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REVIEW ARTICLE

An Overview of PARP Inhibitors for the Treatment of Breast Cancer

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Abstract

Loss-of-function mutations in *BRCA1* and *BRCA2* are detected in at least 5% of unselected patients with breast cancer (BC). These BC susceptibility genes encode proteins critical for DNA homologous recombination repair (HRR). This review provides an update on oral poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of BC. Olaparib and talazoparib are PARP inhibitors approved as monotherapies for deleterious/suspected deleterious germline BRCA-mutated, HER2-negative BC. Olaparib is approved in the USA for metastatic BC and in Europe for locally advanced/metastatic BC. Talazoparib is approved for locally advanced/metastatic BC in the USA and Europe. In phase 3 trials, olaparib and talazoparib monotherapies demonstrated significant progression-free survival benefits compared with chemotherapy. Common toxicities were effectively managed by supportive treatment and dose interruptions/reductions. Veliparib combined with platinum-based chemotherapy has also shown promise for locally advanced/metastatic BC in a phase 3 trial. Differences in efficacy and safety across PARP inhibitors (olaparib, talazoparib, veliparib, niraparib, rucaparib) may relate to differences in potency of PARP trapping on DNA and cytotoxic specificity. PARP inhibitors are being investigated in early BC, in novel combinations, and in patients without germline BRCA mutations, including those with somatic BRCA mutations and other HRR gene mutations. Ongoing phase 2/3 studies include PARP inhibitors combined with immune checkpoint inhibitors for the treatment of triple-negative BC. Wider access to testing for BRCA and other mutations, and to genetic counseling, are required to identify patients who could benefit from PARP inhibitor therapy. The advent of PARP inhibitors has potential benefits for BC treatment beyond the locally advanced/metastatic setting.

1 Introduction

Breast cancer (BC) is the second most common cancer in the world and the most common malignancy in women, with approximately 2.09 million new cases diagnosed in 2018 (accounting for 12% of all cancers) [1]. Men account for fewer than 1% of patients with BC [2]. Although survival rates are improving, BC is still the fourth most common cause of death from cancer (627,000 deaths among women in 2018) [1, 3, 4]. Risk factors for developing BC include family history, age, environmental and lifestyle factors associated with carcinogen exposure, and hormonal changes [5–8]. The risk of developing BC is about two times higher if there is one first-degree relative affected by the disease and may be five times higher if the relative had BC at a young age [7, 8].

Up to 10% of patients with BC have inherited (germline) DNA mutations, often leading to loss of function in genes implicated in DNA repair and cell-cycle checkpoint activation. The remaining ~ 90% of cases are caused by acquired (somatic) genetic and epigenetic alterations [5, 6]. Loss-of-function mutations in two important BC susceptibility genes that are critical in the DNA damage response (DDR), *BRCA1* and *BRCA2*, are detected in at least 5% of unselected patients with BC and in approximately 30% of patients with a positive family history of breast or ovarian cancer [5, 6, 9, 10]. In carriers of *BRCA1* or *BRCA2* mutations, the risk of developing BC by 80 years of age is as high as 70%, compared with a 10% risk for women in the general population [9, 11]. Germline BRCA (gBRCA) mutations are particularly common in certain populations. For example, in a study of 732 women of Ashkenazi Jewish heritage who underwent genetic testing, 11% had one of three gBRCA

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Key Points

This comprehensive literature review provides an update on oral poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of breast cancer (BC).

The review focuses on olaparib and talazoparib, PARP inhibitor monotherapies approved for patients with deleterious/suspected deleterious germline BRCA-mutated, human epidermal growth factor receptor 2-negative BC. Olaparib is approved in the USA for metastatic BC and in Europe for locally advanced/metastatic BC. Talazoparib is approved for locally advanced/metastatic BC in the USA and Europe.

The review also discusses the investigation of PARP inhibitors for the treatment of early-stage BC, as well as in novel combinations and in other BC populations with high unmet needs, including those with triple-negative BC, somatic BRCA mutations, and mutations in other genes associated with defects in homologous recombination repair of DNA.

founder mutations [12]. Extensive analyses have revealed that somatic *BRCA1* mutations are uncommon in unselected patients, although expression of *BRCA1* is often reduced, in non-hereditary (sporadic) BC [10, 12–15]. BRCA mutation and hormone receptor status are also interlinked. Individuals with a g*BRCA1* mutation are more likely to develop triple-negative BC (TNBC) than hormone receptor-positive (HR+) disease, whereas patients with g*BRCA2* mutations tend to develop HR+ BC. gBRCA mutations are found in up to 23% of patients with TNBC and in 5% of patients with HR+ disease [16–21].

Treatment options are limited at present for patients with gBRCA-mutated BC, and the presence of these mutations is associated with younger age at BC diagnosis, aggressive disease characteristics, and higher risk of disease recurrence [22, 23]. Thus, this patient population has a high unmet need. Chemotherapy has been the mainstay of treatment for patients with gBRCA-mutated TNBC, and endocrine therapy plays an important role in gBRCA-mutated HR+ disease [24]. However, despite aggressive treatment, many patients will relapse and eventually die from their disease, and still others present with metastatic disease at initial diagnosis [25–27]. Hence, the goal of producing effective biomarker-targeted oral medications such as poly(ADP-ribose) polymerase (PARP) inhibitors is of major importance.

Two PARP inhibitor monotherapies, olaparib and talazoparib, have been approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for deleterious or suspected deleterious gBRCA-mutated, human epidermal growth factor receptor 2 (HER2)-negative BC, based on positive outcomes in phase 3 trials (OlympiAD and EMBRACA) [28–46]. Specifically, olaparib is FDA-approved for metastatic BC and EMA-approved for locally advanced/metastatic BC, and talazoparib is FDA- and EMA-approved for locally advanced/metastatic BC. Of the other three PARP inhibitors (niraparib, rucaparib, and veliparib) currently in global clinical trials for the treatment of BC, veliparib is in phase 3 development for HER2-negative, gBRCA-mutated locally advanced/metastatic BC and has shown promising outcomes when administered with platinum-based chemotherapy (BROCADE3 trial) [47, 48]. The differing activities of PARP inhibitor therapies may explain potential differences in their clinical efficacy and safety profiles [49–53].

PARP inhibitor therapies are now being investigated for the treatment of earlier stages of BC, as well as in novel combinations and in patients without gBRCA mutations, including somatic BRCA mutations and mutations in other DDR genes. This comprehensive literature review provides an overview of the use of PARP inhibitors in the treatment of BC, including background on their mechanism of action, relevant clinical trials, and discussion of the implications for their use in clinical practice and future directions.

2 DNA Repair, PARP Inhibition, and Synthetic Lethality

DNA damage and deficiencies of repair are central features of cancer pathology. Healthy cells defend themselves against DNA damage through five major DDR pathways, thus maintaining genomic integrity (Fig. 1). Base excision repair deals with single-strand breaks, nucleotide excision repair addresses helix-distorting damage, while mismatch repair corrects replication errors. Double-strand breaks can be repaired either by the homologous recombination repair (HRR) pathway, using the sister chromatid as a template, or by the more error-prone template-independent mechanism of non-homologous end-joining [51, 54, 55].

At least 450 proteins are thought to be involved in DDR pathways, including PARP1 and PARP2 [54]. PARP enzymes are integral to the base excision repair pathway. PARP1 attaches to the damaged DNA strand, allowing nicotinamide adenine dinucleotide (NAD^+) to bind to its active site (Fig. 2). ADP-ribose moieties from NAD^+ are transferred to target proteins, a process called PARylation, which mediates the recruitment of single-strand DNA repair effectors. PARP1 autoPARylates, leading to its release from DNA and restoration of a catalytically inactive state [51, 53, 56].

Double-strand breaks form when single-strand breaks are not repaired. Both BRCA1 and BRCA2 proteins play critical roles in the HRR pathway [55]. Initiation of HRR involves recognition of double-strand breaks by the kinases ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR), and signal transduction by phosphorylated CHK2 (another kinase) and BRCA1 proteins [54, 55, 57]. BRCA1 is a multifunctional protein, with roles beyond direct involvement in HRR, including cell cycle progression, transcription of DDR genes, and apoptosis [51, 58, 59]. In the HRR pathway, BRCA1 forms a multiprotein scaffold that organizes repair proteins at the DNA repair site [57, 60–62]. BRCA2 facilitates HRR by recruiting the recombinase RAD51 at the DNA repair site [57]. Along with *BRCA1* and *BRCA2*, multiple HRR genes, including *ATM*, *BARD1*, *BRIP1*, *CHEK2* (encodes CHK2), *MRE11A*, *PALB2*, *RAD50*, *RAD51C*, and *RAD51D*, are also implicated in hereditary cancer risk [55].

Most late-phase trials of PARP inhibitors have assessed efficacy in patient populations with a vulnerability in their tumor cells, namely HRR deficiency [51, 53, 54, 56, 63, 64]. Tumor cells with HRR gene mutations are targeted by PARP inhibitor therapies through a mechanism known as synthetic lethality (Fig. 3) [51, 54]. PARP inhibitors bind to PARP, inhibiting PARylation, and also trap inactivated PARP on DNA, thereby blocking replication forks, leading to their collapse and the generation of double-strand breaks [51, 52, 54, 56]. If PARP enzymes are inhibited in cells lacking functional HRR proteins (e.g., BRCA1, BRCA2), double-strand breaks can be repaired by the non-homologous end-joining pathway. However, the error-prone nature of this template-independent repair pathway ultimately leads to tumor cell death. By contrast, healthy cells should be spared, thus providing patients with benefits that are not achieved with conventional chemotherapy [54, 56]. In addition to roles in DDR, PARP enzymes are involved in transcription, apoptosis, and immune function; hence, multiple mechanisms of action may contribute to PARP inhibitor efficacy [51].

Preclinical data show that the potency of PARP trapping and cytotoxic specificity for HRR-deficient cells differ among the PARP inhibitors, which may explain differences in their clinical efficacy and safety profiles [49–53]. For example, veliparib is a weak PARP1 trapper and may not elicit the same level of synthetic lethality compared with stronger trappers (olaparib, talazoparib, rucaparib, niraparib). Talazoparib is 100-fold more potent at trapping PARP1 than niraparib, which in turn is more potent than rucaparib and olaparib [50–53, 56]. However, talazoparib has reduced cytotoxic specificity for HRR-deficient cells [50].

3 PARP Inhibitors as Monotherapies for Locally Advanced and/or Metastatic Breast Cancer

Olaparib and talazoparib monotherapies are approved for the treatment of patients with deleterious or suspected deleterious gBRCA-mutated, HER2-negative BC [37–44]. Specifically, olaparib is FDA-approved for metastatic BC and EMA-approved for locally advanced/metastatic BC, and talazoparib is FDA- and EMA-approved for locally advanced/metastatic BC. These approvals were, respectively, gained from the FDA and EMA for olaparib in January 2018 and April 2019 and for talazoparib in October 2018 and June 2019, based on positive outcomes in the OlympiAD and EMBRACA phase 3 trials [29, 33, 38, 40, 41, 44]. Both clinical trials were statistically powered to detect between-treatment differences in the primary endpoint, progression-free survival (PFS), in the overall patient population;

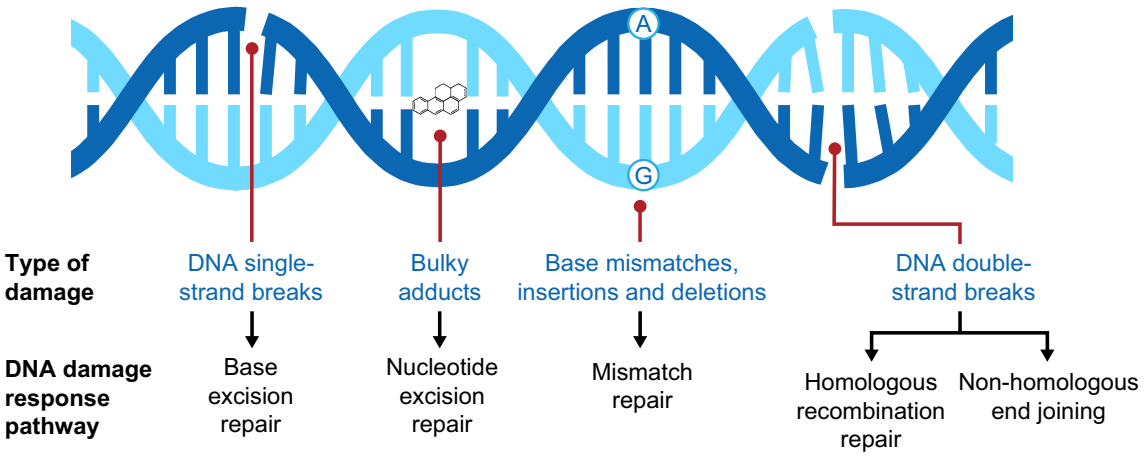

Fig. 1 DNA damage response pathways (modified from O'Connor MJ [54])

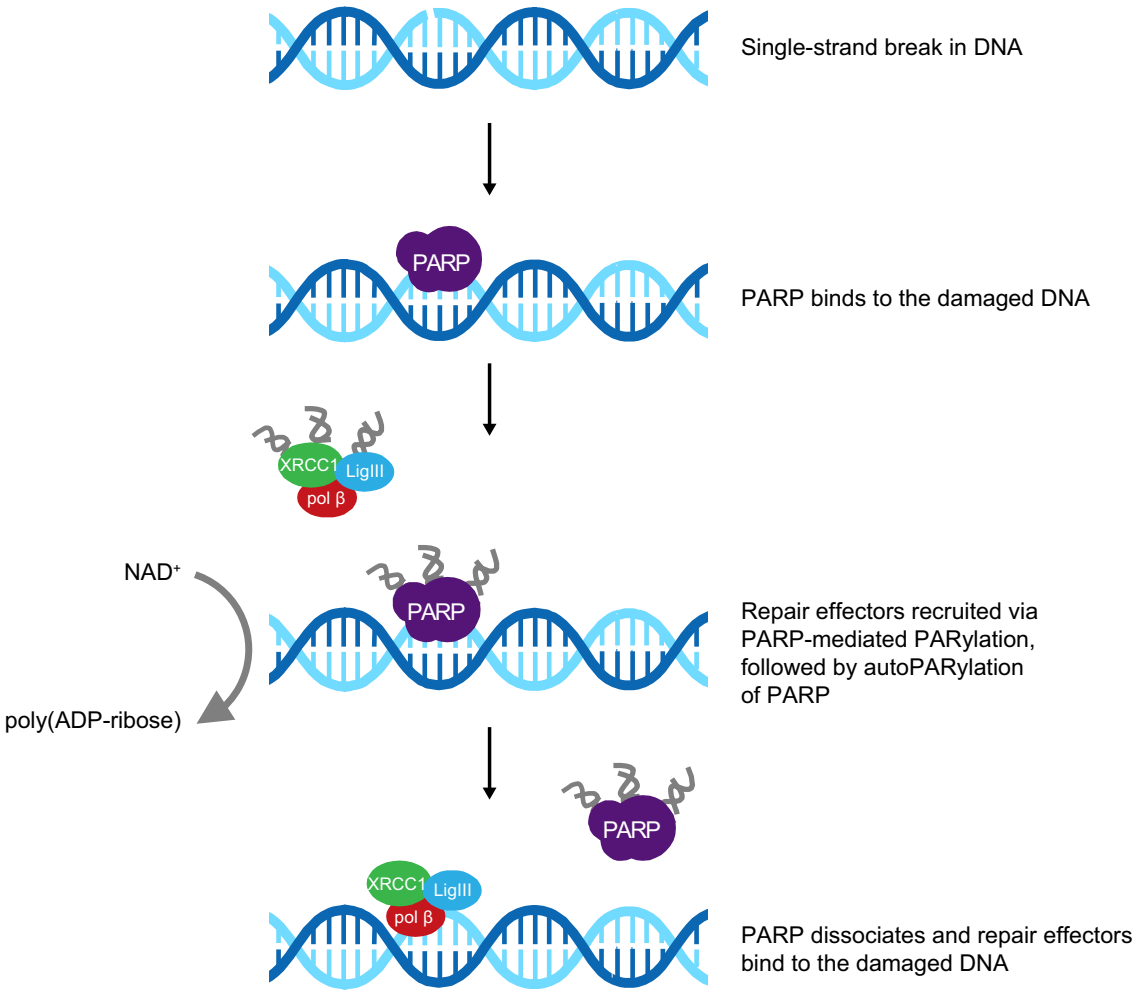

Fig. 2 The role of PARP in base excision repair of single-strand breaks in DNA. *LigIII* DNA ligase 3, *NAD*$^+$ nicotinamide adenine dinucleotide, *PARP* poly(ADP-ribose) polymerase, *pol b*, DNA polymerase beta, *XRCC1*, X-ray repair cross-complementing protein 1

subgroup analyses of PFS often included limited numbers of patients [29, 33]. Niraparib, rucaparib, and veliparib are also in clinical development as monotherapies for BRCA-mutated locally advanced/metastatic BC [65–73]. Enrollment in the BRAVO phase 3 trial of niraparib was stopped prematurely because of a high rate of discontinuation in the control arm [65–67]. A summary of PARP inhibitor monotherapy clinical trials in locally advanced/metastatic BC is shown in Table 1.

3.1 Olaparib in the Phase 3 OlympiAD Trial

OlympiAD was an open-label, randomized, multicenter, international, phase 3 trial comparing the efficacy and safety of olaparib versus single-agent standard therapy of the physician's choice (TPC; capecitabine, eribulin, or vinorelbine in 21-day cycles) in patients with gBRCA-mutated, HER2-negative metastatic BC. An open-label design was required owing to the different treatment options available for use in the TPC arm; however, the intended regimen had to be specified by the physician prior to randomization. All patients had received no more than two prior lines of chemotherapy for metastatic BC. Based on 2:1 randomization, 205 patients were assigned to oral olaparib (300 mg tablet twice daily) and 97 patients to TPC. The primary endpoint of PFS was assessed by blinded independent central review. Prespecified secondary endpoints included overall survival (OS), objective response rate (ORR), and health-related quality of life (HRQoL) [29].

Median PFS was significantly longer with olaparib (7.0 months) versus TPC (4.2 months; hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.43–0.80; $p < 0.001$). PFS HRs were consistent across a range of patient subgroups, including those with and those without prior exposure

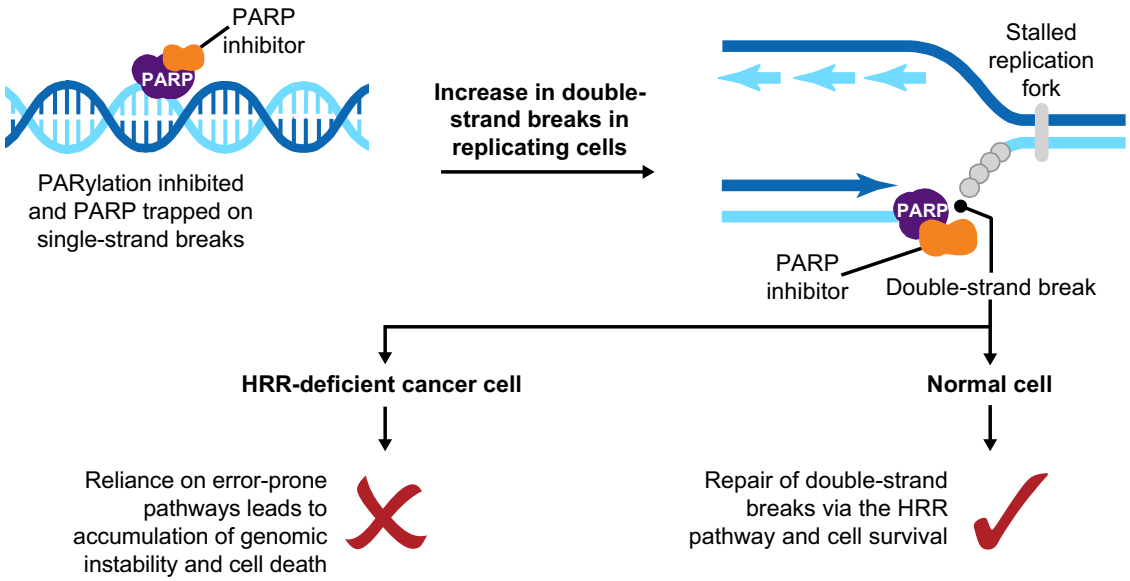

Fig. 3 Synthetic lethality by PARP inhibitors in HRR-deficient cancer cells (modified from O'Connor [54]). *HRR* homologous recombination repair, *PARP* poly(ADP-ribose) polymerase

to chemotherapy for metastatic BC and in patients with TNBC, an important consideration given the limited treatment options available for TNBC [29]. Post hoc analyses suggested that patients with visceral metastases benefit from improvements in PFS, when investigated by location (lung/pleura, liver, and brain/central nervous system) [74]. Another post hoc analysis showed that, in the few patients whose tumors did not show loss of heterozygosity (6% of 125 tested patients), there was no evidence for a reduction in the efficacy of olaparib, based on PFS [30].

In the final prespecified analysis of OS, conducted after 192 deaths (64% of patients), no significant difference was detected in median OS with olaparib (19.3 months) versus TPC (17.1 months; HR 0.90, 95% CI 0.66–1.23; $p = 0.513$) [32]; survival was 18.9% for olaparib versus 14.2% for TPC at 48 months in a post hoc follow-up analysis [28]. In both treatment arms, patients received other medications after discontinuing study treatment (2.0% and 11.3% in the olaparib and TPC arms, respectively, were subsequently treated with a PARP inhibitor), which may have contributed to these OS outcomes [28]. In an exploratory subgroup analysis in the first-line setting for metastatic disease, there appeared to be greater OS benefit for patients treated with olaparib (22.6 months) than TPC (14.7 months; HR 0.51, 95% CI 0.29–0.90; $n = 87$); this difference was greater than that observed between the treatment arms in the overall trial population [32]. The OS benefit in the second- or third-line setting for metastatic disease was 18.8 months for patients treated with olaparib and 17.2 months with TPC (HR 1.13, 95% CI 0.79–1.64; $n = 215$) [32]. Possible differences in OS benefit associated with therapeutic line may be related to clinical factors such as development of resistance to medication [75].

ORR in the olaparib arm was more than double the rate observed with TPC when assessed by blinded independent central review (59.9% vs. 28.8%) [29], and also when investigator-assessed (57.6% vs. 22.2%) [32]. Similarly, ORR with olaparib was more than double that with TPC in patients with visceral metastases (lung/pleura, liver, and brain/central nervous system) in post hoc analyses [74].

HRQoL assessments were based on patient-completed European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item module (EORTC QLQ-C30) questionnaires. HRQoL consistently improved with olaparib versus TPC, with a higher proportion of olaparib-treated patients rating their best overall response as 'improvement' (33.7% vs. 13.4%); median time to deterioration of HRQoL was not reached with olaparib versus 15.3 months with TPC. In post hoc analyses of symptoms and functioning, only nausea/vomiting symptoms were worse during treatment with olaparib than with TPC, and olaparib versus TPC delayed time to deterioration on all functional subscales (physical, role, social, cognitive, and emotional) [31].

In the primary analysis, median treatment duration was 8.2 (range 0.5–28.7) months for olaparib and 3.4 (range 0.7–23.0) months for TPC [29, 32]. Most adverse events (AEs) in the olaparib arm were grade 1/2, and the proportion of patients reporting grade 3 or higher AEs was lower with olaparib (38.0%) than with TPC (49.5%). In the olaparib arm, the most common AEs of any grade were nausea (58.0%), anemia (40.0%), and vomiting (32.2%), and the

Table 1 Clinical trials of oral PARP inhibitors as monotherapies for locally advanced and/or metastatic breast cancer

PARP inhibitor	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/outcomes	Primary and study completion dates (actual or estimated)	FDA and EMA approval
FDA- and EMA-approved as single-agent therapy for BC							
Olaparib	OlympiAD [28–32] NCT02000622	3	gBRCAm, HER2– metastatic BC	Olaparib vs. TPC (2:1 ratio) *N* = 302	Randomized, open-label, multicenter, international Primary endpoint: Median PFS (BICR) favored olaparib vs. TPC: 7.0 vs. 4.2 months (HR 0.58, 95% CI 0.43–0.80; $p < 0.001$) Median OS (final): no significant difference (19.3 months) vs. TPC (17.1 months; HR 0.90, 95% CI 0.66–1.23; $p = 0.513$); possible OS benefit for olaparib vs. TPC in the first-line metastatic setting (22.6 vs. 4.7 months; HR 0.51, 95% CI 0.29–0.90) ORR favored olaparib vs. TPC: 59.9% (95% CI 52.0–67.4) vs. 28.8% (95% CI 18.3–41.3) HRQoL consistently improved with olaparib vs. TPC Rate of grade ≥ 3 AEs lower with olaparib vs. TPC (38.0% vs. 49.5%)	December 2016 December 2020	*FDA approval:* monotherapy in gBRCAm, HER2–metastatic BC [37, 38] *EMA approval:* monotherapy in gBRCAm, HER2–locally advanced or metastatic BC [39, 40]
	Olaparib Expanded [78] NCT03344965	2	HER2– or HER2+ metastatic BC Cohort 1: germline mutations in non-BRCA DDR genes Cohort 2: somatic mutations in non-BRCA DDR genes or sBRCAm, with no gBRCAm	Olaparib *N* = 54, including 3 HER2+ Cohort 1, *n* = 27 Cohort 2, *n* = 27	Open-label, single-arm 87% had a s*BRCA1/2*, *PALB2*, *ATM*, or *CHEK2* mutation Primary endpoint: ORR 33% (*n* = 9/27) in cohort 1, 31% (*n* = 8/27) in cohort 2 Antitumor activity occurred in patients with sBRCAm or g*PALB2*m but not those with *ATM* or *CHEK2* mutations	December 2021 December 2021	
	NOBROLA [79] NCT03367689	2	BRCAwt, HER2–metastatic BC with HRD	Olaparib *N* = 39 (target)	Open-label, single-arm, multicenter, Simon's two-stage Primary outcome: CBR Secondary outcomes: ORR, PFS, OS, AEs	July 2021 November 2021	
	LYNK-002 [80] NCT03742895	2	HRRm or HRD, previously treated metastatic and/or unresectable solid tumors (excluding gBRCAm or sBRCAm BC)	Olaparib *N* = 370 (target)	Open-label, single-arm Primary outcome: ORR Secondary outcomes: DoCR, PFS, OS, AEs	February 2023 February 2023	
	COMETABreast [81] NCT03205761	2	sBRCAm methylation, no gBRCAm metastatic TNBC	Olaparib *N* = 34 (target)	Open-label, single-arm, multicenter Primary outcome: ORR Secondary outcomes: CBR, response duration, OS, PFS, AEs	December 2020 December 2020	
	LUCY [82] NCT03286842	3b	gBRCAm or sBRCAm, HER2–metastatic BC	Olaparib *N* = 256	Open-label, single-arm, multicenter Clinical effectiveness of olaparib in a real-world setting Primary outcome: PFS in patients with gBRCAm Secondary outcomes: OS, CRR, DoCR, AEs in gBRCAm cohort Other outcomes: PFS, OS, CRR, DoCR in sBRCAm cohort	November 2020 November 2020	

Table 1 (continued)

PARP inhibitor	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/outcomes	Primary and study completion dates (actual or estimated)	FDA and EMA approval
Talazoparib	EMBRACA [33–36, 45, 46] NCT01945775	3	gBRCAm, HER2– locally advanced or metastatic BC	Talazoparib vs. TPC (2:1 ratio) $N = 431$	Randomized, open-label, international Primary endpoint: Median PFS (BICR) favored talazoparib vs. TPC: 8.6 vs. 5.6 months (HR 0.54, 95% CI 0.41–0.71; $p < 0.001$) Median OS (final): no significant difference (19.3 months) vs. TPC (19.5 months; HR 0.85, 95% CI 0.67–1.07; $p = 0.17$) ORR favored talazoparib vs. TPC: 62.6% vs. 27.2% (OR 5.0, 95% CI 2.9–8.8; $p < 0.001$) PROs favored talazoparib vs. TPC, including improvements in HRQoL Rate of hematologic grade 3/4 AEs was higher with talazoparib vs. TPC (55% vs. 38%), and rate of non-hematologic grade 3 AEs was lower with talazoparib (32% vs. 38%)	September 2017 September 2020	*FDA and EMA approval:* monotherapy in gBRCAm, HER2– locally advanced or metastatic BC [41–44]
	ABRAZO [83] NCT02034916	2	gBRCAm, HER2– or HER2+ locally advanced or metastatic BC Cohort 1: platinum-sensitive Cohort 2: heavily pre-treated (≥ 3 prior therapies)	Talazoparib $N = 84$ Cohort 1, $n = 49$, including 1 HER2+ Cohort 2, $n = 35$, including 5 HER2+	Open-label, parallel-assignment Overall population: 49% *BRCA1*, 50% *BRCA2* Primary endpoint: ORR 28% (21% cohort 1, 37% cohort 2); 2 CRs, 21 PRs, 36 SD Median DoCR: 4.9 months (5.8 months cohort 1, 3.8 months cohort 2) CBR: 35% (27% cohort 1, 46% cohort 2) ORR: 26% (TNBC), 29% (HR+), 23% (*BRCA1*), 33% (*BRCA2*) Median PFS: 4.0 months (cohort 1) and 5.6 months (cohort 2) Median OS: 12.7 months (cohort 1) and 14.7 months (cohort 2) Grade ≥ 3 hematologic TEAEs: 58% (cohort 1) and 60% (cohort 2); grade ≥ 3 non-hematologic TEAEs: 27% (cohort 1) and 31% (cohort 2) Cohort 1: association between higher ORR and longer median PFS with longer platinum-free interval	September 2016 October 2018	
	NCT02401347 [84]	2	BRCAwt, HRRm, HER2– metastatic or recurrent BC	Talazoparib $N = 20$ BC, $n = 13$, including 1 TNBC	Proof-of-concept, open-label, single-arm Primary endpoint: ORR 25% CBR: 50% Talazoparib was well tolerated (5 patients required dose reduction for hematologic toxicities)	December 2021 December 2022	

Table 1 (continued)

PARP inhibitor	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/outcomes	Primary and study completion dates (actual or estimated)	FDA and EMA approval
Not yet FDA- or EMA-approved for BC							
Niraparib	BRAVO [65–67] NCT01905592	3	gBRCAm, HER2– locally advanced or metastatic BC	Niraparib vs. TPC (2:1 ratio) *N* = 206 (original target 306)	Randomized, open-label, multicenter Study prematurely closed because too many TPC-treated patients were not completing necessary assessments No longer suitable as a registration trial Primary endpoint: Median PFS (BICR), niraparib 4.1 months (95% CI 2.9–4.5) vs. TPC 3.1 months (95% CI 1.6–7.2) Median PFS (investigator assessed): niraparib 5.0 months (95% CI 4.2–5.5) vs. TPC 3.1 months (95% CI 2.7–5.1) Median OS: niraparib 14.5 months (95% CI 11.7–17.2) vs. TPC 15.8 months (95% CI 12.1–18.4) Median TTF: niraparib 4.3 months (95% CI 4.0–5.5) vs. TPC 2.6 months (95% CI 1.6–3.2) Serious AEs: 6.2% niraparib vs. 24.6% TPC	May 2018 December 2022	–
	ABC [68] NCT02826512	2	BRCA1-like, HER2– locally recurrent or metastatic BC, after ≤ 1 prior cytotoxic regimen	Niraparib *N* = 39	Open-label, single-arm, feasibility Primary outcome: PFS Secondary outcome measures: ORR, DoCR, AEs	August 2021 August 2023	
	MK-4827-001 [69] NCT00749502	1	Solid tumors including HER2– locally advanced or metastatic BC after ≤ 1 prior cytotoxic regimen	Niraparib *N* = 100 BC, *n* = 12	Open-label, single-arm, dose-escalation Evidence of antitumor activity in BC (and ovarian cancer) with gBRCAm Of 4 patients with BC and gBRCAm who were evaluable, 2 had PRs Niraparib (300 mg/day) was well tolerated	September 2011 June 2013	
Veliparib	California Cancer Consortium Trial [70] NCT01149083	2	BRCAm, HER2– or HER2+ metastatic BC	Veliparib *N* = 44, including 1 HER2+ *BRCA1*, *n* = 22 *BRCA2*, *n* = 22	Randomized, parallel-assignment, open-label Primary endpoint: ORR 14% (*BRCA1*), 36% (*BRCA2*) Median PFS: 5.2 months (3.6 months [*BRCA1*] vs. 6.6 months [*BRCA2*], $p < 0.05$) Median OS: 14.5 months (11.8 months [*BRCA1*] vs. 14.7 months [*BRCA2*], $p = 0.16$)	December 2020 (primary completion)	–
	M13-695 [71, 72] NCT01853306	1	Metastatic or unresectable solid tumors, including BC	Veliparib-ER and veliparib-IR *N* = 71 BC, *n* = 17	Randomized, crossover-assignment, open-label Primary endpoint: veliparib-ER vs. -IR had an improved pharmacokinetic profile and was well tolerated Of 16 evaluable patients with BRCAm BC, 10 had PRs, including 4 confirmed PRs: ORR 25.0% 6-month TTP (in patients with BC): 53.5%	May 2017 June 2017	

Table 1 (continued)

PARP inhibitor	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/outcomes	Primary and study completion dates (actual or estimated)	FDA and EMA approval
Rucaparib	RUBY [73] NCT02505048	2	gBRCAwt, HER2– metastatic BC with HRD	Rucaparib *N* = 41	Open-label, single-arm Primary endpoint: CBR 13.5% (1 CR, 3 PRs, 1 SD) Antitumor activity favored patients with high LOH (1 CR, 2 PRs) Rate of grade ≥ 3 AEs 46%	February 2019 December 2019	–

Date of table preparation: 21 September 2020 (updated 20 January 2021 for the Olaparib Expanded trial)

AE adverse event, *BC* breast cancer, *BICR* blinded independent central review, *BRCAm* mutation in *BRCA1 or BRCA2*, *BRCAwt* wild-type BRCA, *CBR* clinical benefit rate, *CI* confidence interval, *CR* complete response, *CRR* complete response rate, *DDR* DNA damage response, *DoCR* duration of clinical response, *-ER* -extended release, *EMA* European Medicines Agency, *FDA* United States Food and Drug Administration, *gBRCAm* germline BRCA mutation, *gBRCAwt* wild-type germline BRCA, *gPALB2m* germline *PALB2* mutation, *HER2–* human epidermal growth factor receptor 2 negative, *HER2+* human epidermal growth factor receptor 2 positive, *HR+* hormone receptor-positive, *HR* hazard ratio, *HRD* homologous recombination deficiency, *HRQoL* health-related quality of life, *HRRm* mutation in gene(s) involved in homologous recombination repair, *-IR* -immediate release, *LOH* loss of heterozygosity, *ORR* objective response rate, *OS* overall survival, *PARP* poly(ADP-ribose) polymerase, *PFS* progression-free survival, *PR* partial response, *PRO* patient-reported outcome, *sBRCAm* somatic BRCA mutations, *SD* stable disease, *TEAE* treatment-emergent adverse event, *TTF* time to treatment failure, *TNBC* triple-negative breast cancer, *TPC* chemotherapy of physician's choice, *TTP* time to disease progression

most common grade 3 or higher AEs were anemia (16.1%), neutropenia (9.3%), fatigue (3.4%), and decreased white blood cell count (3.4%) [29, 32]. Cumulative toxicities were not evident [32]. Regarding management of AEs, olaparib dose interruptions did not significantly affect treatment duration, and few patients discontinued olaparib treatment because of AEs (< 5%). These findings indicate that, although patients should be carefully monitored, toxicities can be effectively managed by supportive treatment, dose interruptions, and dose reductions, enabling patients to gain benefit by remaining on treatment with olaparib [32].

3.2 Talazoparib in the Phase 3 EMBRACA Trial

EMBRACA was an open-label, randomized, multicenter, international, phase 3 trial comparing the efficacy and safety of talazoparib versus single-agent standard TPC (capecitabine, eribulin, gemcitabine, or vinorelbine in 21-day cycles) in patients with gBRCA-mutated, locally advanced/metastatic BC. All patients had received no more than three chemotherapy regimens for advanced BC. Based on 2:1 randomization, 287 patients were assigned to treatment with talazoparib (1 mg once daily) and 144 patients to TPC. In both treatment arms, 94% of patients had metastatic disease. The primary endpoint was PFS, assessed by blinded independent central review. Prespecified secondary endpoints included OS and ORR; HRQoL was assessed as an exploratory endpoint [33].

Median PFS was significantly longer with talazoparib (8.6 months) versus TPC (5.6 months; HR 0.54, 95% CI 0.41–0.71; $p < 0.001$). PFS HRs were consistent across a range of patient subgroups, including those with and those without prior exposure to chemotherapy, patients with TNBC and patients with visceral disease [33, 36]. PFS HRs with talazoparib and TPC were also consistent in the TNBC and HR+ patient subgroups when analyzed by prior exposure to one line and at least two lines of chemotherapy and no prior exposure [36].

In the final analysis of OS, conducted after 324 deaths (75% of patients), no significant difference was detected in median OS with talazoparib (19.3 months) versus TPC (19.5 months; HR 0.85, 95% CI 0.67–1.07; $p = 0.17$); survival probability was 0.19 (95% CI 0.14–0.25) for talazoparib versus 0.07 (95% CI 0.02–0.15) for TPC at 48 months. Notably, 4.5% and 32.6% of patients randomized to talazoparib and TPC, respectively, received subsequent therapy with a PARP inhibitor (at the time of the EMBRACA trial, olaparib was an approved treatment for metastatic BC associated with a gBRCA mutation) [45, 46].

Investigator-assessed ORR in the talazoparib arm (62.6%) was more than double that in the TPC arm (27.2%) [33]. As with PFS, ORR was higher with talazoparib than with TPC regardless of exposure or lack of prior exposure to

chemotherapy in the TNBC and HR+ patient subgroups [36].

Compared with TPC, patients who received talazoparib had significant overall improvement in HRQoL, and delay in time to deterioration across multiple functions and symptoms, including pain and fatigue [34, 36]. Improvements in HRQoL and delay in time to deterioration for pain and fatigue observed during treatment with talazoparib versus TPC were irrespective of Eastern Cooperative Oncology Group performance status at baseline [76].

Median treatment duration was 7.0 (range 0.8–36.9) months for talazoparib and 4.5 (range 0.5–18.3) months for TPC [35]. The proportion of patients treated with talazoparib who experienced grade 3 or 4 hematologic AEs was higher (55% vs. 38%), and grade 3 non-hematologic AEs (32% vs. 38%) was lower, than with TPC. The most common AEs of any grade with talazoparib were hematologic (67.8% of patients), including anemia (52.8%), neutropenia (34.6%), and thrombocytopenia (26.9%), which were frequently grade 3 (38.5%, 17.8%, and 11.2%, respectively). The majority of non-hematologic toxicities were grade 1 or 2, including fatigue, nausea, headache, alopecia, and vomiting [33, 35]. In general, cumulative risks of common hematologic AEs (anemia, neutropenia, and thrombocytopenia) and selected non-hematologic AEs (nausea, fatigue, vomiting, and alopecia) plateaued after weeks 25 and 50, respectively. In a post hoc analysis, talazoparib was associated with a lower rate of serious AE-associated hospitalizations than with TPC (46.8 vs. 71.9 hospitalizations per 100 patient-years, respectively). Patients with common AEs (anemia, nausea, or vomiting) reported favorable outcomes such as better HRQoL during treatment with talazoparib compared with TPC. Few patients discontinued talazoparib treatment because of AEs (5.9%), indicating that toxicities could be effectively managed by supportive care and dose modifications [33, 35].

3.3 Indirect Comparison of Olaparib and Talazoparib: OlympiAD Versus EMBRACA

In the absence of head-to-head evidence for olaparib and talazoparib, an indirect treatment comparison using a Bayesian fixed-effect approach has been performed using published data from the OlympiAD and EMBRACA trials [77]. This analysis suggests that olaparib and talazoparib are equally efficacious with respect to PFS in the populations tested. There was no difference in AE-related discontinuations, although their safety profiles differed. Olaparib was predicted to have fewer common hematologic AEs of any grade (anemia, thrombocytopenia, and neutropenia; odds ratio (OR) 0.37, 0.23, 0.54, respectively) and alopecia (OR 0.22), but an increased risk of nausea (OR 2.39) and vomiting (OR 2.13), relative to talazoparib [77]. These indirect treatment comparisons are limited by differences in how AEs are reported in the published literature and by differences in study design. For instance, the chemotherapies used in the TPC control arms of the two studies differed; notably, gemcitabine was allowed in the EMBRACA trial but not in the OlympiAD trial [29, 33, 77].

4 Treatment Pathways: Germline BRCA Mutation Testing and PARP Inhibitor Therapy

Choice of treatment for BC is based on the clinical characteristics of the individual patient, their disease history, and patient preference [85]. Treatment options are influenced by tumor hormone receptor status (presence or absence of estrogen and progesterone receptors) and HER2 gene amplification [85–87]. gBRCA testing, which already has an established predictive role in BC risk assessment, can now be used to inform therapeutic choice. PARP inhibitors are recommended over nonplatinum single-agent chemotherapy for the treatment of patients with advanced BC associated with a gBRCA mutation [87], and platinum compounds also show efficacy [88]. Early provision of genetic counseling and testing, possibly at the time of BC diagnosis, may be beneficial with regard to making informed decisions about primary surgical and other medical interventions [89].

Proposed positions of gBRCA testing and PARP inhibitor therapy in possible treatment pathways for patients with HER2-negative BC are shown in Fig. 4. As indicated in the FDA and EMA labels, patients with BC should be tested for gBRCA mutations before treatment with olaparib or talazoparib [37, 39, 42, 43]. The treatment pathways in Fig. 4 are aligned with the FDA- and EMA-licensed indications for these PARP inhibitors [37, 39, 42, 43] and also with evidence-based US and European treatment guidelines [24, 85, 90]. In particular, olaparib or talazoparib should be used in the treatment of patients with deleterious/suspected deleterious gBRCA-mutated, HER2-negative, locally advanced/metastatic BC after receiving chemotherapy in the (neo) adjuvant or metastatic settings and, if considered appropriate, after patients with HR+ tumors have received endocrine therapy [37, 39, 42, 43]. Olaparib is approved in the USA for metastatic BC and in Europe for locally advanced/metastatic BC; talazoparib is approved for locally advanced/metastatic BC in the USA and Europe.

5 Identification of Patients Who Could Potentially Benefit from PARP Inhibition

The advent of PARP inhibitor therapies provides the prospect of biomarker-targeted treatment for BC; however, there is a need to efficiently identify who may benefit from

treatment and to ensure accessibility to genetic testing [93]. Patients with BC who may be eligible for PARP inhibitor therapy are being missed, even when using established diagnostic guidelines and techniques [94–97]. In the OlympiAD trial of olaparib for metastatic BC, the majority of gBRCA mutations were detected during screening for the trial [29]. Potential reasons for the lack of uptake of BRCA testing are discussed in Sect. 5.1.

5.1 Issues with Uptake of BRCA Mutation Testing

Identification of BRCA mutations through early genetic screening allows increased monitoring and surveillance for breast (and other) cancers, and may provide the patient and their family with the opportunity for counseling, earlier stage BC diagnosis, and risk-reducing interventions [98–100]. However, some patients with BRCA mutations may be missed owing to undertesting; in the USA, only 5.1% and 2.7% of eligible women (based on family history of BRCA mutation-associated cancers) reported uptake of genetic counseling and testing, respectively [101, 102]. Eligibility for and uptake of BRCA testing varies among countries [103–105], and use of international testing criteria is not feasible for all countries owing to disparities in resources [106]. There are racial disparities in BRCA testing uptake [101, 107–112]. Testing rates also vary widely according to BC receptor subtype [104, 113–118].

Potential barriers to BRCA testing uptake and genetic counseling for eligible women with or without a diagnosis of BC include: lack of understanding and knowledge about genetic counseling and testing by physicians and patients; lack of perceived benefits of counseling; lack of perceived risk of having a mutation; cost of testing; and fear of insurance discrimination [94, 109, 119–121]. Patients' attitudes to BRCA testing (the predisposing factor), income (the enabling factor), and risk of carrying a BRCA mutation (the need factor) predict uptake of BRCA testing [122]. Uptake of BRCA testing may be increased in the following ways: provision of free genetic counseling; greater dissemination of information to at-risk individuals; genetic counseling that covers strategies for individuals to discuss their diagnosis with family members; and awareness and implementation of population-based testing as a preventive measure [93, 109, 123–125].

5.2 Future Directions to Identify Eligible Patients

Future avenues to identify patients who may benefit from treatment with PARP inhibitors include early detection of somatic BRCA mutations and other gene mutations that result in HRR deficiency in primary tumors and metastases. PARP inhibitor therapies are now being investigated in patients with non-gBRCA HRR gene mutations (see Sect. 6.3) and in neoadjuvant and adjuvant settings (see Sect. 6.1). Use of PARP inhibitor therapies at early stages of BC and in patients without gBRCA mutations are both subject to confirmation of PARP inhibitor efficacy in clinical trials and have yet to gain approval from licensing authorities, including the FDA and EMA. Increased detection of actionable genetic mutations, at earlier stages of disease, would require wider access to BRCA-specific and multiple-gene panel testing, and validation of predictive models to establish probabilities of having gene mutations [126, 127]. Evaluation of mutations in various HRR genes could be fundamental to identify patients suitable for PARP inhibitor therapy, as has been suggested by studies of prostate cancer [56]. Accordingly, a suite of biomarkers correlating with PARP activity has recently been identified in human cancer cell lines, and this could be used as patient selection criteria for expanding the clinical development of PARP inhibitors [128]. In addition, given that immune checkpoint inhibitors that target the programmed cell death ligand 1 (PD-L1) and the programmed cell death 1 (PD-1) receptor are now being investigated as combination therapies with PARP inhibitors in patients with BC [129–135] (see Sect. 6.2), there may be merit in determining PD-L1 levels in patients who could be eligible for this treatment option [136].

6 Overview of New Directions for PARP Inhibitors

Advances in our knowledge are resulting in potential commencement of PARP inhibitor therapies in patients with earlier stage BC and in combination with other therapies. As with other cancer therapies, resistance to PARP inhibitor therapy occurs in patients with advanced cancer [51]. Resistance to PARP inhibitor therapy may result from multiple mechanisms. For example, HRR could be reactivated by secondary mutations that restore the open reading frames of HRR genes such as *BRCA1*, *BRCA2*, *PALB2*, and *RAD51C/D*, by mutations leading to mitigation of replication stress, or by mutations in genes for PARP1 or drug effluxion pumps. Early-stage tumors should harbor fewer acquired resistance mechanisms that adversely affect duration of response, in comparison to advanced disease [56]. Thus, treatment of earlier stage disease and use of PARP inhibitor combination therapies may enhance their antitumor effects.

6.1 PARP Inhibitors for Early-Stage Breast Cancer

Treatment of early-stage BC with PARP inhibitors is the subject of several clinical studies, including a phase 3 trial of neoadjuvant veliparib, phase 1/2 trials of neoadjuvant

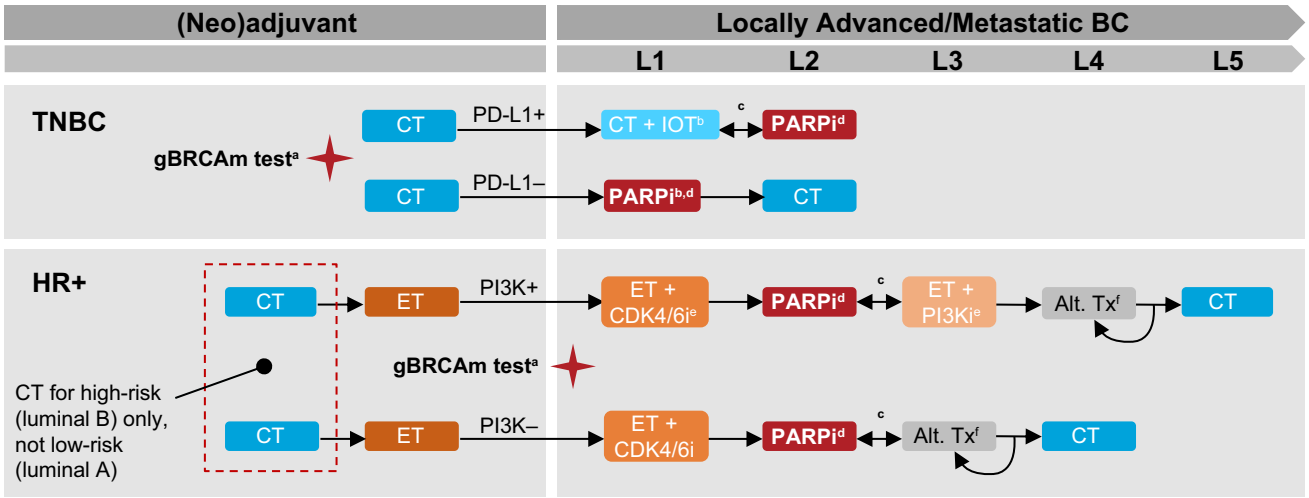

Fig. 4 Possible treatment pathways for germline BRCA-mutated, HER2-negative breast cancer and proposed positions of germline BRCA mutation testing (author opinion, based on treatment guidelines and licensed indications [24, 37, 39, 42, 43, 85, 90–92]). [a]Red star denotes potential positions of gBRCA mutation testing in the treatment pathways. [b]The PD-L1 inhibitor atezolizumab plus albumin-bound paclitaxel. For patients with visceral crisis (organ dysfunction) and PD-L1+, first-line treatment could be CT or PARPi. For patients with visceral crisis (organ dysfunction) and PD-L1-, first-line CT may be appropriate. [c]Double-headed arrows show that therapies can be provided in either sequence. [d]Olaparib and talazoparib are PARPi monotherapies approved for deleterious/suspected deleterious gBRCA-mutated, HER2-negative BC. Olaparib is approved in the USA for gBRCA-mutated metastatic BC and in Europe for gBRCA-mutated locally advanced/metastatic BC; talazoparib is approved for gBRCA-mutated locally advanced/metastatic BC in the USA and Europe. [e]In Europe, the PI3K inhibitor alpelisib plus fulvestrant is approved for use after disease progression following ET as monotherapy. In the USA, alpelisib plus fulvestrant is approved for use after disease progression on or after an ET-based regimen. [f]Alt. Tx includes everolimus plus ET. Return arrows show that patients can receive more than one line of Alt. Tx. *Alt. Tx* alternative treatment to PARPi or CT, *BC* breast cancer, *CDK4/6i* cyclin-dependent kinase 4 and 6 inhibitor, *CT* chemotherapy, *ET* endocrine therapy, *gBRCAm* germline BRCA mutation, *HER2* human epidermal growth factor receptor 2, *HR+* hormone receptor-positive, *IOT* immuno-oncology therapy, *L* line, *PARPi* PARP poly(ADP-ribose) polymerase inhibitor, *PD-L1* programmed cell death ligand 1, *PI3Ki* phosphoinositide 3-kinase inhibitor, *TNBC* triple-negative breast cancer

niraparib and talazoparib, and phase 2/3 trials of olaparib as a neoadjuvant and adjuvant treatment (Table 2).

At present, there are no specific targeted therapies available for TNBC, which shares some phenotypic and molecular similarities with gBRCA-mutated BC. There is increasing evidence that PARP inhibitor therapies may be effective in the treatment of patients with non-gBRCA HRR gene mutations (see Sect. 6.3). TNBCs often harbor somatic BRCA or other HRR mutations, or BRCA genes may be silenced through promoter hypermethylation, which may result in susceptibility to PARP inhibitor therapy [137]. PARTNER is a three-stage phase 2/3 trial, designed to assess the safety, schedule selection, and efficacy of neoadjuvant olaparib in combination with platinum-based chemotherapy for patients with TNBC and/or gBRCA-mutated BC [138, 139]. Based on 159 patients (target $N = 527$), preliminary safety data support the combination. A large phase 2 study, the PETREMAC trial, is also ongoing ($N = 200$); olaparib is one of several treatment options being investigated in this trial for patients with *TP53*-mutated or *TP53*-wild-type BC [137, 140]. The primary outcome measure of PETREMAC is the predictive and prognostic value of mutations in 300 cancer-related genes, assessed in BC tissue by next-generation sequencing before starting neoadjuvant therapy. Olaparib monotherapy in 32 treatment-naïve patients with TNBC yielded a high ORR (56%). Of the 18 responders, 16 had HRR defects (gene mutations or *BRCA1* promotor hypermethylation), which were found in only four of the 14 non-responders. After excluding patients with gBRCA ($n = 4$) or g*PALB2* mutations ($n = 1$), ORR was 52% ($n = 14/27$), thus indicating potential efficacy in patients without gBRCA mutations. In the phase 2 GeparOLA trial ($N = 107$), in patients with HR+ or TNBC and HRR deficiency (deleterious BRCA mutations and/or high HRR deficiency scores), pathological complete response rates were 55.1% with the combination of olaparib and paclitaxel, relative to 48.6% with carboplatin and paclitaxel; both combinations were followed by treatment with epirubicin and cyclophosphamide [141]. Pathological complete response rates were higher with olaparib combination therapy than with carboplatin and paclitaxel in patients under 40 years of age (76.2% vs. 45.5%) and in those with HR+ tumors (52.6% vs. 20.0%).

The results of the phase 3 BrighTNess trial ($N = 634$) generally do not support the addition of veliparib to carboplatin and paclitaxel, followed by doxorubicin and cyclophosphamide, for the neoadjuvant treatment of stage II–III,

high-risk TNBC [142]. The addition of veliparib and carboplatin to paclitaxel increased the proportion of patients who achieved a pathological complete response (53%) versus paclitaxel alone (31%), but not relative to carboplatin and paclitaxel (58%). In the subgroup of 70 patients with BRCA mutations, pathological complete response rates were 57% with the veliparib combination and 50% with the combination of carboplatin and paclitaxel.

Positive efficacy data have been reported from two phase 1 studies of neoadjuvant niraparib and talazoparib monotherapy [143–145]. Niraparib was administered to 21 patients with somatic or gBRCA-mutated BC, mainly TNBC. Based on 18 patients with magnetic resonance imaging (MRI) and ultrasound results after 2 months of treatment, tumor response rate was 89% by MRI, and all patients had responded according to at least one imaging technique [143, 144]. The pilot study of neoadjuvant talazoparib, which had a planned recruitment of 20 patients, was stopped after recruitment of 13 patients owing to favorable efficacy and safety findings. In the 13 patients, who had gBRCA-mutated BC ($n = 9$ with TNBC), tumor volumes decreased by a median of 88% (range 30–98%) after 2 months of treatment with neoadjuvant talazoparib [145]. The pilot study was modified into a phase 2 trial ($N = 20$, $n = 15$ with TNBC), in which 53% of patients experienced a pathological complete response after 6 months of treatment [146]. A phase 2 study of neoadjuvant talazoparib, with a planned enrollment of 112 evaluable patients with gBRCA-mutated, stage I-III TNBC, was terminated in September 2020 (following recruitment of 61 patients) owing to a change in the sponsor's clinical development strategy, a decision not related to safety and efficacy [147, 148].

In the adjuvant setting, the phase 3 OlympiA trial is ongoing, investigating olaparib monotherapy in patients with gBRCA-mutated, high-risk, HER2-negative primary BC ($N = 1836$) [149, 150]. Eligible patients had completed neoadjuvant chemotherapy and surgery or adjuvant chemotherapy. The primary objective is invasive disease-free survival.

6.2 PARP Inhibitors in Combination Therapies, Including with Immunotherapies

The combination of PARP inhibitors and immune checkpoint inhibitors is based on evidence for an interaction between the abnormal presence of unrepaired DNA in the cytoplasm and the stimulator of interferon genes (STING) pathway. STING activation leads to the release of interferons and induction of tumor infiltration by T-cells [151]. PARP inhibitor monotherapies have been shown to trigger antitumor immunity in BRCA1-deficient mice, an effect that was augmented when the PARP inhibitor was combined with an immune checkpoint inhibitor [151–153]. Monoclonal antibodies that inhibit the interaction of PD-L1 with the PD-1 receptor, allowing the immune system to target tumor cells, include pembrolizumab, durvalumab, atezolizumab, and avelumab.

Promising efficacy and safety findings have been reported for niraparib combined with pembrolizumab and for olaparib plus durvalumab in two single-armed phase 2 studies, TOPACIO and MEDIOLA (Table 3). In TOPACIO ($N = 47$ for efficacy, $N = 55$ for safety), the combination of niraparib and pembrolizumab conferred antitumor activity, regardless of BRCA mutation status, in patients with somatic or gBRCA-mutated and wild-type BRCA advanced/metastatic TNBC [129]. ORR was 21% in the overall population ($n = 10/47$) and 47% in patients with tumor BRCA mutations ($n = 7/15$). Disease control rate (DCR) was 49% (80% in patients with tumor BRCA mutations). For the five patients harboring non-BRCA HRR pathway mutations, ORR was 20% ($n = 1/5$) and DCR was 80% ($n = 4/5$). In the overall population, ORR was numerically higher in patients with PD-L1-positive TNBC (32%; $n = 9/28$) than in those with PD-L1-negative TNBC (8%; $n = 1/13$). In MEDIOLA ($N = 30$ for efficacy, $N = 34$ for safety), the combination of olaparib and durvalumab was associated with DCRs of 80% and 50% after 12 and 28 weeks, respectively, and favorable tolerability in patients with gBRCA-mutated metastatic BC [130, 131]. Other ongoing trials of PARP inhibitors combined with immune checkpoint inhibitors include DORA, a phase 2 study of olaparib and durvalumab in platinum-responsive locally advanced (inoperable) or metastatic TNBC, and KEYLYNK-009, a phase 2/3 trial of olaparib and pembrolizumab in locally recurrent inoperable or metastatic TNBC [132–135, 154–156].

PARP inhibitors are also being evaluated in combination therapies with other agents to treat locally advanced or metastatic BC [47, 48, 157]. In the phase 3 BROCADE3 trial ($N = 509$), addition of veliparib to carboplatin and paclitaxel resulted in significant improvement in median PFS compared with placebo added to carboplatin and paclitaxel (14.5 vs. 12.6 months; HR 0.71, 95% CI 0.57–0.88; $p = 0.002$) in patients with gBRCA-mutated, HER2-negative, locally advanced or metastatic BC. The PFS benefit was durable and no additional toxicities were seen, although there was a high degree of toxicity in both treatment arms [47, 48]. A subset of patients ($n = 194$) were transferred from the combination therapies to veliparib or placebo monotherapy for reasons other than disease progression. Patients treated with veliparib appeared to derive PFS benefit from both monotherapy (HR 0.49, 95% CI 0.33–0.73) and combination therapy (HR 0.81, 95% CI 0.62–1.06). Similar benefit was gained with veliparib monotherapy in patients who transferred from ≤ 6 cycles versus patients who transferred from 7–12 cycles of combination therapy, indicating that the number of prior cycles of combination therapy may not influence the efficacy of subsequent veliparib monotherapy. Overall, these results

Table 2 Clinical trials of oral PARP inhibitors for early breast cancer in the neoadjuvant and adjuvant settings

Treatment	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/outcomes	Primary and study completion dates (actual or estimated)
Neoadjuvant setting						
Talazoparib	Pilot study [145, 146] NCT02282345	1/2	Operable, gBRCAm, HER2– BC	Talazoparib $N = 33$ $n = 13$ in the initial cohort $n = 20$ in the expansion cohort	Open-label, single-arm, multicenter In the initial cohort: Primary endpoint: recruitment was shown to be feasible Tumor volume decreased in all patients after 2 months of talazoparib by a median of 88% (range 30–98%) No grade 4 toxicities, and one patient required dose reduction due to grade 3 neutropenia In the expansion cohort: Primary endpoint: 10 of 19 patients (53%) achieved pCR at 6 months, before surgery One patient experienced grade 4 toxicity (thrombocytopenia), and nine patients required dose reductions	April 2020 April 2021
	NCT03499353 [147, 148]	2	gBRCAm early (stage I–III) TNBC	Talazoparib $N = 61$ (target of 112 evaluable patients)	Open-label, single-arm, multicenter Primary outcome: pCR (ICR) at 24 weeks Secondary outcomes: pCR (investigator assessed), RCB, OS, AEs, PROs including HRQoL	Early termination, September 2020

Table 2 (continued)

Treatment	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/outcomes	Primary and study completion dates (actual or estimated)
Niraparib	Pilot study [143, 144] NCT03329937	1	gBRCAm or sBRCAm, HER2– localized BC	Niraparib *N* = 21 *n* = 18 MRI and ultrasound data	Open-label, single-arm Primary endpoint: TRR, measured by MRI after 2 months of treatment, was 89% Most common (≥ 10%) drug-related TEAEs: nausea, fatigue, anemia, insomnia, decreased appetite Drug-related grade ≥ 3 toxicity in ≥ 10% of patients: anemia (3 patients)	January 2020 March 2020
Olaparib + platinum-based chemotherapy	PARTNER [138, 139] NCT03150576	2/3	TNBC and/or gBRCAm, HER2–, HR+ BC	Stages 1 and 2 randomization (1:1:1): CP, CP + olaparib from day –2 or CP + olaparib from day 3 *N* = 159 in stages 1 and 2 Stage 3 randomization (1:1) to either control or research arm selected in stage 2 *N* = 527 (target)	Randomized, three-stage, open-label Primary endpoint: stage 1 – safety; stage 2 – schedule selection; stage 3 – efficacy (pCR rate) In pooled safety analysis of stages 1 and 2, combination olaparib with neoadjuvant CP showed an acceptable and manageable toxicity profile Most common grade ≥ 3 AEs were hematologic events (neutropenia 19%, anemia 15%, and thrombocytopenia 5%)	January 2022 January 2032
Olaparib	PETREMAC [137, 140] NCT02624973	2	Treatment-naïve BC; olaparib-treated patients had TNBC	Several treatment options investigated *N* = 200 Olaparib followed by chemotherapy *n* = 31	Open-label, single-arm Primary outcome: predictive and prognostic value of mutations in 300 cancer-related genes, assessed in BC tissue by next-generation sequencing ORR with olaparib, 56.3% (16 out of 18 responders had HRD) After excluding 5 patients with gBRCA or g*PALB2* mutations, ORR with olaparib was 51.9%	June 2020 June 2030

Table 2 (continued)

Treatment	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/outcomes	Primary and study completion dates (actual or estimated)
Olaparib + paclitaxel	GeparOla [141] NCT02789332	2	HER2–, operable and locally advanced BC with HRD (deleterious gBRCAm or tBRCAm and/or high HRD score)	Randomization to olaparib + P or CP followed by epirubicin + cyclophosphamide *N* = 107	Randomized, open-label, multicenter Primary endpoint: pCR rate was 55.1% with olaparib combination therapy vs. 48.6% with CP pCR rates were higher with olaparib combination therapy vs. CP in patients < 40 years of age (76.2% vs. 45.5%) and in those with hormone receptor-positive tumors (52.6% vs. 20.0%)	February 2019 February 2020
Veliparib + standard neoadjuvant therapy	BrighTNess [142] NCT02032277	3	Stage II–III TNBC	Randomization (2:1:1) in segment 1 to: CP + veliparib, CP or P; in segment 2 all patients received doxorubicin + cyclophosphamide *N* = 634	Randomized, double-blind, placebo-controlled, multicenter, international Primary endpoint: pCR, 53% CP + veliparib, 58% CP, 31% P ($p = 0.36$ for CP + veliparib vs. CP; $p < 0.0001$ for CP + veliparib vs. P) Grade 3/4 AEs and serious AEs were more common in patients receiving C, with veliparib not appearing to markedly increase toxicity	March 2016 October 2020
Adjuvant setting (after neoadjuvant or adjuvant chemotherapy)						
Olaparib	OlympiA [149, 150] NCT02032823	3	High-risk, gBRCAm, HER2–BC	Randomization (1:1) to olaparib or placebo *N* = 1836	Randomized, double-blind, parallel-group, placebo-controlled, multicenter Primary outcome: invasive DFS with up to 10 years of follow-up Secondary outcomes: OS, distant DFS, incidence of new primary cancers including contralateral BC, PK, fatigue, GI symptoms, HRQoL Other outcomes: safety, tolerability	November 2020 November 2028

suggest that veliparib monotherapy may be beneficial following a discontinuation of combination therapy with veliparib plus carboplatin and paclitaxel [158]. Looking further ahead, ongoing trials are investigating PARP inhibitors in novel combinations, including olaparib plus inhibitors of DDR molecules (ATR or Wee1) for metastatic TNBC (VIOLETTE trial), olaparib plus trastuzumab for HER2-positive BC (OPHELIA trial), and talazoparib plus a bromodomain inhibitor (ZEN003694) or a dual mTOR/PI3K inhibitor (gedatolisib) for metastatic or recurrent/unresectable TNBC [159–163].

6.3 PARP Inhibition in Broader Populations of HRR-Deficient Breast Cancer

PARP inhibitors are being investigated for the treatment of BC in patients with non-gBRCA HRR gene mutations or without documented gBRCA mutations (Tables 1, 2, 3) [73, 78–80, 84, 133, 134, 137, 154, 157, 160–162].

Clinical studies that have positive findings for PARP inhibitors in settings other than gBRCA-mutated BC include single-arm phase 2 studies of rucaparib, olaparib, and talazoparib monotherapy (Table 1). In the RUBY trial, rucaparib monotherapy was investigated in 41 patients with homologous recombination deficiency, including four patients harboring somatic BRCA mutations. Five patients (13.5%) demonstrated clinical benefit, comprising three patients with high loss of heterozygosity (complete response, $n = 1$; partial response, $n = 2$), one with a somatic *BRCA1* mutation (stable disease) and one patient with a somatic *BRCA2* mutation (partial response) [73]. In the Olaparib Expanded study, in 54 patients with metastatic BC and germline mutations in various non-BRCA DDR genes (cohort 1) or somatic mutations in DDR genes including BRCA (cohort 2), ORR was 33% and 31%, respectively. Antitumor activity was reported in patients with somatic BRCA or g*PALB2* mutations but not in those with *ATM* or *CHEK2* mutations [78]. The phase 2 study of single-agent talazoparib enrolled patients with BRCA wild-type, HER2-negative, advanced BC and non-BRCA HRR pathway mutations. Based on 12 evaluable patients, ORR was 25% after 6 months (two of the three responders had g*PALB2* mutations, the other had g*CHEK2*, g*FANCA* and somatic *PTEN* mutations) and the clinical benefit rate was 50% (the three additional patients harbored g*PALB2*, somatic *ATR*, or somatic *PTEN* mutations) [84].

7 Conclusions

PARP inhibitor therapies are a welcome addition to the treatment arsenal for patients with locally advanced or metastatic gBRCA-mutated, HER2-negative BC. Given that this additional option provides targeted therapy for

Table 2 (continued)

Date of table preparation: 21 September 2020 (updated 8 January 2021 for the PETREMAC and GeparOLA trials)

AE adverse event, *BC* breast cancer, *BRCAm* germline or somatic BRCA mutation, *C* carboplatin, *CP* carboplatin and paclitaxel, *DFS* disease-free survival, *gBRCAm* germline BRCA mutation, *GI* gastrointestinal, *HER2–* human epidermal growth factor receptor 2 negative, *HR+* hormone receptor-positive, *HRD* homologous recombination deficiency, *HRQoL* health-related quality of life, *ICR* independent central review, *MRI* magnetic resonance imaging, *ORR* objective response rate, *P* paclitaxel, *PARP* poly(ADP-ribose) polymerase, *pCR* pathological complete response, *PK* pharmacokinetics, *PRO* patient-reported outcome, *sBRCAm* somatic BRCA mutation, *tBRCAm* tumor BRCA mutation, *RCB* residual cancer burden, *TEAE* treatment-emergent adverse event, *TNBC* triple-negative breast cancer, *TRR* tumor response rate

Table 3 Clinical trials of oral PARP inhibitors in combination with immunotherapies and other combinations for the treatment of breast cancer

Treatment	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/findings	Primary and study completion dates (actual or estimated)
PARP inhibitors in combination with immunotherapies						
Niraparib + pembrolizumab	TOPACIO [129] NCT02657889	2	Advanced (unresectable) metastatic TNBC	Niraparib + pembrolizumab $N = 47$ (efficacy) $N = 55$ (safety)	Open-label, single-arm, multicenter Primary endpoint: ORR 21% (47% in patients with tBRCAm) DCR: 49% (80% in patients with tBRCAm) Median PFS: 2.3 months (8.3 months in patients with tBRCAm) Most common treatment-related grade ≥ 3 AEs were anemia (18%), thrombocytopenia (15%) and fatigue (7%)	May 2018 March 2020
Olaparib + durvalumab	MEDIOLA [130, 131] NCT02734004	2	gBRCAm, HER2–metastatic BC	Olaparib + durvalumab $N = 30$ (efficacy) $N = 34$ (safety)	Open-label, single-arm, multicenter Primary endpoint: DCR 80% at 12 weeks DCR: 50% at 28 weeks Median PFS: 8.2 months Median OS: 20.5 months Median DoCR: 9.2 months Most common grade ≥ 3 AEs: anemia ($n = 4$), neutropenia ($n = 3$), pancreatitis ($n = 2$)	August 2022 August 2022
	NCT03801369 [133]	2	BRCAwt metastatic TNBC	Olaparib induction (4 weeks) followed by olaparib + durvalumab $N = 28$ (target)	Open-label, single-arm Primary outcome: ORR Secondary outcomes: CBR, OS, PFS, DoCR, grade ≥ 3 acute toxicity	December 2020 December 2020
	DORA [134] NCT03167619	2	Platinum-responsive locally advanced or metastatic TNBC	Olaparib vs. olaparib + durvalumab $N = 60$ (target)	Randomized, multicenter, international, maintenance Primary outcome: PFS Secondary outcomes: OS, CBR, safety	March 2021 May 2021
Olaparib + atezolizumab	NCT02849496 [135]	2	BRCAm, non-HER2+, unresectable locally advanced unresectable or metastatic BC	Olaparib vs. olaparib + atezolizumab $N = 72$ (target)	Randomized, open-label, crossover Primary outcome: PFS Secondary outcomes: ORR, DoCR	August 2021 (primary completion)

Table 3 (continued)

Treatment	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/findings	Primary and study completion dates (actual or estimated)
Olaparib + pembrolizumab	KEYLYNK-007 [164] NCT04123366	2	Previously treated metastatic and/or unresectable solid tumor with HRRm or HRD, including BC	Olaparib + pembrolizumab *N* = 300 (target)	Open-label, single-arm Primary outcome: ORR Secondary outcomes: DoCR, PFS, OS	December 2023 December 2023
Olaparib + pembrolizumab	KEYLYNK-009 [156] NCT04191135	2/3	Locally recurrent inoperable or metastatic TNBC	Randomization (1:1) to olaparib + pembrolizumab or carboplatin, gemcitabine + pembrolizumab; after induction with chemotherapy *N* = 932 (target)	Randomized, open-label Primary outcomes: PFS (BICR), OS Secondary outcomes: PFS and OS in patients with BRCAm, AEs, HRQoL	January 2026 January 2026
Talazoparib + avelumab	JAVELIN BRCA/ATM [154, 155] NCT03565991	2	BRCAm or ATM-mutated, locally advanced or metastatic solid tumors[a]	Talazoparib + avelumab *N* = 202	Open-label, single-arm, multicenter, international Primary outcome: confirmed OR (BICR) Secondary outcomes: safety, confirmed OR (investigator assessed), time to tumor response, duration of response, PFS, OS, PK, potential predictive biomarkers	March 2021 December 2022
	TALAVE [132] NCT03964532	1/2	HER2– advanced BC	Talazoparib induction (4 weeks) followed by talazoparib + avelumab *N* = 24 (target)	Open-label, multicenter Primary objective: safety and tolerability of combination Secondary objectives: ORR, OS, PFS, DoCR, DCR	December 2020 December 2021

Table 3 (continued)

Treatment	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/findings	Primary and study completion dates (actual or estimated)
PARP inhibitors in other combinations						
Veliparib + platinum-based chemotherapy	BROCADE3 [47, 48] NCT02163694	3	gBRCAm, HER2– locally advanced (unresectable) or metastatic BC	Randomization (2:1) to CP + veliparib or CP + placebo *N* = 509	Randomized, double-blind, placebo-controlled Primary endpoint: median PFS (investigator assessed) 14.5 months for CP + veliparib vs. 12.6 months for CP (HR 0.71, 95% CI 0.57–0.88; $p = 0.002$) 3-year PFS: 26% vs. 11% Median OS (interim): 33.5 vs. 28.2 months Serious AEs: 33.1% veliparib, 30.9% control Prespecified subgroup analysis in patients with no previous cytotoxic chemotherapy for metastatic disease Median PFS: 16.6 months for CP + veliparib vs. 13.1 months for CP	April 2019 November 2021
Veliparib + carboplatin	California Cancer Consortium Trial [70] NCT01149083	1	BRCAm, HER2– or HER2+ metastatic BC	Veliparib + carboplatin *N* = 27, including 2 HER2+	Primary endpoints: DLTs were nausea, dehydration, and thrombocytopenia (MTD: veliparib 150 mg twice daily and carboplatin [area under the curve of 5]) 75% of patients experienced treatment-altering cytopenia (cycles 1–3) ORR: 56% (53% for ER+/PgR+, 63% for ER–/PgR–) CBR: 59% Median PFS: 8.7 months (8.5 months [*BRCA1*] vs. 9.5 months [*BRCA2*]) Median OS: 18.8 months (21.8 months [*BRCA1*] vs. 17.6 months [*BRCA2*])	December 2020 (primary completion)

Table 3 (continued)

Treatment	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/findings	Primary and study completion dates (actual or estimated)
Olaparib + trabectedin	NCT03127215 [157]	2	Locally advanced or metastatic solid tumors with HRD	Randomization (1:1) to olaparib + trabectedin or physician's choice *N* = 90 (target)	Randomized, open-label, parallel-assignment, multicenter Primary outcome: DCR and TRR at 16 weeks Secondary outcomes: PFS, OS, quality of life, safety	March 2020 March 2021
Olaparib + sapacitabine	NCT03641755 [159]	1/2	gBRCAm metastatic or unresectable BC	Olaparib + sapacitabine *N* = 64 (target)	Open-label, single-arm Primary outcomes: MTD, RP2D, ORR Secondary outcomes: PFS, DLT	June 2020 June 2025
Olaparib + DNA damage response inhibitors	VIOLETTE [160] NCT03330847	2	HRRm, HER2–metastatic TNBC	Randomization (1:1:1) to olaparib + AZD6738 (an ATR inhibitor), olaparib + adavosertib (a Wee1 inhibitor) or olaparib *N* = 450 (target)	Randomized, open-label, multicenter Primary outcome: PFS (BICR) Secondary outcomes: ORR, DoCR, change in tumor size, OS, safety	March 2023 March 2023
Olaparib + trastuzumab	OPHELIA [162] NCT03931551	2	gBRCAm or HRD, HER2+, locally regionally recurrent or metastatic BC	Olaparib + trastuzumab *N* = 33 (target)	Open-label, single-arm, multicenter, two-cohort, Simon's two-stage Primary outcomes: ORR, PFS Secondary outcomes: CBR, OS, safety, quality of life	September 2022 September 2022
Olaparib + radiation therapy	RadioPARP [165] NCT03109080	1	TNBC inoperable after neoadjuvant chemotherapy or with residual disease after surgery	Olaparib + radiation therapy *N* = 24	Open-label, single-arm Primary endpoint: olaparib escalated to target dose (200 mg twice daily), without DLT Most olaparib-related AEs were grade 1 or 2 Two patients (8.7%) experienced acute grade 3 dermatitis The only grade 3 or 4 hematologic AE was lymphopenia (46%) No grade 4 AEs related to radiation therapy	April 2020 April 2022

Table 3 (continued)

Treatment	Clinical trial	Phase	Patient population	Study treatments, *N*	Study design and key endpoints/findings	Primary and study completion dates (actual or estimated)
Olaparib + hyperthermia	Pilot study [166] NCT03955640	1	gBRCAwt, HER2– or HER2+ locally advanced or metastatic BC with chest wall recurrences	Olaparib at three escalating doses + chest wall hyperthermia twice a week *N* = 12 (target)	Open-label, single-arm Primary outcome: incidence of AEs (to determine DLT and MTD of olaparib) Secondary outcomes: PFS, ORR, quality of life, pain scores	October 2022 October 2023
Talazoparib + ZEN003694	NCT03901469 [161]	2	Metastatic or recurrent TNBC	Talazoparib + ZEN003694 *N* = 49 (target)	Open-label, single-arm, two-part Part 1, dose escalation; part 2, Simon's two-stage Primary outcomes, part 1: incidence of DLT, safety Primary outcomes, part 2: ORR, safety	September 2020 January 2021
Talazoparib + gedatolisib	NCT03911973 [163]	1/2	gBRCAwt, metastatic or unresectable TNBC or gBRCAm HER2– metastatic or unresectable BC	Talazoparib + gedatolisib *N* = 54 (target)	Open-label, single-arm Primary outcomes: MTD, ORR Secondary outcomes: PFS, DoCR, CBR, OS, safety	May 2021 May 2022
Rucaparib + lucitanib or sacituzumab govitecan	SEASTAR [167] NCT03992131	1/2	Advanced or metastatic solid malignancy, including TNBC	Rucaparib + lucitanib or sacituzumab govitecan *N* = 329 (target; unclear how many will have TNBC)	Open-label, parallel-arm Primary outcomes: MTD, safety, ORR Secondary outcomes: PFS, DoCR, OS, pharmacokinetics	October 2023 March 2024

Date of table preparation: 21 September 2020

[a]It is not explicitly stated in the references that patients with BC have been enrolled in the JAVELIN BRCA/ATM study. *AE* adverse event, *BC* breast cancer, *BICR* blinded independent central review, *BRCAm* BRCA mutation, *BRCAwt* wild-type BRCA, *CBR* clinical benefit rate, *CP* carboplatin and paclitaxel, *DCR* disease control rate, *DLT* dose-limiting toxicity, *DoCR* duration of clinical response, *ER+/PgR+* estrogen receptor/progesterone receptor positive, *ER–/PgR–* estrogen receptor/progesterone receptor negative, *HRQoL* health-related quality of life, *gBRCAm* germline BRCA mutation, *gBRCAwt* wild-type germline BRCA, *HER2+/–* human epidermal growth factor receptor positive/negative, *HR* hazard ratio, *HRD* homologous recombination deficiency, *HRRm* homologous recombination repair mutation, *MTD* maximum tolerated dose, *OR* objective response, *ORR* objective response rate, *OS* overall survival, *PARP* poly(ADP-ribose) polymerase, *PFS* progression-free survival, *PK* pharmacokinetics, *RP2D* recommended phase 2 dose, *tBRCAm* tumor BRCA mutation, *TNBC* triple-negative breast cancer, *TRR* tumor response rate

patients presenting with a gBRCA mutation, patients and healthcare professionals require clear guidance on testing for these mutations. The oral formulation of PARP inhibitors, together with their safety and HRQoL profiles, which are more favorable than for chemotherapy agents, have the potential to improve patient experience and adherence [168]. The most common AEs observed during treatment with PARP inhibitors are generally manageable, but patients should be monitored regularly. New directions for evaluation of PARP inhibitors include earlier stages of BC and in combination with agents that target other HRR-related pathways, with a view to potentially avoiding resistance to PARP inhibitor therapy and expanding indications beyond the gBRCA-mutated population. The advent of PARP inhibitor therapies is likely to have significant implications for the treatment of patients with BC beyond the locally advanced/metastatic setting.

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