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Review Article

PARP inhibitors in HRD BRCAness breast cancer patients

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Abstract

Breast Cancer patients with germline Breast Cancer Gene (BRCA) mutations have a greater advantage from targeted therapy with Poly (ADP-ribose) Polymerase (PARP) inhibitors (PARPi). The identification of patients with homologous recombination deficiency (HRD) tumors that may be sensitive to PARPi besides those with germline BRCA1/2 mutations remains an important point of research. There is increasing evidence demonstrating that breast tumors with BRCAness may benefit from PARPi and there are studies ongoing to identify those subtypes which may benefit the most. Pancreatic cancer with HRD non-BRCA mutations seem to have very little benefit from PARPi, but in HRD non-BRCA ovarian and prostate cancer, PARP inhibition appears to be a reasonable therapeutic target. Also, there is data showing that genomic instability caused by mutations in HRD genes, potentially makes cancer cells susceptible to chemotherapeutic drugs, such as anthracyclines or platinum salts. Widespread use of next generation sequencing could increase the role of hallmarks influencing the DNA repair system and therefore increase the therapeutic possibilities for cancer patients. In this review we evaluate the latest advances with PARPi in BRCAness Breast Cancer patients.

Keywords: Breast Cancer; BRCA mutations; HRD; BRCAness; PARP inhibitors

Introduction

Breast cancer (BC) remains the most frequent malignancy and is still the first cause of cancer related death in women all across the world, according to Globocan [1].

Consistent with some reports, up to 40% of hereditary and sporadic BC have HRD alterations [2]. BC Gene (BRCA) 1 and BRCA 2 mutations are, up to the present time, one of the most clinically important and applicable in the clinic, genetic biomarkers of homologous recombination repair deficiency (HRD) [3]. BRCA mutations are associated with BC and other types of malignancies, as ovarian, pancreatic and prostate cancers [3]. These genes involved in the homologous recombination repair (HRR) pathway repair deoxyribonucleic acid (DNA) double-strand breaks (DSB). HRD-mediated DNA repair deficiency occurs mostly through genetic or epigenetic inactivation of the BRCA1/2 genes and it is essential to the initiation and evolution of many different tumor types [4].

There are other genes included in the HRR pathway, such as partner and localizer of BRCA2 (PALB2), cyclin-dependent kinase 12 (CDK12), RAD51, ataxia-telangiectasia mutated (ATM) and checkpoint kinase (CHEK) 1/2, and variations on these genes can conduct to HRD [3,5]. The greatest sensitivity of tumors with BRCA 1/2 mutations to poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) gives an opportunity for tumors with HRD to be treated with targeted therapy [4,6]. PARP is an essential enzyme capable of repairing DNA single-strand breaks (SSB). Therefore, the synergistic inhibition of the PARP enzyme in tumors with HRD will intensify genomic instability and precipitate cell death [5]. Patients who harbor germline or somatic BRCA mutations have benefit not only from targeted therapies as PARPi, but also from platinum salts [3,5]. Inactivation through promoter methylation of BRCA1 and RAD51C also lead do HRD and these tumors also have improved sensitivity to PARPi and platinum-based chemotherapy [3,7].

Additionally, this PARPi's sensitivity of tumors harboring BRCA1/2 mutations gave rise to

extended use of these drugs in patients with breast, ovarian, pancreatic and prostate cancers with HRD [4].

In Europe, Olaparib and Talazoparib have been approved in patients with human epidermal growth factor receptor-type (HER) 2 negative locally advanced or metastatic BC, previously treated, with germline BRCA1/2 mutation. These approvals were based on the improvement in progression-free survival (PFS) of the two phase III trials which evaluated PARPi versus treatment of physician's choice [8,9]. Also, Olaparib is approved in adjuvant setting for patients harboring germline BRCA1/2 mutations diagnosed with high risk HER2 negative BC previously treated with neo(adjuvant) chemotherapy [9].

In a phase II trial that tests the efficacy of Talazoparib in non-BRCA1/2 tumors, of the 20 patients included, there were 8 patients who had HRD status tested on both primary tumor and metastasis. The authors verified that in these 8 patients' tumors the HRD score was significantly higher in metastasis than in primary tumor (p=0.01) [10].

There is a lack of trials comparing the efficacy of PARPi in HRD-positive patients versus HRD-negative BC patients, which makes more complex the assessment of the benefit of PARPi conditioned on the tumor's HRD status [5].

In this review, we summarize the latest advances with PARPi in BC with BRCAness phenotype.

Which Genes are Involved in Non-BRCA HRD Phenotype and How to Detect It?

The HRD phenotype and their possible sensitivity to PARPI requires a number of genetic and epigenetic alterations which is yet to be fully clarified [6].

Hereditary BRCA1/2 mutations occur in about 7% of all BC cases and in about 11–15% of TNBC. Somatic BRCA1/2 alterations are present in 10% of all BC patients and in 3 to 5% in TNBC [11,12]. BRCA1/2 mutations were first identified as a consequence of their relation with inherited breast and ovarian cancers. Since then, screening for BRCA mutations has become a significant tool for clinical risk evaluation and management [6].

BRCA 1/2, RAD51 and PALB2 are genes that take part in the HRR pathway and the DSB repair mechanism acts in phase S and G2 of the cell cycle. If there is a mutations in one of these genes of the DNA repair system, this will cause deficient DNA repair capacity [12]. ATM and CHEK2 mutations seem to be associated with all subtypes of BC except for TNBC and RAD51C and RAD51D mutations are expressed more frequently in receptor estrogen negative tumors only [2]. PALB2 germline mutations are found in 0.6% to 2.7% of cases of BC and by the age of 70, the risk of developing BC in patients carrying these mutations is around 35%, which is similar to those patients harboring BRCA2 germline mutations [13]. PALB2 and BRCA1 Associated RING Domain 1 (BARD1) are classified as high-risk BC susceptibility genes and critical to the correct function of the HR repair pathway and cell cycle checkpoints. There are other genes involved in HR and cell cycle checkpoints, as TP53, BRCA1 Interacting Helicase 1 (BRIP1), and RAD51C, however these are responsible for moderate BC risk, because they have a quite accessory role in this mechanism [14].

Besides BRCA and PALB2 mutations, there are other combined biomarkers such as loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transition (LST) which can determine HRD status. These alterations can also be identified in tumors that do not harbor BRCA1/2 mutations, describing a subgroup of patients mentioned as BRCAness [8,12,15]. The term "BRCAness" is used for tumors that do not arise in a patient with germline BRCA1/2 mutation, but they share some phenotypes, such as the HRR defect [16].

There are some cohort studies suggesting BRCAness tumors are associated with increased immune cells infiltration and these tumor-infiltrating immune cells are attracted to tumor microenvironment through neoantigens produced by tumor mutation burden [17,18].

BRCAness's tumors result in HRD and have similar clinicopathologic characteristics and responses to DNA damaging drugs when compared with tumors carrying BRCA mutations [11].

That is the reason why it is important to look for these mutations and characterize them, since this can influence the therapeutic strategy. Improvements in tumor sequencing have been made resulting in the development of methods that recognize HRD tumors, as mutational signatures [3,8]. According to literature, there are more than 30-40% of tumors with HRD not harboring any mutation in well known HR-related genes, which suggests that regular tests for mutations in known HRR genes will miss a substantial amount of HRD tumors, specially if HRD arises from some unknown gene [3]. Mutational signatures have shown 20–30% more BC patients with HRD features using whole-genome sequencing (WGS) data than what can be detected applying the BRCA1/2 genotype only [6]. These HRD detection techniques also present a chance to identify different drivers of the HRD phenotype and new therapeutic targets [6]. To predict response to DNA-damaging chemotherapeutic agents in the (neo)adjuvant settings, there is a test called DNA Damage Immune Response assay that has been validated [19]. The MYRIAD/ MyChoice test, based on the levels of LOH, TAI and LST throughout the genome, is analytically and clinically validated and, so far, is the only commercially accessible HRD test. Nonetheless, there was a considerable number of patients who apparently benefited from PARPi or platinum agents and were not categorized as HRD by this tool. There are other tests developed to predict HRD, such as Classifier of HOmologous Recombination Deficiency (CHORD) which is a novel genome-wide mutational scar-based tool, still awaiting validation [20].

The most common methods to detect tumors with HRD by genomics approach are the BROCA cancer risk gene panel and the Foundation medicine T5 next generation sequencing (NGS) assay [11].

WGS analysis is highly time and resource consuming, which requires expertise and infrastructure for long term storage. For all of these reasons, analytical steps to get HRD scoring tools constitute a limitation to daily practice at the moment [8].

The widespread use of NGS techniques can increase the number of genes influencing DNA repair pathway and consequently increase the therapeutic possibilities for cancer patients [12].

There is a lack of information in literature concerning the frequency of these mutations. Nevertheless, the authors believe the majority of non-BRCA HRD mutations are diagnosed when searching for therapeutic target alterations, trying to identify

mutations associated with therapeutic benefit or looking for hereditary alterations during genetic counseling. Further studies are required to clarify the extent of their contribution to hereditary predisposition.

Mechanism of Action of PARPi

The PARPi act on the basis of the principle of Synthetic Lethality. This is an effect that occurs when a single defect in one out of two genes has little or no effect on the cell of the organism, but the combination of two altered genes leads to cell death. An example of a Synthetic Lethal interaction occurs between PARP inhibition and BRCA1/2 mutation [14,16].

When BRCA1/2 are functional, they have the capability to repair the DNA damage (DSB repair) and keep the cell viable. However, in mutated cells, the mechanism of PARP inhibition will cause these SSB to accumulate in DSBs (since there is no DNA repair mechanism), wich will ultimately lead to cell death via apoptosis [14].

There is a pharmacological chance in the cells that have an HRR deficient mechanism, where the PARP inhibition mechanism reduces the capacity of cells for fixing DNA damage [through the Base Excision Repair (BER) pathway]. The cells that are HRR deficient become uncapable of persuing with the repair of DNA damage (whether by HRR or BER). This creates a synthetic lethal phenotype that results in death of the cancer cell. For this reason, when HRR deficiency and PARP inhibition are simultaneously present, this is fatal for the cell [15].

Trough the blockage of the PARP enzyme in tumors with genetic or epigenetic modifications in the proteins involved in the HRR, we create a synthetic lethal phenomenon that destroys cancer cell [21].

Olaparib, Rucaparib, Niraparib, and Talazoparib act by a "trapping" mechanism of the PARP1 on the DNA binding site, and by this mechanism occurs the inhibition of autoPARylation and PARP1 separation. The PARP1 protein, when trapped, becomes cytotoxic. Veliparib has a distinct mechanism from the other PARPi, as it acts directly in inhibiting the autoPARylation (without the "trapping" mechanism) [22].

The question remains whether the synthetic lethality also applies to other HRD mutations than BRCA1/2.

PARP inhibition is a synthetic lethal strategy that target BRCAness, which is a clear driver of malignancy [21].

It was preclinically studied that PARPi had an effect in tumors that were not BRCA mutated but had a deficiency in another HR pathway component, therefore showing an alternative pairing possibility for synthetic lethality [22].

There has been demonstration that deficiencies in other tumor suppressor genes involved in HRR such as the ATM, ataxia telangiectasia and Rad3-related protein (ATR), PALB2, CHEK1 [(encoding CHK1(Checkpoint kinase 1)], and CHEK2 and the Fanconi Anemia (FANCA) gene family, also confer sensitivity to PARPi [16,22].

Taking the example of the ATR, it has a substrate which is CHK1, that once activated inhibits the activity of CDK. CHK1 is an important regulator of the checkpoints G2/M and intra-S. CHK1 inhibitors have a potent synergy with antimetabolites, which produce replication-dependent DNA injury. A relation of synthetic lethality has been described between ATR and inhibition of CHK1, where the combination block leads to a replication fork arrest [21]. For this reason, this ATR/CHK1 relationship was identified as a possible target of synthetic lethality. Pre-clinical studies showed that ATR inhibitors are small molecules that can sensitize cells, not only to radiation but also to chemotherapy, and they also induce synthetic lethality in p53 and ATM-deficient cells. This ATR/CHK1 inhibition also acts as a sensitizer of cells to PARPi, which explains the rational of the treatment combination [22]. Another synthetic lethal relationship with PARPi has been described with PALB2 and Histone Deacetylase 2 (HDAC2) [21].

Targeting mutations (heterozygous somatic or germline) with this strategy is still a challenge since the benefit is not clear yet. It's a complex study since we don't know the consequences of the mutations that occur in the DNA Damage Response (DDR) genes [21].

It is not known whether the second allele loss is needed to predict sensitivity to therapy in most of the genes linked to DDR. Tumours with BRCA1/2 germline mutations are knowkn to be good responders to platinum salts and PARPi. Preclinical studies show that new targeted DDR agents (both ATM and ATR inhibitors), have potential benefits. It is crutial that we study patient selection markers to better select them [21].

PARPi in HRD Non-BRCA in Breast Cancer

The identification of patients with tumors that may be sensitive to PARPi besides those with germline BRCA1/2 mutations remains an important goal [23].

There is a growing interest in finding out whether PARPi can be used for BRCAness patients independent of the presence of BRCA mutations [17].

An effort has been made to create scores that can quantify BRCAness in BC and therefore predict clinical outcomes and response to PARPi.

Clinical studies have been demonstrating that a high HRD score may be an indicator not only of the existance of BRCA1/2 mutations, but also mutations or methylation in other HR-related genes. For this reason, tumors that express a high HRD score are a subtype to consider for treatment with PARPi [10]. **Table 1** summarizes the clinical trials that assess the use of PARPi in BC with HRD BRCAness.

The phase II trial RIO investigated the activity of PARPi in patients with untreated TNBC, with the goal of identifying biomarkers that are predictors to PARPi response in sporadic TNBC. This study enrolled a total of 43 newly diagnosed patients that have not received any treatment, 35 of them (81.4%) with TNBC and BRCA wildtype. These patients were treated with Rucaparib for 2 weeks prior to surgery or neoadjuvant chemotherapy [24]. As secondary endpoint, HRD was identified in 69% of the patients. This trial showed that most of the TNBC have a deficiency in the DNA repair mechanism that can be a target for PARPi. In this study, enzyme PARP induced pro-inflammatory/interferon response in HRD TNBC, and the authors highlight the potential of using WGS mutational signatures to guide cancer treatment, exploring the combination of PARPi with Programmed Death - Ligand 1 (PD-L1)

Table 1. Clinical trials assessing the use of PARPi in HRD breast cancer.

Study	Population / Setting	Treatment	Main results
RIO [24] Phase II	TNBC or not TNBC, with or without known BRCA1/2 mutation Neoadjuvant setting	Rucaparib	No association was observed between Ki67 change with BRCA1/2 mutated cancers (primary endpoint) Identified mutational processes characteristic of HRD in 69% locally assessed TNBC
Talazoparib Beyond BRCA, TBB (NCT02401347) [25] Phase II	HER2-negative breast cancer (HR positive or TNBC) Other tumor types	Talazoparib	In BC: ORR of 31% and a CBR of 54% All patients with germline PALB2 showed tumor regression
Olaparib Expanded (TBCRC 048) [26] Phase II	Metastatic BC	Olaparib	PARP inhibition is also an effective treatment for advanced BC patients with germline PALB2 PFS in the germline PALB2 populations: 13.3 months
RUBY [8] Phase II	Metastatic BC with HRD, without germline BRCA1/2 mutation	Rucaparib	13.5% of HRD patients showed CBR
Talazoparib monotherapy in PALB2 mutation associated advanced BC (NCT04756765) [29] Phase II	Advanced BC associated with a PALB2 mutation	Talazoparib	Ongoing
NOBROLA [28] Phase II	Non-BRCA TNBC	Olaparib	Waiting for results

BC: Breast Cancer; BRCA1/2: Breast Cancer Gene; CBR: Clinical Benefit Rate; HER2: Human Epidermal Growth Factor Receptor-type 2; HRD: Homologous Recombination Repair Deficiency; ORR: Overall Response Rate; PALB2: Partner and Localizer of BRCA2; PFS: Progression Free Survival; TNBC: Triple Negative Breast Cancer

or Programmed Death 1 (PD-1) immune checkpoint inhibitors, in sporadic TNBC with HRD [24].

The phase II Talazoparib Beyond BRCA trial studied the role of Talazoparib in patients with advanced HER2-negative BC that have been previously treated (13 in total: 11 hormone receptors positive and 2 TNBC) and other solid tumors (7 in total: 3 pancreas, colon, testicular, parotid, uterous) with other mutations in the HR pathway genes (non-BRCA1/2). Among the 13 patients, 4 patients (31%) achieved partial response; 6 patients (46%) had stable disease and 3 patients (23%) had progressive disease as their best response - overall response rate (ORR) of 31% and a clinical benefit rate (CBR) of 54% in this subgroup. In this trial it was demonstrated that all patients with PALB2 germline mutations had uniformly high HRD scores and tumor regression, confirming the sensitivity of germline PALB2 BC to PARPi [10,25].

The phase II Olaparib Expanded trial (TBCRC 048) evaluated the response with Olaparib in patients with the diagnosis of metastatic BC with somatic BRCA1/2 mutations and other mutations in HRD related genes (besides BRCA1/2). This study enrolled 54 patients, from which 76% had estrogen receptor positive/HER2 negative disease. Eighty seven percent of them had mutations in PALB2, somatic BRCA1/2, ATM or CHEK2 [26]. The primary endpoint was ORR, that was 33% in the germline mutations in non BRCA1/2 HRD-related genes, and 31% in the somatic BRCA1/2 cohort. Confirmed responses were seen only with germline PALB2 mutations (82%). Median PFS was significantly higher in the germline PALB2 populations, when compared with somatic BRCA1/2 mutation carriers (13.3 vs. 6.3 months). In this study no responses were observed in patients with ATM or CHEK2 mutations alone which lead the authors to conclude that patients with these mutations alone do not seem to respond to PARPi [27]. With this evidence, we can get to the conclusion that PARPi might be an effective and promising treatment for metastatic BC patients with germline PALB2 or somatic BRCA1/2, and this significantly increases the population of patients who is expected to respond and have clinical benefit with PARP inhibition [26].

The phase II RUBY trial included 42 metastatic BC patients with HRD and germline BRCA wild-type that were treated with Rucaparib. This trial showed a clinical benefit in a subgroup of patients with germline BRCA wild-type advanced BC with high LOH. It reported a CBR of 13.5% (primary end-point not reached). Two high LOH patients with no somatic BRCA1/2 mutations had a complete and durable response (12 and 28.5 months). With a median follow-up of 25.8 months, the median duration of Rucaparib treatment was 47 days, median PFS was 1.7 months and median overall survival (OS) was 6.7 months [8].

There are other trials studying the sensitivity to PARPi in this cancer patients' subgroup, such as "NOBROLA Phase II trial

for non-BRCA metastatic BC with HRD treated with Olaparib Single Agent" and "Talazoparib monotherapy in PALB2 mutation associated advanced BC" [28,29]. The NOBROLA trial is evaluating the efficacy of Olaparib in previously treated metastatic BC patients, with non-BRCA HRD-related mutation [28]. The phase II trial "Talazoparib monotherapy in PALB2 mutation associated advanced BC" is an ongoint trial (still in recruitment) that intends to evaluate if this PARPi in monotherapy can induce an ORR of 30% in PALB2 mutated patients with advanced BC [29].

PARP in HRD Non-BRCA in Other Tumors

HRD is a mechanism not restricted to BC tumors. Ovarian, prostate, pancreatic and other tumors also seem to have these defects. In fact, the activity of PARPi was first demonstrated for ovarian cancer patients, and only thereafter tested for other cancer types.

Ovarian cancer

Up to 50% of high grade serous ovarian cancer patients may exhibit HRD [30]. This fact justifies the rationale for testing PARPi in these patients. PARPi pivotal trials were conducted in previously treated ovarian cancer patients, showing clinical benefit for BRCA1/2 mutation carriers [31-34], but also for patients unselected for these genetic alterations [35]. Niraparib improved ORR in patients with HRD-positive tumors, regardless of the presence of BRCA mutations, though it is not used in advanced disease [35].

Nowadays, the use of PARPi in ovarian cancer is mostly restricted to maintenance therapy for patients with stage III and IV ovarian cancer, after partial or complete response to platinum salts. The studies that led to Olaparib approval in platinum sensitive disease, either as first line therapy [36] or in platinum-sensitive relapse [37] were restricted to BRCA 1/2 carriers. On the other hand, trials that tested Niraparib and Rucaparib after platinum response did not select patients according to the presence of this mutation or HRD status and showed benefit in the overall population [38-42]. Veliparib was also tested in addition to first line chemotherapy and continued as maintenance, in advanced high-grade serous ovarian carcinoma, in a population unselected for BRCA 1/2 or HRD status [41]. In these trials, the magnitude of benefit seems to be defined by the BRCA and HRD status: BRCA patients are the ones who benefit the most, followed by patients with other HRD besides BRCA. These findings are valid either for the use as maintenance after first line therapy or in platinum-sensitive relapse [38-42]. As such, these drugs seem to be effective in all high grade serous ovarian cancer independent of HRD.

The combination of Olaparib with bevacizumab, after response to platinum-based chemotherapy plus bevacizumab, also seems to prolong PFS in patients unselected for BRCA mutations. The benefit was also more pronounced for patients with HRD, either BRCA-associated or non-BRCA associated [43].

Table 2 highlights the evidence from phase III trials on the use of PARPi in ovarian cancer patients with HRD.

Table 2. Evidence from phase III trials for the use of PARPi in ovarian cancer patients with HRD.

Study	Study population	Study arms	HRD patients	mPFS in HRD patients
PRIMA [38]	Newly diagnosed advanced ovarian cancer after a response to first-line platinum-based chemotherapy	Niraparib vs placebo	373/733 (50.9%)	21.9 vs. 10.4 months; HR 0.43; 95% CI [0.31-0.59]; p<0.001
PRIME [39]	Newly diagnosed advanced ovarian cancer with response to first-line chemotherapy	Niraparib vs placebo	257/384 (66.9%	HRD population (HR 0.48)
NOVA [40]	Platinum-sensitive relapsed ovarian cancer	Niraparib vs placebo	162/533 (30.5%) (non-germinal BRCA HRD patients)	12.9 months vs. 3.8 months in the non-germinal BRCA cohort for patients who had tumors with HRD (HR 0.38; 95% CI, 0.24 - 0.59)
ATHENA [42]	Newly diagnosed advanced ovarian cancer after a response to first-line platinum-based chemotherapy	Rucaparib vs placebo	234/538 (43.4%)	28.7 vs. 11.3 months HR 0.47; 95% CI [0.31- 0.72]; p= 0.0004
PAOLA-1 [43]	Newly diagnosed, advanced ovarian cancer with response after first-line platinum-taxane chemotherapy plus bevacizumab	Olaparib + bevacizumab vs. placebo + bevacizumab	387/806 (48%)	37.2 vs. 17.7 months; HR 0.33 95% CI [0.25-0.45]; 28.1 vs. 16.6 months; HR 0.43 95% CI [0.28-0.66] in HRD non-germinal BRCA patients
VELIA [41]	Previously untreated stage III or IV high-grade serous ovarian carcinoma	Chemotherapy + placebo followed by placebo vs. chemotherapy + veliparib followed by placebo vs. chemotherapy + veliparib followed by veliparib	421/1140 (36,9%)	31.9 vs. 20.5 months; HR 0.57; 95% CI, [0.43-0.76]; p<0.001

BRCA: Breast Cancer Gene; CI: Confidence Interval; HR: Hazard Ratio; HRD: Homologous Recombination Repair Deficiency; PFS: Progression Free Survival

Prostate cancer

Up to 25% of metastatic prostate cancers harbor defects in DNA repair genes [44]. There are some studies focusing in PARPi in patients with metastatic castration-resistant prostate cancer (mCRPC) harboring HRD.

A phase II trial treated mCRPC patients progressing after systemic therapy with Olaparib and found higher response rate in patients whose tumors had defects in DNA-repair genes. In the 16 patients with homozygous deletions, deleterious mutations or both in DNA-repair genes, 88% responded to the iPARP [45]. Another phase II trial also validated the association between DDR gene aberrations and response to Olaparib in mCRPC patients previously treated with taxane [46].

The phase III PROfund trial evaluated Olaparib in mCRPC in patients with HRD tumors and whose disease had progression after a new generation hormonal agent. This trial had two cohorts, both of which included non-BRCA HRD patients: for cohort A, patients were included if an alteration were present in BRCA1/2 or ATM. Cohort B included patients with alteration in any of 12 other prespecified genes. In cohort A, either PFS and OS were better with Olaparib vs. treatment of physician's choice of enzalutamide or abiraterone: PFS 7.4 vs. 3.6 months [Hazard ratio (HR) 0.34; 95% CI (0.25 - 0.47), p<0.001)]; OS 18.5 months with Olaparib vs. 15.1 months in the control group. Imaging-based PFS in the overall population was also better in the Olaparib group (median 5.8 vs. 3.5 months; HR 0.49; 95% CI (0.38 - 0.63), p<0.001). As such, all patients with tumors with HRD defects included seem to benefit [47,48]. These studies support the use of Olaparib in mCRPC patients.

Niraparib was also studied in a phase II trial in pretreated with an androgen signaling inhibitor and a taxane mCRPC patients with biallelic DNA-repair gene defects (DRD). This study had two cohorts: BRCA cohort (germline or somatic biallelic pathogenic alterations in BRCA1/2) and non-BRCA cohort (biallelic alterations in other prespecified DRDs). This study also supports a possible role of Niraparib in this mCRPC patient population, since ORR was 34.2% [(95% confidence interval (CI) 23.7-46.0)] in the BRCA cohort and 10.6% (95% CI 3.5-23.1) in the non-BRCA cohort [49]. Rucaparib was studied in TRITON2 trial in patients pretreated with one or two lines of next-generation androgen receptor-directed therapy and one taxane-based chemotherapy for mCRPC. The investigators reported a subanalysis on patients with non-BRCA DDR gene alterations that included 78 patients. Majority of patients had an ATM (n=49), CDK12 (n=15) or CHEK2 (n=12) alteration. As opposed to other trials, responses were only observed in a limited number of patients with the mentioned alterations, with radiographic and prostate specific antigen (PSA) responses seen in less than 17% of patients [50]. TRITON 3 is studying Rucaparib vs. treatment of physician's choice among abiraterone, enzalutamide or docetaxel in mCRPC harboring HRD (BRCA 1/2 or ATM gene) whose disease had progressed on one prior next generation androgen receptor-targeted therapy (NCT02975934) [51]. Talazoparib was also studied in a phase II trial that included patients with mCRPC with alterations in HRR genes and that have received taxane-based chemotherapy regimens, and progressed on enzalutamide, abiraterone, or both. The ORR was 29.8% (31 of 104 patients; 95% CI 21.2–39.6), presenting activity of this drug in this population [52].

Pancreatic cancer

In pancreatic cancer, HRD prevalence ranges between 14.5%-16.5% through targeted NGS [53].

Olaparib monotherapy was tested in phase II trials including previously treated pancreatic cancer patients harboring non-BRCA HRD mutations, with disappointing results [54]. As so, and in contrast to BRCA 1/2 mutated pancreatic cancer patients [55], the role of PARPi in pancreatic cancer patients with non-BRCA HRD defects is yet to be established.

Other tumors

Talazoparib beyond BRCA evaluated Talazoparib in patients with alterations in HRR genes other than BRCA1/2. Besides the majority of the population were BC patients (n=13), 7 out of the 20 had other tumors (3 pancreatic cancer, 1 colon cancer, 1 mixed mullerian uterine tumor, 1 testicular cancer, 1 parotid acinic cell carcinoma). The overall population had mutations (either germline or somatic) in ATM, ATR, BRIP1, CHEK2, FANCA, PALB2, Phosphatase and Tensin Homolog (PTEN) and/or RAD50 genes. HRD was assessed by Myriad myChoice HRD CDx. All patients with germline mutations in PALB2 had tumor regression and higher HRD scores were correlated with better response to Talazoparib. Also, exploratory *de novo* mutational signature analysis found one predominant signature in samples collected from patients with only germline PALB2 mutations, and association of the presence of this signature with tumor response [10]. A phase II study is also being initiated to evaluate the role of Niraparib in patients with HRD uterine leiomyosarcoma or other rare gynecologic malignancies [56].

Platinums and other Pharmacologic Therapies in HRD BRCA and Non-BRCA in Breast Cancer

Another possible strategy for BC with variants associated with DNA repair is to use a DNA-damaging agent. Genomic instability caused by mutations in HRD genes potentially makes cancer cells susceptible to chemotherapeutic drugs, such as anthracyclines or platinum compounds, which act directly to damage DNA [2,57].

Several prospective clinical trials evaluated the clinical net impact of platinum in patients with germline HRD. This clinical relevance has also been demonstrated by the frequent cure rate of advanced high grade serous ovarian cancer patients with BRCA mutations that were only treated with platinum salts and taxanes. Platinum compounds exert their action primarily through cytotoxic mechanisms. First, the influx of platinum salts into the cell is performed by the high affinity copper uptake protein 1 (SLC31A1), second these salts suffer aquation, getting high reaction to DNA, creating monoadducts and DNA strand links that alters DNA structure. Such damage to the double helix structure results in interruption of DNA replication and transcription. Platinum doses have impact on its mechanism of action: high intensity cisplatin doses cause necrosis, whereas low chronic doses induce apoptosis. However, its action is not confined merely to DNA damaging. Platinum salts function on messenger ribonucleic acid (mRNA) translation and on DNA repair mechanisms too. Some studies have described a role for BER in repairing DNA bulky lesions and in the repair of other effects caused by cisplatin. Indeed, some observations have been made regarding known genetic defects of these DNA repair pathways, as BCRA mutations, that may be a good predictive biomarker of platinum agent's effectiveness [58].

Therapies that damage DNA or inhibit its repair such as doxorubicin (causes DNA DSB) or cyclophosphamide (induces DNA cross-linking causing to DSB) have benefit if used in tumors with DNA repair deficiency phenotype. TNBC is considered enriched for the HRD pathway and HRD status is prognostic in TNBC, possibly identifying patients who receive greater benefit from AC-based chemotherapy [59]. This is a very relevant clinical observation because there is a high frequency (over 50%) of pathological complete response (pCR) in TNBC patients that are treated with neoadjuvant chemotherapy [60,61]. This shows that not all patients with early onset TNBC harbor deleterious prognosis. Several clinical trials have been conducted to explore the role of platinums in the treatment of BC. These studies select patients by germline BRCA mutation status, HRD status or TNBC patients. Patients with BRCA 1/2 mutation with/without high HRD status treated with platinum have higher sensitivity to this chemotherapy agent, higher response rates, higher pCR rates and prolonged PFS. The efficacy of platinum and anthracyclines is demonstrated in patients with TNBC and high HRD status with proven benefit in pCR rates, PFS and OS, although there is still some uncertainty about what should be the threshold for HRD status. Also, immunotherapy has proven efficacy in TNBC with high pCR rates and prolonged PFS.

When comparing with other subtypes, TNBC has more immunogenic properties because it has high levels of tumor mutational burden, PD-L1 expression and tumor infiltrating lymphocytes. The high mutational burden is responsible for the creation of anomalous proteins, which function as "neoantigens" which are going to be identified by the antigen-presenting cells, therefore triggering an antitumor immune response [62]. *In vitro* studies have highlighted the role which PARPi plays in stimulating intrinsic immunity and upregulating interferon release, leading to increased expression of PD-L1 in the tumor and infiltration of CD8 T cells, allowing the subsequent use of PD-L1 blockers [63].

Table 3 summarizes the studies about chemotherapy and other therapies in BC with HRD.

Table 3. Clinical trials assessing the use of chemotherapeutic agents in BC with HRD.

Reference	Setting	Treatment	Results
Biomarker: BRCA 1/2 mutations			
TNT [64] phase III	Stage IV TNBC	Docetaxel or carboplatin in first line	Carboplatin showed more favorable objective response rates (68% vs. 33%, p = 0.03) and PFS (6.8 vs. 4.4 months, p = 0.002). However, such a benefit was not observed in patients with TNBC with BRCA1 methylation, BRCA1 mRNA-low tumors, or a high score in a Myriad HRD assay
Byrski et al. [65]	Neoadjuvant	Neoadjuvant cisplatin	Higher pCR rates in patients treated with platinum monotherapy for BRCA1 mutated BC
Wang et al. **Meta-Analysis: GeparSixto, Inform and Brightness trials** [66]	Breast cancer with BRCA mutations	Platinum-based neoadjuvant chemotherapy	The addition of platinum to neoadjuvant chemotherapy did not significantly improve pCR
Caramelo et al. systematic review and meta-analysis [67]	TNBC neoadjuvant	Platinum-based neoadjuvant chemotherapy	There was no statistical difference in pCR rates
Biomarker: HRD Status			
Galland et al. [57]	Metastatic BC	Platinum-based chemotherapy (regardless of the line of treatment)	Metastatic BC patients with high HRD score or high S3 tumor level do not seem to benefit more from platinum-based chemotherapy than the others, in terms of response and/or PFS.
Telli et al. [68]	TNBC neoadjuvant setting	Platinum-containing neoadjuvant chemotherapy	High pCR rates in patients treated by platinum monotherapy for HRD BC
GeparSixto [69] Phase II	Localized TNBC	Carboplatin added to an anthracycline/taxane based neoadjuvant chemotherapy	Patients with TNBC with high HRD scores (≥42) yielded favorable responses to platinum-based. Demonstrated 3-year PFS and 3-year OS rates were higher in patients with TNBC with HRD-positive results who underwent platinum-based neoadjuvant than those who were HRD negative
NCT01372579 [70] Phase II	Early-stage TNBC	Carboplatin and eribulin	Patients with TNBC with high HRD scores (≥42) yielded favorable responses to platinum-based

TBCRC 008 [71]	HER2-negative primary operable breast cancer	Platinum-based	Patients with TNBC with high HRD scores (≥42) yielded favorable responses to platinum-based chemotherapy. 30% of HER2-negative luminal B subtype HRD-positive patients and 5% of HER2-negative luminal B subtype HRD-negative patients achieved pCR
BrighTNess [60] phase III	Stage II-III TNBC Neoadjuvant setting	Carboplatin +/– veliparib	Patients with TNBC with high HRD scores (≥42) yielded favorable responses to platinum based. HRD score was not observed as a predictor of pathological response with an HRD score threshold of 33
TBCRC 030 [72] phase II	Early stage TNBC neoadjuvant	Cisplatin versus paclitaxel	High-HRD scores were not associated with pCR HRD score was not observed as a predictor of pathological response with an HRD score threshold of 33
SWOG S9313 [59] phase III	TNBC adjuvant	Doxorubicin and cyclophosphamide	HRD positivity was observed in two-thirds of TNBC patients receiving adjuvant treatment and was associated with better PFS
Biomarker: BRCA 1/2 mutations and HRD status			
TBCRC 009 [73] phase II	Metastatic TNBC	Platinum monotherapy (80% first line)	Higher HRD scores in responding patients, whatever the BRCA 1/2 mutational status
Chai et al. Systematic Review and Meta-Analysis [74]	Early-stage TNBC neoadjuvant C chemotherapy	Platinum-based neoadjuvant chemotherapy	Higher efficacy of platinum-based neoadjuvant chemotherapy was observed in BRCA 1/2-mutated/HRD-positive TNBC, compared with BRCA 1/2-wildtype and HRD negative TNBC.
PrECOG 0105 [75] Phase II	TNBC neoadjuvant chemotherapy	Gemcitabine, carboplatin, and iniparib	Patients lacking a BRCA1/2 mutation but with an elevated HRD score achieved a favorable pathologic response
Biomarker: TNBC			
CALGB 40603 [61]	Localized TNBC stage II-III neoadjuvant chemotherapy	Addition of carboplatin and/or bevacizumab to neoadjuvant paclitaxel followed by dose-dense doxorubicin and cyclophosphamide	Increase clinical response and pCR rates
GeparSixto; GBG 66 [76] phase II	Localized TNBC Stage II-III and HER2 positive	Neoadjuvant carboplatin	Improved pCR rates for patients with TNBC, but not HER2-positive disease
Saleh et al. [77] Meta-analysis	Early-stage TNBC neoadjuvant or adjuvant	Platinum-based	Improves PFS but not OS
Birkbak et al. [78]	TNBC and serous ovarian cancers	Cisplatin neoadjuvant	Overexpression of the Bloom helicase (BLM) and Fanconi anemia complementation group I (FANCI) genes promotes DNA damage and induces sensitivity to cisplatin but has no effect on paclitaxel sensitivity
IMpassion130 [79] phase III	Metastatic TNBC	Atezolizumab and nab-paclitaxel	Atezolizumab plus nab-paclitaxel prolonged progression-free survival

BC: Breast Cancer; BLM: Bloom Helicase Gene; BRCA: Breast Cancer Gene; DNA: Deoxyribonucleic Acid; FANCI: Fanconi Anemia Complementation Group I Gene; HER 2: Human Epidermal Growth Factor Receptor-type 2; HRD: Homologous Recombination Repair Deficiency; mRNA: Messenger Ribonucleic Acid; OS: Overall Survival; pCR- Pathological Complete Response; PFS: Progression Free Survival; TNBC: Triple Negative Breast Cancer

From the global analysis of the studies summarized in the **Table 3**, and despite some discrepancies, we can conclude that BC with HRD and TNBC present better outcomes if they are treated with platinum agents, anthracyclines and immunotherapy.

Conclusions

PARPi are a recent target therapy approved for treatment of a variety of cancers with BRCA mutations, either germinal or somatic. The importance of testing for inherited and acquired defects in HRD genes, is not only for cancer risk assessment but also as response biomarkers, as therapeutic targets, in prediction of treatment effectiveness and informative of cancer prognosis. It is widely known that patients with BRCA mutations have an enhanced benefit not only from targeted therapies such as PARPi, but also from platinum-based chemotherapy. Nowadays, PARPi (Olaparib and Talazoparib) are only an option in BC patients with germline BRCA mutations. We proposed to review PARPi's role in HRD BRCAness BC (with ATM, PALB2, CHECK2, RAD51 alterations), which remains an important point of research. NGS techniques are of widespread use and can increase the therapeutic possibilities for cancer patients, but this is still a limitation in daily practice. There are some phase II studies showing promising results with PARPi in BRCAness metastatic BC patients regarding ORR, CBR and PFS. HRD non-BRCA ovarian cancer has phase III studies indicating benefit of PARPi respecting PFS. HRD non-BRCA prostate cancer also seems to benefit from PARPi based on phase two clinical trials. On the other hand, HRD BRCAness pancreatic cancer had disappointing results in phase two studies, with very little benefit from PARPi. Despite existing results, there is a pivotal need of phase III clinical trials with PARPi in BRCAness BC patients, for these target therapies to become widely used.

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Institutional Review Board Statement

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Informed Consent Statement

Patient consent was waived for this study since this is a review article.

Conflicts of Interest

The authors declare no conflict of interest.

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