibitor/ATR inhibitor	Olaparib + durvalumab/selumetinib/capivasertib/ceralasertib
NCT04039230[84]	1/2	DLT	TNBC	NR	NS	75	PARP inhibitor + ADC	Talazoparib + sacituzumab govitecan
NCT05358639[85]	1	RP2D	TNBC	*s/gBRCA1/2* or *PALB2*	Allowed	36	PARP inhibitor + BCL2 inhibitor	Olaparib + navitoclax

Abbreviations: ADC, antibody-drug conjugate; ATR, ataxia telangiectasia and Rad3-related; BC, breast cancer; CDK, cyclin-dependent kinase; DLT, dose-limiting toxic effects; dsDNA, double-strand DNA; *gBRCA*, germline *BRCA*; HRD, homologous recombination deficiency; IO, immunotherapy; MP, microtubule polymerization; MTD, maximum tolerated dose; NR, not required; NS, not specified; ORR, objective response rate; PARP, poly(adenosine diphosphate–ribose) polymerase; PFS, progression-free survival; RP2D, recommended phase 2 dose; *sBRCA*, somatic *BRCA*; TNBC, triple-negative breast cancer; XPO1, nuclear export protein.

Integrating PARP Inhibitors in the Treatment Landscape for Patients With Breast Cancer

As the therapeutic landscape of breast cancer broadens, novel questions arise about the optimal use of PARP inhibitors. First, genetic testing is not universally offered to patients with breast cancer despite its potential therapeutic implications.[100] The practice-changing results of OlympiA stress the urgent need to reconsider eligibility criteria for genomic testing and support *gBRCA1/2* testing for all patients with high-risk ERBB2-negative early breast cancer, consistent with multiple guidelines.[101] Second, how olaparib should be integrated with available (neo)adjuvant therapies, such as pembrolizumab for TNBC and abemaciclib for ER-positive disease, is debated. In the KEYNOTE-522 trial, in which pembrolizumab was added to neoadjuvant chemotherapy and administered adjuvantly, event-free survival was prolonged, precluding adjuvant olaparib.[102] No patients in OlympiA received pembrolizumab. Whether patients with residual disease after neoadjuvant pembrolizumab-chemotherapy should receive olaparib, pembrolizumab, or both is unknown.[103] Adjuvant capecitabine also proved to prolong survival in patients with high-risk TNBC, complicating further the treatment choice.[104] As patients with *gBRCA1/2* variants are excluded from most of the ongoing trials in this setting, it is unlikely that randomized data will soon clarify which is the best approach for these patients.

In the monarchE trial, abemaciclib plus endocrine therapy reduced the risk of recurrence in patients with ER-positive, ERBB2-negative, high-risk early-stage breast cancer.[105] Inclusion criteria of monarchE partially overlap with those of OlympiA, but information about the *gBRCA1/2* status of patients enrolled in monarchE is not available. Similar results have been reported with adjuvant ribociclib in the NATALEE trial,[106] also without subgroup analyses by *gBRCA1/2* status. Acknowledging the lack of head-to-head comparisons, the survival benefits proven with olaparib and not yet with adjuvant cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors may favor the former compared with the latter.

When patients with *gBRCA1/2*-associated metastatic breast cancer should receive PARP inhibitors is also debated. For patients with ER-positive disease, it is unknown whether CDK4/6 inhibitors plus endocrine therapy should be preferred to PARP inhibitors as first-line therapy. Retrospective analyses showed that outcomes with CDK4/6 inhibitors may be poorer in carriers of *gBRCA1/2* variants compared with wild-type patients.[107] In cases of *gBRCA2* variants, this might be due to the co-occurrence of *BRCA2* loss of heterozygosity and loss of *RB1*, a gene located in proximity to *BRCA2* on chromosome 13, in which loss is a well-known mechanism of resistance to CDK4/6 inhibitors.[108] Furthermore, *gBRCA*-associated tumors are more often nonluminal compared with sporadic ER-positive tumors.[109] These data may collectively suggest that some tumors from carriers of *gBRCA1/2* variants may be intrinsically resistant to CDK4/6 inhibitors. A trial comparing first-line inhibitors plus endocrine therapy vs PARP inhibitors is warranted.

For patients with TNBC and *gBRCA1/2*, to our knowledge, no existing evidence suggests how PARP inhibitors should be prioritized to newer options of chemoimmunotherapy or ADCs (eg, sacituzumab govitecan and trastuzumab deruxtecan). Informative subgroup analyses by *gBRCA1/2* alterations from phase 3 trials have not been published. As in OlympiAD, olaparib had the highest benefit when administered as first-line treatment but did not improve survival compared with chemotherapy. It may be reasonable to prioritize first-line immunotherapy-based regimens and favor second-line olaparib while acknowledging the lack of data to support any sequential strategy in this setting.

Furthermore, whether and to what extent the activities of PARP inhibitors and platinum chemotherapy overlap is debated. Their mechanism of action is similar, as are their sensitivity and resistance spectra. However, head-to-head comparisons between platinum chemotherapy and PARP inhibitors are lacking, and little is known about the activity of PARP inhibitors after platinum chemotherapy, and vice versa. Results from BROCADE suggested that PARP inhibitors may improve outcomes when added to carboplatin,[28] but opposite evidence emerged from BrighTNess.[37] Data from GeparOLA, though not comparative in its design, suggested that olaparib and carboplatin may be equivalent in the early-stage setting.[38] Future studies combining platinum salts with less toxic PARP1-selective inhibitors may help to clarify whether these agents have synergic or redundant activity. If shown to be equivalent, PARP inhibitors may be privileged to platinum chemotherapy given the better safety profile; however, the different cost-effectiveness profiles should also be considered.

Finally, the role of maintenance PARP inhibitors after chemotherapy should be clarified. The aforementioned data from the BROCADE3[28] and DORA trial[34] support this strategy, and further efforts are ongoing (KEYLYNK-009 trial, NCT04191135).[110]

Conclusions

PARP inhibitors are the first agents approved selectively for patients with hereditary tumors, and the first drugs exploiting the mechanism of synthetic lethality. However, many questions remain to be answered. The clinical benefit varies significantly across distinct tumor types, but the reason that long-term benefits seen in patients with ovarian cancer are rarely achieved in patients with breast cancer is unknown. Future research should (1) identify predictive biomarkers of response to PARP inhibitors beyond *BRCA/PALB2* status, (2) clarify how to best integrate these agents in the treatment landscape of early-stage and metastatic breast cancer, and (3) develop novel treatment strategies to overcome the different mechanisms of resistance. In this context, translational efforts should be integrated into any clinical trial to both characterize the omics profile of these tumors and to potentially generate preclinical models for therapeutic investigations. In parallel, the development of novel drugs with better safety profiles will allow investigations of new combinations to be pursued.

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