Clinical Applications of PARP Inhibitors in Breast, Ovarian, and Prostate Cancer: Current Insights and Future Directions

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Abstract: Poly(ADP-ribose) polymerase (PARP) inhibitors have emerged as an important therapeutic option for patients with homologous recombination repair (HRR)–deficient cancers, especially those with *BRCA1/2* mutations. Since the initial US Food Administration approval of olaparib in 2014, PARP inhibitors have shown efficacy across ovarian, breast, and prostate cancers, although differences in trial design and biomarker strategies have resulted in tumor-specific indications. Homologous recombination deficiency (HRD) arises from germline or somatic mutations in HRR genes or from epigenetic inactivation, and it can be assessed through genomic "scars" such as loss of heterozygosity and mutational signatures. Although *BRCA1/2* alterations confer the strongest sensitivity to PARP inhibitors, non-*BRCA* HRR gene mutations demonstrate heterogeneous responses, highlighting the need for more precise HRD assessment, including the role of biallelic vs monoallelic inactivation. Despite initial success, both primary and acquired resistance—through reversion mutations, replication fork stabilization, and therapy-induced clonal hematopoiesis—limit the durability of the response to PARP inhibition. Ongoing studies are evaluating rational combinations targeting complementary DNA damage response pathways (ATR/CHK1/WEE1, PI3K/AKT) and integrating immunotherapy or hormonal agents to extend benefit. Moving forward, harmonizing HRD testing across tumor types, accounting for germline, somatic, and liquid biopsy–derived alterations, and refining patient selection will be essential to maximize therapeutic efficacy and safely expand PARP inhibitor use beyond canonical *BRCA*-mutated cancers.

Keywords
BRCA mutations, breast cancer, homologous recombination deficiency (HRD), ovarian cancer, PARP inhibitors, prostate cancer

Introduction

The first poly(ADP-ribose) polymerase (PARP) inhibitor, olaparib (Lynparza, AstraZeneca), was approved in 2014 for patients who had

advanced ovarian carcinoma with germline *BRCA1/2* mutations. Since then, the clinical use of PARP inhibitors has been studied in various cancer types and stages.[1] The use of PARP inhibitors in solid tumor malignancies like ovarian, breast, and prostate cancers has been shown to be effective for patients with pathogenic mutations in *BRCA* and other genes involved in homologous recombination repair (HRR). Although the mechanisms of action of various PARP inhibitors remain grossly the same, differences in clinical trial design have contributed to distinct indications for each of the drugs. Further, data regarding toxicity and resistance patterns are emerging that suggest that drugs in this family can differ in regard to normal tissue tolerance as well as resistance mechanisms. In addition to exploring the prevalence of homologous recombination deficiency (HRD) in ovarian, breast, and prostate cancers, this review examines currently approved uses of PARP inhibitors to treat these malignancies, highlighting the differences among tumor types. Additionally, it addresses key challenges in optimizing PARP inhibitor therapy, including pinpointing the ideal patient populations most likely to benefit, understanding the mechanisms behind emerging drug resistance, and exploring the potential for expanding PARP inhibitor applications beyond cancers with pathogenic HRR gene mutations.

PARP Mechanism of Action

PARPs are a family of 17 enzymes involved in cellular stress responses, chromatin remodeling, DNA repair, and apoptosis. Among them, PARP1 and PARP2 detect and repair single-strand DNA breaks through base excision repair and other pathways, such as nucleotide excision repair and nonhomologous end joining.[2] When these enzymes sense DNA damage, their catalytic activity relaxes chromatin and recruits repair machinery to the site of injury.

In cancers such as breast, ovarian, and prostate cancers, loss or dysfunction of HRR genes (eg, *BRCA1/2*) through mutation, epigenetic silencing, or genomic alteration creates HRD.[3] These tumors rely on alternative repair mechanisms, including PARP-mediated base excision repair. Inhibition of PARP1/2 leads to an accumulation of single-strand breaks that collapse into double-strand breaks during replication. In HRD cells unable to repair such lesions, PARP inhibition results in *synthetic lethality* and tumor cell death. PARP inhibition also promotes error-prone nonhomologous end joining, further enhancing cytotoxicity.

By exploiting synthetic lethality in HRD tumors, PARP inhibitors selectively target cancer cells while sparing normal tissue—a strategy that has revolutionized treatment for ovarian, breast, and prostate cancers during the past decade.[4]

HRD Prevalence and Measurement

BRCA1 and *BRCA2* play central roles in HRR, and their loss through germline or somatic mutation, chromosomal rearrangement, or epigenetic silencing is the most studied cause of HRD in breast, ovarian, and prostate cancers.[5] Pathogenic alterations in other HRR genes (eg, *PALB2*, *ATM*, *CHEK2*, *ARID1A*, *ATRX*) can also produce HRD phenotypes. In a molecular profiling study of more than 17,000 solid tumors, HRR gene mutations were detected in 17.4% of cases—most frequently in *ARID1A* (7.2%), *BRCA2* (3.0%), *BRCA1* (2.8%), *ATM* (1.3%), *ATRX* (1.3%), and *CHEK2* (1.3%).[5] Ongoing trials continue to define the predictive value of non-*BRCA* HRR genes for PARP inhibitor response.[6,7]

HRD can be assessed by identifying its *causes* (deleterious HRR gene alterations via germline or somatic sequencing) or its *effects* (the genomic "scars" that reflect defective HRR).[3,8] These scars—loss of heterozygosity (LOH), telomeric allelic imbalance, large-scale state transitions, and mutational signatures such as SBS3—form the basis of composite HRD scores (eg, the MyChoice CDx HRD test).[8-11,12] However, all HRR gene mutations do not confer equivalent HRD, and genomic scars may persist even after HRR function is restored (eg, via *BRCA* reversion mutations).[5-6] Thus, although HRD assays provide valuable insights, their predictive accuracy for therapeutic sensitivity to PARP inhibitors is constrained by tumor heterogeneity, assay variability, and the potential for acquired resistance mechanisms.

Ovarian Cancer

Approximately 41% to 50% of ovarian carcinomas exhibit HRD due to either genetic or epigenetic alterations of HRR pathway genes, particularly serous and endometrioid histologic subtypes.[13-14] The Cancer Genome Atlas (TCGA) project has consistently shown that high-grade serous ovarian cancers are characterized by frequent genetic and epigenetic alterations of HRR pathway genes, most commonly the *BRCA1* and *BRCA2* genes.[15] The TCGA demonstrated an 8.5% prevalence of germline *BRCA1* mutations and a 6.3% prevalence of *BRCA2* mutations. Similarly, the prevalence of somatic *BRCA1* mutations was 3.2% and the prevalence of somatic *BRCA2* mutations was 2.9%. The frequency of both germline and somatic changes (mutation, deletion, or amplification) in non-*BRCA* HRR genes in ovarian carcinoma is much lower and more heterogeneous.

Breast Cancer

Germline *BRCA1* and *BRCA2* mutations account for up to 7% of all breast cancers and have been found in approximately 11% to 15% of patients with triple-negative breast cancer (TNBC).[16-18] *BRCA1* mutations are most

commonly associated with the TNBC clinical subtype, whereas *BRCA2* mutations are more frequently associated with estrogen receptor (ER)–positive tumors.[19] Additional germline mutations in other non-*BRCA1/2* HRR-related genes (eg, *PALB2*, *ATM*, *CHEK2*, *BARD1*, and *RAD51D*) have been associated with an increased risk of breast cancer. In a study of more than 113,000 women with breast cancer, both *ATM* and *CHEK2* were more strongly associated with ER-positive breast cancers.[19] In contrast, *BARD1*, *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, and *RAD51D* were more strongly associated with ER-negative disease.[19] In more recent studies, both functional and genomic metrics of HRD have been used to assess HRD in breast cancer; stricter HRD criteria were found to have a higher concordance with *BRCA*ness, high tumor-infiltrating lymphocyte density, or high programmed death ligand 1 expression among both TNBC and non-TNBC subtypes, suggesting that a more refined definition of HRD could help predict functional HRD more precisely.[20]

Prostate Cancer

Deleterious genomic abnormalities in HRR genes have been described in 10% of patients with localized prostate cancer and up to 30% of patients with metastatic castration-resistant prostate cancer (mCRPC).[21] Of those patients, approximately 8% to 12% with advanced prostate cancer harbor a germline mutation in a gene associated with DNA repair.[21] The most commonly altered genes in the HRR pathway in advanced prostate cancer include *BRCA1* or *BRCA2* (11%-13%), *ATM* (4%-6%), *CHEK2* (1.4%-2%), *CHEK1* (0.9%-2%), *CDK12* (1.3%-8%), *PALB2* (0.3%-3%), *BARD1* (1.2%-1.4%), and *FANCL* (1.2%).[23] Marshall and colleagues found that these alterations are significantly enriched in tumors with relatively aggressive pathologic features; men with Gleason grade group 3 or higher or pathologic stage pT3 to pT4 disease were roughly twice as likely to carry HRR mutations as were men with lower-grade or earlier-stage disease.[24] When both a high Gleason grade and advanced pathologic stage were present, the prevalence rose to higher than 20% for any HRR gene mutation and nearly 12% for a *BRCA1/2* or *ATM* mutation. In contrast, clinical T stage and nodal status were not strongly associated with mutation prevalence. These findings suggest that even in patients with localized disease, higher-risk pathologic features may help identify those most likely to benefit from DNA repair gene testing and potentially HRR-targeted therapies.

Currently Approved Clinical Indications for PARP Inhibitors

Ovarian Cancer

The concept of synthetic lethality between *BRCA*-mutated cells and PARP inhibition was first demonstrated in 2005 and was led to clinical translation with Study 42. This phase 2 trial of olaparib in heavily pretreated patients with *BRCA1/2*-mutated ovarian cancer showed an overall response rate of 34% and resulted in the first US Food and Drug Administration (FDA) approval of a PARP inhibitor in 2014.[2,25-26] Subsequent approvals for rucaparib (Rubraca, Clovis Oncology) and niraparib (Zejula, GSK) followed in both the first-line and recurrent settings.

Three phase 3 trials—SOLO-1 (olaparib, 2018),[27] PRIMA (niraparib, 2019),[28] and ATHENA-MONO (rucaparib, 2022)[29]—established first-line maintenance PARP inhibitor benefit in stage III to IV ovarian, peritoneal, or fallopian tube cancers responding to platinum therapy. SOLO-1 enrolled patients with *BRCA*-mutated tumors, whereas PRIMA and ATHENA-MONO included patients with all biomarker groups; all studies showed significant improvement in progression-free survival (PFS), particularly among patients with *BRCA*-mutated or HRD-positive tumors, leading to FDA approvals of olaparib and niraparib for first-line maintenance. In PAOLA-1,[30] olaparib plus bevacizumab further improved PFS and overall survival (OS) in HRD-positive patients, resulting in approval of the combination regimen; similar findings were observed with niraparib plus bevacizumab in OVARIO.[31]

In the setting of recurrent, platinum-sensitive disease, olaparib gained approval as maintenance monotherapy on the basis of Study 19 and SOLO-2, followed by niraparib (NOVA) and rucaparib (ARIEL3).[32-35] Initial approvals spanned all biomarker groups, but updated analyses showed that OS benefit was limited to *BRCA*-mutated cohorts. This finding prompted label restrictions of niraparib and rucaparib in 2022 to relapsed, platinum-sensitive, germline *BRCA*-mutated ovarian cancers.[36-37]

For later-line therapy, olaparib (Study 42), rucaparib (ARIEL2), and niraparib (QUADRA) initially received approvals for *BRCA*-mutated or HRD-positive recurrent disease.[2,38-39] However, final OS analyses from SOLO-3 and ARIEL4 suggested diminished or adverse survival outcomes with PARP inhibition vs chemotherapy in heavily pretreated patients, leading to the voluntary withdrawal of these later-line monotherapy indications.[40-41] Table 1 summarizes the current FDA approvals of PARP inhibitors for patients with advanced ovarian cancer.

Breast Cancer

At present, the FDA has approved two PARP inhibitors for the treatment of breast cancer: olaparib and talazoparib (Talzenna, Pfizer). The OlympiAD trial evaluated olaparib monotherapy vs single-agent chemotherapy in patients with a germline *BRCA* mutation and human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer who had received no more than

Table 1. Key Clinical Trials Supporting FDA Approvals of PARP Inhibitors in Ovarian Cancer*

PARP inhibitor	Relevant study	Indication	Mutational requirement	Year of FDA approval
Olaparib	Study 42	Advanced ovarian carcinoma with ≥3 prior chemotherapies	Germline *BRCA1/2*m	2014
	SOLO-2	Recurring ovarian, fallopian tube, and primary peritoneal carcinoma	None	2017
	SOLO-1	First-line maintenance treatment of advanced ovarian, fallopian tube, and primary peritoneal carcinoma after complete or partial chemotherapy response	*BRCA1/2*m	2018
	PAOLA-1	First-line treatment of advanced ovarian, fallopian tube, and primary peritoneal carcinoma + bevacizumab after complete or partial chemotherapy response	HRD-positive	2020
	SOLO-3	Platinum-sensitive, relapsed ovarian cancer after ≥2 prior platinum-based chemotherapies	Germline *BRCA1/2*m	Voluntarily withdrawn for indication in 2022
Rucaparib	ARIEL2 and Study 10	Advanced ovarian carcinomas after ≥2 lines of chemotherapy	*BRCA1/2*m	2016
	ARIEL3	Maintenance treatment of platinum-sensitive advanced ovarian, fallopian tube, and primary peritoneal carcinoma after ≥2 prior platinum-based chemotherapies	None	2018; later, in 2022, restricted to patients with *BRCA1/2*m disease
	ATHENA-MONO	First-line maintenance treatment of advanced ovarian, fallopian tube, and primary peritoneal carcinoma after complete or partial chemotherapy response	None	2018
	ARIEL4	Relapsed high-grade ovarian carcinoma after ≥2 prior chemotherapies	*BRCA1/2*m	Voluntarily withdrawn for indication in 2022
Niraparib	NOVA	Recurring ovarian, fallopian tube, and primary peritoneal carcinoma	None	2017; later, in 2022, restricted to patients with germline *BRCA*m, platinum-sensitive, relapsed ovarian cancer
	QUADRA	Advanced ovarian carcinoma with ≥3 prior chemotherapies	HRD-positive (*BRCA*m and/or genomic instability)	2019; voluntarily withdrawn for indication in 2022
	PRIMA	First-line maintenance treatment of advanced ovarian, fallopian tube, and primary peritoneal carcinoma after complete or partial chemotherapy response	None	2020

*BRCA1/2*m, *BRCA1/2*-mutated; FDA, US Food and Drug Administration; HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase.

*Summary of pivotal trials evaluating olaparib, rucaparib, and niraparib in ovarian, fallopian tube, and primary peritoneal carcinomas. Approvals are listed by study, indication, biomarker requirement, and year. Early indications were restricted to *BRCA1/2*-mutated, platinum-treated populations and later expanded to maintenance settings regardless of biomarker status. Following updated analyses of overall survival, several later-line indications were voluntarily withdrawn or label-restricted in 2022.

2 prior chemotherapy regimens for metastatic disease.[42] Median PFS was significantly longer with olaparib than with chemotherapy (7.0 vs 4.2 months). In the final OS analysis, however, no significant difference was detected in median OS in a comparison of olaparib vs chemotherapy. OS benefit was greater for patients treated with olaparib in the first-line metastatic setting than for those in a later-line setting. The results of this study led to the FDA approval of olaparib monotherapy in germline *BRCA*-mutated, HER2-negative metastatic breast cancer in January 2018. More recently, the National Comprehensive Cancer Network (NCCN) guidelines now include the use of PARP inhibition for HER2-negative metastatic breast cancer with somatic *BRCA1/2* or germline *PALB2* mutations on the basis of the TBCRC 048 study.[7]

Similarly, the subsequent EMBRACA study compared talazoparib monotherapy with standard-of-care therapy in patients who had advanced breast cancer harboring a germline *BRCA* mutation and who had received no more than 3 prior chemotherapy regimens for advanced breast cancer.[43] Median PFS was longer in the talazoparib group than in the standard-of-care group (8.6 vs 5.6 months), leading to the approval of talazoparib for the treatment of patients with deleterious or suspected deleterious germline *BRCA*-mutated HER2-negative breast cancer in October 2018. Talazoparib did not improve OS in comparison with standard-of-care therapy; however, a significant improvement in health-related quality of life and a delay in time to deterioration were noted.

In the adjuvant setting, the phase 3 OlympiA trial evaluated 1 year of olaparib monotherapy vs placebo after chemotherapy in patients with high-risk HER2-negative breast cancer harboring a germline *BRCA* mutation.[44] Olaparib reduced the risk of recurrence (4-year invasive disease–free survival rate, 83% vs 75%; hazard ratio [HR], 0.63 [95% CI, 0.50-0.78]; $P<.001$) and demonstrated a 32% reduction in risk of death (4-year OS, 90% vs 86%; HR, 0.68 [95% CI, 0.47-0.97]; $P=.01$).[45] In 2022, these results led to the approval of olaparib for the adjuvant treatment of patients with deleterious or suspected deleterious germline *BRCA*-mutated, HER2-negative, high-risk early breast cancer who had been treated with neoadjuvant or adjuvant chemotherapy.

Prostate Cancer

In 2020, rucaparib was the first PARP inhibitor approved for mCRPC after the phase 2 TRITON2 trial demonstrated robust activity in patients with *BRCA*-mutated disease: prostate-specific antigen (PSA) responses in 52% and RECIST responses in 44% of evaluable patients.[46] The subsequent phase 3 TRITON3 trial confirmed these findings, supporting the role of rucaparib in this setting.[47]

The phase 3 PROfound trial compared olaparib with physician's choice of enzalutamide (Xtandi, Astellas) or abiraterone in patients with HRR gene–mutated mCRPC that had progressed on prior androgen receptor (AR) pathway inhibitors.[48] Olaparib significantly improved radiographic PFS (18.5 vs 15.1 months) and OS[49], particularly among those with *BRCA1/2* or *ATM* mutations[50], leading to its FDA approval for mCRPC with deleterious HRR alterations in genes beyond *BRCA* (*ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*).

Building on preclinical synergy between PARP inhibition and AR blockade, PARP inhibitor/AR pathway inhibitor combinations have been evaluated as first-line therapy.[51] In PROpel, olaparib plus abiraterone and prednisone (AAP) prolonged radiographic PFS in comparison with AAP alone in all-comers,[52] although OS benefit was seen mainly in patients with *BRCA*-mutated tumors—prompting the 2023 FDA approval of olaparib plus AAP for *BRCA*-mutated mCRPC.[53] Similarly, MAGNITUDE demonstrated improved PFS with niraparib plus AAP in patients with *BRCA* mutations but not in subgroups with other HRR gene mutations or without HRR gene mutations, so that approval was restricted to *BRCA*-mutated mCRPC.[54-55]

Finally, TALAPRO-2 evaluated talazoparib plus enzalutamide vs enzalutamide alone in mCRPC, showing a significant radiographic PFS improvement, with the greatest benefit in patients with HRR gene–mutated tumors.[56-57] This resulted in the FDA approval of talazoparib plus enzalutamide for patients with deleterious alterations in at least one of 12 HRR genes (*BRCA1/2*, *PALB2*, *ATM*, *ATR*, *CHEK2*, *FANCA*, *RAD51C*, *NBN*, *MLH1*, *MRE11A*, and *CDK12*).[58] Table 2 summarizes all currently FDA-approved PARP inhibitors for patients with advanced prostate cancer.

The clinical development of PARP inhibitors has yielded differing indications across ovarian, breast, and prostate cancers, largely reflecting nuances in trial design. In ovarian cancer, early pivotal studies such as SOLO-1[27] and ARIEL2[59] prospectively incorporated both *BRCA* status and functional HRD assays, establishing efficacy not only in *BRCA*-mutated tumors but also in genomically unstable, *BRCA* wild-type subgroups.[35] In breast cancer, by contrast, registration trials were restricted to patients with germline *BRCA* mutations, and exploratory studies such as TBCRC 048 demonstrated that responses were far more limited in patients with non-*BRCA* HRR gene alterations, reinforcing a narrower approval.[7] Prostate cancer trials such as PROfound and TALAPRO-2 employed broader gene panels that included *BRCA1/2*, *ATM*, and other HRR genes, which led to approvals encompassing multiple DNA damage response alterations—although subgroup analyses consistently showed that clinical benefit was most pronounced in *BRCA2*-mutated disease.[48,50-52]

Collectively, these differences underscore how eligibility criteria, biomarker strategies, and prespecified subgroups in trial design directly shaped the regulatory landscape, resulting in PARP inhibitor indications in ovarian and prostate cancers broader than the more selective approvals in breast cancer.

Current Challenges and Future Directions: Defining HRD

As is evident from the variable subgroup analyses and subsequent regulatory approvals of PARP inhibitors based on trial design, one of the major challenges in PARP inhibitor use remains developing a consensus regarding HRD definition so that the patients most likely to benefit from this therapy can be selected more accurately.

BRCA vs Non-BRCA Mutations

Ovarian Cancer. It is generally thought that deleterious mutations of *BRCA1* or *BRCA2* confer some form of HRD. Therefore, early clinical trials assessing the use of PARP inhibitors in ovarian cancer often focused primary analysis or exploratory subgroup analysis on *BRCA* mutation status, as seen in the SOLO-1 trial or Study 42.[27,60] These studies concluded that patients with a non-*BRCA* HRR gene–mutated tumor derived benefit from PARP inhibitor treatment vs placebo, although to a lesser extent than those with a *BRCA*-mutated tumor. Other randomized controlled trials investigating the use of PARP inhibition in ovarian cancer also evaluated patients on the basis of functional HRD status. In the ARIEL2 trial, in addition to *BRCA* mutation status, patients were assessed for percentage of genomic LOH in pretreatment biopsy specimens to provide an overall prediction of sensitivity to rucaparib.[34, 38] The FoundationOne NGS assay (Foundation Medicine) was used to stratify participants into 3 predefined HRD subgroups: tumor *BRCA*-mutated, *BRCA* wild-type/LOH-high, and *BRCA* wild-type/LOH-low.[59] Similarly, in both QUADRA and PAOLA-1, in addition to determining tumor *BRCA* mutation status, the MyChoice HRD Plus assay (Myriad Genetic Laboratories) was used to determine a prespecified tumor HRD status retrospectively before primary analysis; a positive test result was defined as a tumor *BRCA* mutation and/or a genomic instability score of at least 42.[39,61]

Breast Cancer. The PARP inhibitors olaparib and talazoparib are currently approved for the treatment of HER2-negative breast cancers in the metastatic and adjuvant settings only for patients harboring a germline *BRCA1/2* mutation. That said, the phase 2 TBCRC 048 trial sought to assess the efficacy of olaparib in patients who had metastatic breast cancer with a germline or somatic mutation in a non-*BRCA* HR-related gene or with a somatic *BRCA1/2* mutation. Of the 54 patients enrolled, 87% had mutations in *PALB2* (germline), *BRCA1/2* (somatic), *ATM* (germline), or *CHEK2* (germline).[7] Confirmed responses to olaparib monotherapy were seen in patients with germline *PALB2* mutations (median PFS, 13.3 months), whereas no responses were observed in patients with *ATM* or *CHEK2* mutations alone. On the basis of the results of this study, the NCCN has incorporated the use of PARP inhibitors for patients who have metastatic breast cancer with somatic *BRCA1/2* mutations or germline *PALB2* mutations into its guidelines.

Prostate Cancer. PARP inhibitor sensitivity in non-*BRCA* HRR-related gene–mutated tumors has been most frequently explored in mCRPC, given the high frequency of HRR gene mutations in prostate cancer. Numerous studies have documented a more aggressive phenotype and poorer outcomes in patients with *BRCA2*-mutated tumors than in those with *BRCA1*-mutated or non-*BRCA* HRR gene–mutated tumors.[62] In the PROfound trial, a prespecified secondary endpoint analysis demonstrated better image-based PFS with olaparib monotherapy than with standard-of-care therapy in the overall study population, which included patients with at least one qualifying deleterious alteration in 1 of 15 prespecified HRR genes (*BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*).[48] Improved PFS was particularly noted in cohort A, which included patients with *BRCA1*, *BRCA2*, or *ATM* mutations. This finding led to the approval of olaparib monotherapy after progression on a novel AR pathway inhibitor for patients with mCRPC or for any patient with a qualifying deleterious alteration in 1 of the 15 HRR-related genes previously noted. Of note, a significant OS benefit was seen in cohort A but not in the overall population.[49] Post hoc subgroup analysis of the patients who had mCRPC with *BRCA* alterations showed prolonged responses to olaparib (16.6 months vs not reached) in those with *BRCA2* homozygous deletion.[50] Similarly, the phase 3 TALAPRO-2 study demonstrated significantly better PFS with talazoparib plus enzalutamide than with placebo plus enzalutamide in the HRR gene-mutated population (median PFS, not reached vs 13.8 months; HR, 0.45; 95% CI, 0.33-0.61; $P<.0001$), and this result led to the FDA approval of enzalutamide in the first-line setting for mCRPC.[56] Follow-up analysis demonstrated improved OS with the addition of talazoparib to first-line enzalutamide, both in patients with HRR-deficient mCRPC and in the overall unselected population.[58] Of note, in an exploratory analysis by *BRCA* mutation status, the HR for radiographic PFS was 0.20 (95% CI, 0.11-0.36) in patients with *BRCA*-mutated mCRPC and 0.72 (95% CI, 0.49-1.07) in patients with non-*BRCA* HRR gene-mutated mCRPC, findings that suggested an improved clinical benefit for

Table 2. Key Clinical Trials Supporting FDA Approvals of PARP Inhibitors in mCRPC*

PARP inhibitor	Relevant study	Indication	Mutational requirement	Year of FDA approval
Monotherapy				
Rucaparib	TRITON2	Patients with mCRPC	*BRCA1/2*m	2020
Olaparib	PROfound	Patients with mCRPC who received a prior androgen receptor pathway inhibitor	HRRm**	2020
Combination therapy				
Olaparib	PROpel	Patients with mCRPC + **abiraterone + prednisone** in the frontline setting	*BRCA1/2*m	2023
Talazoparib	TALAPRO-2	Patients with mCRPC + **enzalutamide** in the frontline setting	HRRm***	2023
Niraparib	MAGNITUDE	Patients with mCRPC + **abiraterone + prednisone** in the frontline setting	*BRCA1/2*m	2023

*BRCA1/2*m, *BRCA1/2*-mutated; FDA, US Food and Drug Administration; HRD, homologous recombination deficiency; HRRm, homologous recombination repair–mutated; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly(ADP-ribose) polymerase.

*Summary of pivotal trials evaluating PARP inhibitor monotherapy and combination therapy in mCRPC. Approvals are listed by study, indication, biomarker requirement, and year. Early approvals (TRITON2 and PROfound) established PARP inhibitor efficacy in *BRCA1/2*- and HRR-mutated disease following progression on androgen receptor pathway inhibitors. More recent frontline combination approvals (PROpel, TALAPRO-2, MAGNITUDE) integrate PARP inhibition with androgen receptor–targeted therapy, demonstrating benefit in biomarker-defined subsets.

**Patients were considered to have HRD if they had or were suspected to have a deleterious alteration in at least one of the following 15 prespecified genes selected for their direct or indirect role in HRR: *BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.

***Patients were considered to have HRD if they had or were suspected to have a deleterious alteration in at least one of the following 12 prespecified genes selected for their direct or indirect role in HRR: *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *ATR*, *CHEK2*, *FANCA*, *RAD51C*, *NBN*, *MLH1*, *MRE11A*, and *CDK12*.

those with a *BRCA1* or *BRCA2* mutation.[63] Therefore, recent NCCN guidelines recommend that tumor testing for HRR gene mutations (*BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *PALB2*, *FANCA*, *RAD51D*, and *CDK12*) be considered for all men with metastatic, regional, or clinically localized high-risk prostate cancer.

Further studies have assessed if different HRR gene mutations result in differences in sensitivity to PARP inhibition in prostate cancer. Consistently higher PSA response rates to androgen deprivation therapy plus PARP inhibition are seen in patients with *BRCA2*-altered prostate cancer than in those with other HRR gene alterations.[46,64-66] Fallah and colleagues noted that the benefit of PARP inhibitors plus AR pathway inhibitors in mCRPC varied substantially by HRR gene; they showed the strongest effect on survival endpoints in patients with *BRCA2* mutations (radiographic PFS HR, ~0.31; OS HR, ~0.66), some benefit in those with *CDK12* and *BRCA1* mutations, and no clear improvement in those with *ATM* and *CHEK2* mutations.[67] Similarly, Orme and colleagues found that responses to PARP inhibitors were markedly better in patients with both *BRCA2* and *SPOP* mutations than in those with *BRCA2* mutations alone; they demonstrated higher PSA responses, longer PFS, and longer OS.[68] Co-occurring *SPOP* mutations were associated with elevated HRD signature (SBS3) scores, suggesting increased functional HRR deficiency in the double mutants. These findings suggest not only that different HRR genes drive very different magnitudes of PARP inhibitor sensitivity but also that the presence of co-occurring somatic mutations (eg, *SPOP*) can modulate response in prostate cancer, possibly by intensifying HRD or related phenotypes.

Germline vs Somatic Mutations

Almost half of all high-grade serous tubo-ovarian carcinomas have either a germline or somatic pathogenic variant in *BRCA1/2*.[69] Studies have shown that germline *BRCA1/2* pathogenic variants are associated with favorable survival, a higher rate of response to platinum-based chemotherapies, and increased sensitivity to PARP inhibitors.[14] Somatic *BRCA1/2* mutations have been assumed

to confer a similar phenotype. Hollis and colleagues compared somatic *BRCA1/2* vs germline *BRCA1/2* variants in ovarian cancer and found that germline and somatic *BRCA1/2* mutations are equivalent in their association with prolonged survival.[69] Similarly, both germline and somatic *BRCA1/2* variants were associated with high HRD scores. In breast cancer, the phase 2 TBCRC 048 trial sought to assess the efficacy of olaparib in patients who had metastatic breast cancer with a germline or somatic *BRCA1/2* mutation.[7] The study showed that for those with somatic *BRCA1/2* mutations, the median PFS on olaparib was 6.3 months. This was less than the median PFS for those with germline *PALB2* mutations, which was 12.3 months.

Research directly comparing the association of somatic vs germline HRD-related pathogenic variants with clinical outcomes is limited in prostate cancer.

Biallelic vs Monoallelic Mutations

The hypothesis of PARP-induced synthetic lethality theoretically requires biallelic inactivation; however, biallelic loss is rarely reported in many PARP inhibitor trials. Studies have shown that biallelic inactivation of *BRCA1*, *BRCA2*, *RAD51C*, and *PALB2* is the most frequent genetic cause of HRD cancer across types in both primary and metastatic cancer. However, research on the clinical implications of biallelic vs monoallelic mutations is limited.[70] In a phase 2 study by Marshall and colleagues looking at the effect of olaparib in patients with biochemically recurrent prostate cancer following prostatectomy, PSA50 responses were more frequent in patients with biallelic than in those with monoallelic HRR gene alterations.[64]

Liquid Biopsy for HRD Assessment and the Confounding Role of Clonal Hematopoiesis

Plasma-based assays can assess HRD by detecting pathogenic alterations in HR-related genes, by evaluating genomic scar scores such as LOH, large-scale transition, and telomeric allelic imbalance, or by identifying mutational signatures consistent with HRD. Although these liquid biopsy approaches overcome the limitations of tissue testing, interpretation is complicated by clonal hematopoiesis (CH), in which age- or therapy-related hematopoietic clones shed DNA into the circulation that can be mistakenly attributed to the tumor. Large-scale studies, including the Circulating Cell-free Genome Atlas (CCGA) exploratory analysis, have demonstrated that CH is common and increases with age, with many cases involving genes relevant to DNA repair.[71]

CH frequently affects genes such as *ATM* and *CHEK2*, which overlap with HRD-associated pathways. Misclassification of these alterations as tumor-derived can falsely increase the prevalence of HRD and lead to inappropriate treatment with PARP inhibitors. Marshall and colleagues reported that CH is particularly enriched among patients with solid tumors who have received prior systemic therapy, further heightening the risk of plasma cell-free DNA misinterpretation.[72] In prostate cancer specifically, Jensen and colleagues showed that CH in DNA repair genes interfered directly with cell-free DNA test interpretation, with *ATM* mutations a recurrent source of false-positive tumor calls.[73]

Mitigation strategies include sequencing paired white blood cells to filter out CH, applying conservative bioinformatic algorithms to flag variants in CH-prone genes, and requiring additional supporting evidence, such as biallelic loss, concordant tissue findings, or HRD-associated genomic scars. Isolated *ATM* variants particularly should be interpreted with caution because clinical benefit from PARP inhibitors in *ATM*-mutated prostate cancer has been inconsistent even when alterations are tumor-derived.

In summary, liquid biopsy can contribute significantly to HRD assessment, but CH—especially in DNA damage response (DDR) genes like *ATM*—poses a well-documented risk of misclassification. The incorporation of white blood cell controls, multiple signal confirmation, and careful clinical interpretation are essential to avoid inappropriate categorization and therapeutic decision making.[71-73]

Mechanisms of PARP Inhibitor Resistance and Combination Strategies

Despite the efficacy of PARP inhibitors in HRR-deficient tumors, resistance—both primary and acquired—remains a major challenge. In the best-known mechanism, secondary "reversion" mutations restore *BRCA1/2* or other HRR gene function, thereby reconstituting homologous recombination. Recent studies have identified polyclonal reversion events with convergent evolution, in which distinct secondary mutations simultaneously restore HRR capacity.[74] Additional mechanisms include replication fork stabilization, reduced PARP1 trapping, altered drug efflux, and rewiring of DNA damage response pathways.[75] Notably, PARP inhibitors can also select for DDR–related CH, potentially contributing to resistance and poor outcomes.[76-78]

To counter resistance, rational combinations are under study. Targeting ATR/CHK1/WEE1 can disrupt replication stress responses and resensitize tumors with restored HRR, whereas PI3K/AKT inhibition suppresses *BRCA1/2* and induces synthetic lethality.[79-80] Other promising approaches include pairing PARP inhibitors with immune checkpoint blockers, antiangiogenic agents, or AR inhibitors in prostate cancer.[81-82] Collectively, these strategies aim to delay or overcome resistance and extend

PARP inhibitor benefit across HRR-deficient and even HRR-proficient disease.

Conclusion

Across breast, ovarian, and prostate cancers, PARP inhibitors have expanded the therapeutic options for patients with HRD. However, gene-specific effects, biomarker definitions, trial designs, underlying disease biology, co-occurring molecular drivers, and differences in existing treatment landscapes have driven divergent regulatory approvals and clinical expectations. Germline and somatic *BRCA* alterations remain the ones most predictive of benefit, whereas non-*BRCA* HRR genes show variable sensitivity, underscoring the need for gene- and disease-specific selection. Resistance through reversions, fork protection, reduced PARP1 trapping, and therapy-induced DDR-CH is common, but rational combinations (ATR/CHK1/WEE1, PI3K/AKT targeting agent, antiangiogenic agent, AR pathway inhibitor, and immunotherapy) may extend efficacy.

Moving forward, the precision use of PARP inhibitors will require harmonizing cross-tumor insights and emphasizing biallelic vs monoallelic alterations, given their differing effects on PARP inhibitor response. Future trials should integrate functional HRD assays, account for somatic vs germline and CH contributions, and test rational combinations to refine indications and maximize benefit.

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