Clinical Application of PARP Inhibitors in Breast Cancer: Current Evidence, Biomarkers, Resistance, and Future Directions

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Abstract

Poly(ADP-ribose) polymerase (PARP) inhibitors have established a precision-treatment paradigm in breast cancer by exploiting synthetic lethality in tumors with defective homologous-recombination repair. Olaparib and talazoparib improve progression-free survival and patient-reported outcomes compared with single-agent chemotherapy in germline BRCA1/2-mutated, HER2-negative advanced breast cancer, while one year of adjuvant olaparib provides sustained invasive disease-free, distant disease-free, and overall-survival benefits in patients with germline BRCA1/2-mutated, HER2-negative high-risk early disease. Six-year follow-up of OlympiA confirms that the benefit persists after treatment completion, supporting early germline testing when the result may alter systemic therapy. Nevertheless, BRCA1/2 mutation is not a uniform predictor of response, and the clinical value of PARP inhibition depends on mutation origin, functional homologous-recombination deficiency, previous platinum exposure, disease setting, and competing treatment options. Phase II evidence supports substantial activity in germline PALB2-mutated and somatic BRCA1/2-mutated metastatic breast cancer, whereas isolated ATM or CHEK2 mutations have not reliably predicted benefit. Attempts to extend PARP inhibition to unselected triple-negative disease or to intensify platinum-containing chemotherapy have produced mixed or negative randomized results. Resistance arises through BRCA reversion, restoration of homologous recombination, replication-fork protection, altered PARP1 function, and drug efflux. Hematologic toxicity, fatigue, gastrointestinal symptoms, renal function, drug interactions, reproductive risk, and the rare possibility of myelodysplastic syndrome or acute myeloid leukemia require structured monitoring. This review summarizes the biological rationale, pivotal clinical trials, biomarker selection, treatment sequencing, resistance mechanisms, safety management, and emerging combinations of PARP inhibitors in breast cancer. Their future value will depend on functional biomarker development and rational integration with platinum agents, immunotherapy, targeted therapy, and antibody–drug conjugates rather than indiscriminate expansion beyond biologically sensitive disease.

Key words

Breast cancer, PARP inhibitors, BRCA1, BRCA2, Homologous recombination deficiency, Synthetic lethality, Olaparib, Talazoparib

1. Introduction

Breast cancer comprises biologically diverse diseases in which inherited and acquired defects in DNA-damage repair can influence both carcinogenesis and treatment sensitivity. Pathogenic germline variants in BRCA1 and BRCA2 confer a substantially increased lifetime risk of breast and ovarian cancer and are enriched in patients with early-onset disease, triple-negative breast cancer, male breast cancer, bilateral disease, and a suggestive family history. BRCA1-associated tumors are frequently triple negative and basal-like, whereas BRCA2-associated tumors more often retain estrogen-receptor expression. Despite these phenotypic tendencies, receptor status alone cannot substitute for genetic testing, and clinically relevant BRCA-associated cancers occur across both triple-negative and hormone receptor-positive, HER2-negative subtypes.

The therapeutic importance of BRCA1/2 extends beyond inherited risk. BRCA1 and BRCA2 are essential components of high-fidelity homologous-recombination repair of DNA double-strand breaks and stalled replication forks. Tumor cells that lose the remaining functional BRCA allele become highly dependent on alternative repair and damage-tolerance pathways. Inhibition of poly(ADP-ribose) polymerase 1 and 2 (PARP1/2) exploits this dependency, converting otherwise repairable lesions into replication-associated damage that homologous-recombination-deficient cells cannot adequately resolve. The resulting synthetic lethality provides a therapeutic window between BRCA-deficient tumor cells and normal tissues that retain homologous-recombination capacity[1–4].

Olaparib and talazoparib are established treatments for deleterious or suspected deleterious germline BRCA1/2-mutated, HER2-negative locally advanced or metastatic breast cancer. Olaparib is additionally approved as adjuvant therapy for germline BRCA1/2-mutated, HER2-negative high-risk early breast cancer after neoadjuvant or adjuvant chemotherapy[14–15]. These indications represent one of the clearest examples of genomic selection in breast oncology. However, important uncertainties remain regarding the optimal timing relative to platinum, endocrine therapy, immune checkpoint blockade, capecitabine, CDK4/6 inhibition, and antibody–drug conjugates; the role of somatic BRCA1/2 or non-BRCA homologous-recombination genes; and treatment after acquired resistance.

The clinical literature also cautions against treating PARP inhibition as a universal strategy for triple-negative or genomically unstable breast cancer. Randomized trials combining weaker PARP trapping with platinum chemotherapy have sometimes improved progression-free survival, but have not consistently improved overall survival or demonstrated a contribution independent of platinum. In germline BRCA-wild-type triple-negative disease, adding olaparib to platinum-based neoadjuvant chemotherapy failed to increase pathologic complete response. Accordingly, this review distinguishes validated indications from biologically plausible but unproven extensions and emphasizes the relationship among genotype, functional repair state, treatment context, and clinical outcome.

2. Biological Foundation and Pharmacologic Characteristics

PARP1 is a nuclear DNA-damage sensor that binds rapidly to single-strand breaks and selected forms of replication stress. After binding, PARP1 uses nicotinamide adenine dinucleotide as a substrate to synthesize poly(ADP-ribose) chains on itself and neighboring proteins. This PARylation recruits repair factors, alters chromatin, and facilitates resolution of DNA lesions. Auto-PARylation also promotes release of PARP1 from DNA after repair has been initiated. PARP2 has partially overlapping functions, while other members of the PARP family participate in diverse processes that are not equally inhibited by clinically used agents.

Clinical PARP inhibitors act through at least two related mechanisms. Catalytic inhibition prevents PARylation and compromises repair of single-strand lesions. More importantly for some agents, the inhibitor stabilizes PARP–DNA complexes, a phenomenon known as PARP trapping. Trapped complexes obstruct replication forks and are more cytotoxic than an unrepaired single-strand break alone. Talazoparib has particularly strong trapping potency, whereas veliparib is relatively weak; olaparib occupies an intermediate position. Trapping potency does not alone determine clinical superiority because exposure, dose, off-target effects, tolerability, tumor pharmacology, and the comparator regimen all influence outcome[2].

During S phase, unrepaired lesions and trapped PARP complexes can generate one-ended DNA double-strand breaks. Homologous recombination normally repairs these lesions using the sister chromatid as a template. BRCA1 coordinates end resection and pathway choice, while BRCA2 loads RAD51 onto single-stranded DNA to form the nucleoprotein filament required for homology search and strand invasion. When BRCA1/2 function is lost, cells rely on error-prone repair, accumulate chromosome aberrations, and become vulnerable to further disruption of PARP-dependent repair. The same biological principle may apply to

selected defects in PALB2, which links BRCA1 and BRCA2, but does not extend uniformly to every gene annotated within a broad DNA-repair panel.

Olaparib is generally administered at 300 mg orally twice daily using the tablet formulation, whereas talazoparib is administered at 1 mg orally once daily in patients with adequate renal function. Both agents commonly cause anemia, fatigue, nausea, and other gastrointestinal symptoms, but talazoparib produces comparatively prominent myelosuppression, consistent with its high trapping potency. Olaparib is metabolized mainly through CYP3A and is susceptible to strong or moderate CYP3A inhibitors and inducers. Talazoparib is transported by P-glycoprotein and requires attention to transporter inhibitors and renal clearance. These differences affect individual selection even though no head-to-head breast-cancer trial has established one agent as universally superior.

PARP inhibition is cytotoxic rather than merely cytostatic, but response remains heterogeneous. A pathogenic germline variant does not guarantee that a tumor has lost the wild-type allele or remains homologous-recombination deficient at treatment. Conversely, a tumor may acquire a functionally equivalent repair defect through somatic BRCA1/2 alteration, PALB2 loss, BRCA1 promoter methylation, or another mechanism. Static sequencing therefore captures only part of the relevant biology. The central clinical challenge is to identify tumors that remain functionally unable to repair replication-associated DNA damage at the moment treatment is given.

3. Advanced HER2-Negative BRCA-Mutated Breast Cancer

OlympiAD established olaparib monotherapy as an effective option for HER2-negative metastatic breast cancer with a deleterious or suspected deleterious germline BRCA1/2 mutation. Patients who had received no more than two previous chemotherapy regimens for metastatic disease were randomized to olaparib or physician's choice of capecitabine, eribulin, or vinorelbine. Median progression-free survival was 7.0 months with olaparib and 4.2 months with chemotherapy, and objective response was substantially higher with olaparib[5]. Global quality of life improved relative to chemotherapy, supporting the value of an oral targeted treatment that can delay conventional cytotoxic therapy.

Final overall-survival analysis of OlympiAD did not show a statistically significant difference in the entire population, with median overall survival of approximately 19.3 months for olaparib and 17.1 months for chemotherapy. An exploratory subgroup without previous chemotherapy for metastatic disease had a favorable hazard ratio, suggesting that earlier use may be advantageous, but the study was not powered to establish a definitive line-specific survival effect[6]. Subsequent treatment, including later platinum or PARP inhibition, and the modest sample size complicated interpretation. The trial nevertheless demonstrated clinically meaningful disease control and tolerability and led to regulatory approval of olaparib for germline BRCA1/2-mutated, HER2-negative metastatic breast cancer.

EMBRACA compared talazoparib with physician's choice of capecitabine, eribulin, gemcitabine, or vinorelbine in germline BRCA1/2-mutated, HER2-negative locally advanced or metastatic disease. Median progression-free survival was 8.6 months with talazoparib and 5.6 months with chemotherapy, with a hazard ratio of 0.54; objective response and patient-reported global health status also favored talazoparib[7]. Hematologic toxicity, particularly anemia, was frequent, but nonhematologic toxicity was generally manageable and alopecia was less burdensome than with several chemotherapy options.

As in OlympiAD, the final EMBRACA overall-survival analysis was not statistically positive. Median overall survival was approximately 19.3 months with talazoparib and 19.5 months with chemotherapy, and substantial use of subsequent platinum and PARP inhibitors may have diluted a survival difference[8]. The absence of an overall-survival advantage should not be interpreted as absence of clinical value, because progression-free survival, response, symptom control, and quality of life all favored talazoparib. It does, however, require accurate counseling: in metastatic breast cancer, the randomized evidence establishes superior disease control compared with selected single-agent chemotherapies, not a proven overall-survival advantage for either olaparib or talazoparib.

Veliparib was evaluated with carboplatin and paclitaxel in BROCADE3. The addition of veliparib increased median progression-free survival from 12.6 to 14.5 months and produced a durable tail on the progression-free survival curve in germline BRCA1/2-mutated, HER2-negative advanced disease[9]. Final median overall survival was 32.4 versus 28.2 months and was not statistically different[10]. Because both groups received an active platinum-taxane regimen and veliparib has relatively weak trapping activity, the study demonstrates that a PARP inhibitor can be combined with platinum but does not establish veliparib as a standard substitute for approved PARP monotherapy. Veliparib has not achieved the same routine breast-cancer role as olaparib or talazoparib.

Treatment selection in advanced disease should consider receptor subtype and competing standards. In triple-negative disease, a germline BRCA1/2 mutation

supports PARP inhibition, but PD-L1 status, previous immunotherapy, platinum sensitivity, disease tempo, antibody–drug conjugate eligibility, central nervous system involvement, and prior adjuvant olaparib may alter sequencing. In hormone receptor-positive disease, PARP inhibition competes with endocrine-based strategies, including CDK4/6, PI3K/AKT-pathway, and estrogen-receptor-directed therapies. Most patients without visceral crisis should receive effective endocrine-based therapy before chemotherapy, but a germline BRCA mutation creates an additional targeted option when endocrine resistance develops.

There is no randomized head-to-head comparison between a PARP inhibitor and platinum specifically designed to define the preferred first cytotoxic strategy in germline BRCA-mutated metastatic breast cancer. The TNT trial showed that carboplatin produced a markedly higher response than docetaxel in the germline BRCA subgroup, confirming platinum sensitivity, although carboplatin was not superior in unselected triple-negative disease[19]. Cross-resistance can occur because both platinum and PARP inhibition exploit defective homologous recombination. A prolonged platinum-free interval and absence of platinum-refractory progression may favor subsequent PARP activity, whereas rapid progression on platinum raises concern that homologous recombination has been restored.

4. Adjuvant and Neoadjuvant Treatment of Early Breast Cancer

OlympiA transformed management of germline BRCA1/2-mutated, HER2-negative high-risk early breast cancer. The phase III trial randomized 1,836 patients who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy to one year of olaparib or placebo. The first primary analysis showed a substantial improvement in invasive disease-free and distant disease-free survival[11]. A later prespecified analysis demonstrated a statistically significant overall-survival benefit, making olaparib the first PARP inhibitor to improve survival in the adjuvant breast-cancer setting[12].

Longer follow-up reinforces the durability of benefit after treatment ends. At a median follow-up of 6.1 years, olaparib reduced the risk of invasive recurrence, second cancer, or death by approximately 35% and the risk of death by 28%. Six-year invasive disease-free survival was 79.6% versus 70.3%, distant disease-free survival was 83.5% versus 75.7%, and overall survival was 87.5% versus 83.2%[13]. Benefits were observed in both triple-negative and hormone receptor-positive subgroups, although the trial was not designed to compare effect magnitude between them. No new long-term safety signal emerged, and myelodysplastic syndrome or acute myeloid leukemia did not appear increased relative to placebo at this follow-up.

OlympiA eligibility should be applied carefully. Patients with triple-negative disease treated with neoadjuvant chemotherapy were required to have residual invasive disease, whereas those treated with adjuvant chemotherapy generally had node-positive disease or a primary tumor larger than 2 cm. For hormone receptor-positive disease, patients treated neoadjuvantly required residual disease with a CPS+EG score of at least 3, while those treated with adjuvant chemotherapy required at least four positive lymph nodes. These trial-defined thresholds identify a population with sufficient baseline recurrence risk to justify one year of treatment; they should not be replaced by a vague concept of “BRCA-positive” early breast cancer.

Adjuvant olaparib may overlap conceptually with capecitabine in residual triple-negative disease, pembrolizumab in high-risk triple-negative disease, and abemaciclib or ribociclib in high-risk hormone receptor-positive disease. Direct randomized evidence defining concurrent or sequential use is limited. Concurrent olaparib with strongly myelosuppressive chemotherapy is generally avoided, and combining olaparib with CDK4/6 inhibition outside a trial may produce prohibitive marrow toxicity. In a patient eligible for several post-neoadjuvant interventions, decisions should integrate germline BRCA status, residual burden, previous pembrolizumab, endocrine requirements, toxicity, and the strength of survival evidence. Sequential use may be reasonable, but the optimal order and total treatment burden remain uncertain.

Neoadjuvant PARP inhibition has shown biological activity but has not established a general standard. In a small phase II study, six months of talazoparib monotherapy produced high pathologic complete response rates in operable germline BRCA-mutated, HER2-negative breast cancer, demonstrating that marked tumor regression can occur without conventional chemotherapy[22]. GeparOLA suggested activity of olaparib combined with paclitaxel in tumors selected for homologous-recombination deficiency, but the randomized phase II design and comparator do not justify replacement of standard chemotherapy[23]. These studies support de-escalation research for carefully selected mutation carriers rather than routine omission of chemotherapy.

Randomized neoadjuvant trials in broader triple-negative populations have clarified the limits of the strategy. In BrighTNess, adding carboplatin improved

pathologic complete response and event-free survival, but adding veliparib to carboplatin did not provide additional long-term benefit[20]. PARTNER enrolled germline BRCA1/2-wild-type triple-negative breast cancer and found that adding intermittent olaparib to carboplatin–paclitaxel did not increase pathologic complete response, event-free survival, or overall survival[21]. These results indicate that basal-like phenotype or triple-negative status alone is insufficient to predict additional benefit from a PARP inhibitor when active platinum therapy is already delivered.

5. Biomarker Selection and Genetic Testing

Germline BRCA1/2 testing is the validated companion strategy for approved breast-cancer indications. Testing must distinguish pathogenic or likely pathogenic variants from variants of uncertain significance. A variant of uncertain significance should not be used to prescribe a PARP inhibitor, intensify surgery, or trigger predictive testing in relatives. Because a germline result has implications for systemic therapy, future cancer risk, risk-reducing surgery, and family members, pretest information and access to qualified genetic counseling are important even when rapid treatment decisions require streamlined testing.

The 2024 ASCO–Society of Surgical Oncology guideline recommends offering BRCA1/2 germline testing to all newly diagnosed patients aged 65 years or younger and to selected patients older than 65 years based on personal history, family history, ancestry, triple-negative phenotype, male sex, or candidacy for PARP inhibitor therapy. Testing is also relevant in recurrent disease when the result may affect treatment[18]. Regional guidelines and reimbursement differ, but the therapeutic indication has shifted testing from a purely hereditary-risk exercise to an integral part of systemic treatment planning. Delayed testing can cause a patient to miss an adjuvant olaparib window.

Evidence beyond germline BRCA1/2 is strongest for germline PALB2 and somatic BRCA1/2 alterations. In the original TBCRC 048 study, olaparib produced confirmed responses predominantly in germline PALB2-mutated and somatic BRCA1/2-mutated metastatic breast cancer, with objective response rates of 82% and 50%, respectively; no responses were observed with isolated ATM or CHEK2 mutations[16]. The 2026 expansion cohorts confirmed clinically meaningful activity in larger germline PALB2 and somatic BRCA1/2 groups, strengthening the biological case for PARP inhibition beyond the current germline BRCA label in selected metastatic patients[17]. Access may nevertheless depend on regional approval, guideline endorsement, and payer policy.

Not every homologous-recombination-related gene is equivalent. PALB2 loss can phenocopy BRCA2 dysfunction because PALB2 is required for BRCA2 recruitment and RAD51 loading. In contrast, monoallelic ATM or CHEK2 variants may not create the profound homologous-recombination defect necessary for PARP monotherapy. Tumor-only sequencing can also identify a BRCA1/2 alteration without establishing whether it is germline; a possible germline finding should therefore be confirmed in blood or another non-tumor sample. Conversely, a negative tumor panel does not reliably exclude a germline variant if coverage or variant detection is incomplete.

Genomic-scar assays quantify historical consequences of homologous-recombination deficiency, such as loss of heterozygosity, telomeric allelic imbalance, or large-scale state transitions. These assays have value in ovarian cancer and research, but no genomic-scar threshold has been prospectively validated as a stand-alone selector for PARP monotherapy in breast cancer. A scar can persist after a tumor restores homologous recombination, so it may document past deficiency rather than current vulnerability. Functional assays based on irradiation-induced RAD51 nuclear foci may more directly measure current homologous-recombination competence and have shown promise as predictors of PARP and platinum sensitivity[29]. Standardization, tissue quality, timing, and prospective clinical validation remain barriers.

Circulating tumor DNA may help identify somatic BRCA alterations and emerging resistance mutations. Detection of a BRCA reversion in plasma can explain progression and warn against immediate reuse of platinum or another PARP inhibitor. However, negative ctDNA does not exclude a relevant alteration when tumor shedding is low, and clonal hematopoiesis may confound interpretation of some DNA-repair genes. Molecular results should be integrated with treatment history, allele status, tumor content, and clinical phenotype rather than interpreted from a gene name alone.

6. Combination Strategies and Treatment Sequencing

Combining PARP inhibition with platinum is biologically attractive because both increase replication-associated DNA damage, but overlapping myelosuppression narrows the therapeutic window. BROCADE3 showed a modest progression-free survival improvement with veliparib plus carboplatin–paclitaxel, yet no overall-survival benefit[9–10]. BrighTNess and

PARTNER failed to show an independent contribution from veliparib or olaparib when added to effective platinum-based neoadjuvant chemotherapy[20–21]. These findings favor sequencing an approved PARP inhibitor and platinum rather than routine concurrent intensification, except within a trial or a specifically validated regimen.

Immune combinations are supported by the hypothesis that unrepaired DNA damage increases neoantigen exposure, activates the cGAS–STING pathway, and upregulates immune signaling. MEDIOLA reported encouraging response and disease-control rates with olaparib plus durvalumab in germline BRCA-mutated metastatic breast cancer, with manageable toxicity[24]. TOPACIO/KEYNOTE-162 found activity of niraparib plus pembrolizumab in metastatic triple-negative breast cancer, including some patients without a tumor BRCA mutation[25]. These single-arm studies demonstrate feasibility but cannot establish superiority over PARP monotherapy or modern immunotherapy standards. No PARP–checkpoint combination has replaced approved biomarker-directed first-line regimens in routine breast-cancer care.

PARP inhibition may also increase dependence on ATR, WEE1, DNA-PK, or other replication-stress checkpoints. Combinations with ATR inhibitors are being investigated as a means of overcoming restored homologous recombination or replication-fork protection. Early studies show antitumor activity but also anemia, neutropenia, thrombocytopenia, fatigue, and gastrointestinal toxicity. The therapeutic objective is not simply to create more DNA damage, but to identify a schedule and biomarker-defined population in which tumor-selective stress exceeds normal-tissue injury.

HER2-directed combinations remain investigational. A small phase II study of olaparib plus trastuzumab in HER2-positive advanced breast cancer with germline BRCA1/2 mutations reported feasibility and signals of activity, but enrollment was limited and the study cannot redefine standard HER2-directed therapy[26]. In hormone receptor-positive disease, combinations with endocrine therapy are pharmacologically feasible, but direct evidence is limited; adding a CDK4/6 inhibitor creates substantial overlapping marrow suppression. Sequential use according to endocrine sensitivity and germline BRCA status is generally more defensible than empiric triple targeted therapy.

Antibody–drug conjugates complicate sequencing in both triple-negative and hormone receptor-positive metastatic disease. Sacituzumab govitecan, trastuzumab deruxtecan for HER2-low or HER2-positive disease, and other emerging conjugates can produce high response rates after prior therapy. No randomized trial has definitively established whether a PARP inhibitor should precede an antibody–drug conjugate in every germline BRCA carrier. Earlier PARP use is supported by its oral administration, biomarker specificity, quality-of-life data, and the exploratory first-line signal in OlympiAD, while rapidly progressive disease, previous adjuvant olaparib, central nervous system involvement, and receptor-defined approvals may favor another option.

Retreatment after adjuvant olaparib is an increasingly important problem. A patient who relapses years after completing one year of olaparib may still have a PARP-sensitive tumor, whereas relapse during treatment or shortly afterward suggests primary or acquired resistance. No prospective trial defines a minimum PARP-free interval or proves benefit from switching to talazoparib. Rebiopsy and ctDNA can identify BRCA reversion or alternative drivers, but absence of a known resistance mechanism does not guarantee response. Until dedicated evidence emerges, metastatic rechallenge should be individualized rather than assumed to be a class effect.

7. Mechanisms of Resistance

Restoration of homologous recombination is a central mechanism of acquired resistance. Secondary mutations can restore the BRCA1 or BRCA2 reading frame and generate a partially functional protein, a process termed BRCA reversion. Reversions may arise under either platinum or PARP-inhibitor pressure and can be detected in tissue or ctDNA. Because they restore the shared repair defect targeted by both drug classes, they provide a mechanistic basis for cross-resistance. Multiple independent reversion clones may coexist, illustrating convergent evolution under therapy[27].

BRCA1-deficient cells can also restore end resection without correcting BRCA1 itself. Loss of 53BP1, RIF1, REV7, or components of the Shieldin complex shifts DNA repair toward homologous recombination and can reduce PARP sensitivity. In BRCA2-deficient cells, changes that protect stalled replication forks from nucleolytic degradation can confer resistance even when homologous recombination remains impaired. Upregulation of FANCD2, loss of fork-remodeling factors, or altered chromatin can stabilize forks sufficiently to permit survival under replication stress[28].

Alterations in the drug target and intracellular exposure provide additional routes. PARP1 mutations may reduce DNA binding or trapping while preserving enough repair function for viability. Increased expression of ATP-binding cassette transporters can lower intracellular inhibitor concentration. Reduced drug uptake, altered metabolism, and lineage plasticity may also contribute. Some mechanisms are agent dependent:

a change that primarily prevents trapping may have a different effect on talazoparib than on an inhibitor with weaker trapping potency, although clinically validated switching rules are not available.

Resistance is dynamic and spatially heterogeneous. A progressing lesion may contain a reversion that is absent from another metastasis, and a single archival primary-tumor specimen may not represent metastatic repair status. A long initial response, platinum sensitivity, and continued absence of RAD51 foci suggest persistent homologous-recombination deficiency, whereas rapid progression on both platinum and PARP inhibition suggests pathway restoration or an alternative dominant driver. Clinical trials that pair serial tissue, ctDNA, and functional assays are required to convert these mechanistic observations into treatment decisions.

8. Safety Management and Individualized Use

Myelosuppression is the principal clinically important toxicity. Complete blood counts should be assessed before treatment and regularly during therapy, with greater frequency when cytopenia develops. Anemia may require interruption, dose reduction, investigation of bleeding or nutritional deficiency, and occasionally transfusion. Talazoparib is particularly associated with grade 3–4 anemia, while neutropenia and thrombocytopenia also occur. Persistent pancytopenia after interruption warrants evaluation for marrow disease, myelodysplastic syndrome, or acute leukemia rather than repeated empiric dose reduction alone.

Nausea, fatigue, vomiting, reduced appetite, dyspepsia, and diarrhea are usually low grade but can meaningfully impair adherence. Proactive antiemetic treatment, administration guidance, nutrition support, and early dose modification can preserve treatment duration. Fatigue should not automatically be attributed to the drug; anemia, sleep disturbance, depression, endocrine dysfunction, infection, and disease progression should be considered. Alopecia is generally less frequent and less severe than with many chemotherapy regimens, an outcome that contributes to patient-reported preference.

Myelodysplastic syndrome and acute myeloid leukemia are rare but serious class risks, often occurring in patients previously exposed to platinum, alkylating agents, or radiotherapy. The absolute risk in breast-cancer trials is low, and six-year OlympiA follow-up did not demonstrate an excess over placebo[13]. Nevertheless, unexplained prolonged cytopenia requires interruption and hematologic evaluation. PARP inhibitors are potentially teratogenic and should not be used during pregnancy; effective contraception and reproductive counseling are necessary for patients with childbearing potential, and breastfeeding should be avoided according to the product label.

Renal function and drug interactions affect dosing. Olaparib exposure increases in moderate renal impairment and requires dose reduction; data are limited in severe renal dysfunction. Strong CYP3A inhibitors should be avoided or accompanied by label-directed olaparib dose reduction, while strong CYP3A inducers can substantially reduce exposure. Talazoparib requires renal dose adjustment and attention to P-glycoprotein inhibitors. Medication reconciliation should include prescription drugs, herbal products, supplements, and intermittent anti-infective therapy.

In early breast cancer, treatment tolerance must be judged against an absolute recurrence-risk reduction in a potentially cured population. One year of olaparib offers a meaningful survival advantage in OlympiA-eligible patients, but adherence, fertility, employment, monitoring, and overlapping post-chemotherapy fatigue remain important. In metastatic disease, the goals include tumor control, symptom improvement, quality of life, and preservation of later options. Dose reduction that enables continued therapy is usually preferable to prolonged severe toxicity or abrupt permanent discontinuation.

9. Future Perspectives

The next stage of PARP-inhibitor development will depend on functional rather than purely categorical biomarkers. Germline BRCA1/2 remains the most validated marker, and germline PALB2 and somatic BRCA1/2 are the clearest candidates for broader implementation. Prospective studies should determine whether RAD51 foci, real-time ctDNA, biallelic loss, mutational signatures, and replication-fork markers can identify current sensitivity and distinguish historical genomic scarring from active repair deficiency. Biomarker development must be linked to predefined treatment decisions rather than evaluated only through retrospective association.

Early-disease research should address de-escalation and rational sequencing. Talazoparib monotherapy has shown that profound responses can occur before surgery in germline BRCA carriers, but omitting standard chemotherapy requires randomized survival evidence. For patients eligible for olaparib plus pembrolizumab, capecitabine, or a CDK4/6 inhibitor, trials should compare complete treatment strategies and report cumulative toxicity, adherence, fertility, patient-reported function, and financial burden. Molecular residual-disease assays may eventually identify patients who require escalation, but ctDNA positivity should not

currently be used outside trials as an automatic indication for PARP therapy.

In metastatic disease, combinations that target ATR, WEE1, POLQ, DNA-PK, or replication-fork protection may overcome defined resistance states. Intermittent schedules and next-generation PARP1-selective inhibitors may reduce marrow toxicity while preserving tumor trapping. PARP1 degraders and agents designed to retain activity against selected resistance mutations are also entering development. Their success will require comparison with increasingly effective antibody–drug conjugates and receptor-directed therapies, not merely demonstration of activity in heavily pretreated single-arm cohorts.

Equitable implementation is a clinical priority. Germline testing, genetic counseling, variant interpretation, and access to approved targeted therapy remain uneven across regions and populations. Testing criteria based too narrowly on family history can miss patients with small families, limited records, paternal inheritance, or de novo presentations. Integrating rapid germline testing into the pathway of high-risk HER2-negative early breast cancer is necessary to translate the OlympiA survival benefit into routine practice.

10. Conclusion

PARP inhibitors have established synthetic lethality as a clinically effective strategy in breast cancer. Olaparib and talazoparib improve progression-free survival, response, and patient-reported outcomes in germline BRCA1/2-mutated, HER2-negative advanced disease compared with selected single-agent chemotherapies. In high-risk early breast cancer, one year of adjuvant olaparib produces durable invasive disease-free, distant disease-free, and overall-survival benefits that remain evident at six years. These findings make timely germline BRCA1/2 testing an essential component of treatment planning rather than an optional hereditary-risk assessment.

The benefit of PARP inhibition cannot be generalized to every triple-negative tumor or every alteration on a DNA-repair panel. Germline PALB2 and somatic BRCA1/2 mutations show compelling metastatic activity, whereas ATM or CHEK2 mutations alone are insufficient predictors. Randomized trials have not supported routine addition of a PARP inhibitor to platinum-based neoadjuvant therapy in unselected germline BRCA-wild-type triple-negative disease. Future progress will depend on functional homologous-recombination biomarkers, resistance-informed treatment, and rational sequencing with platinum, endocrine therapy, immunotherapy, and antibody–drug conjugates. The appropriate use of PARP inhibitors is therefore defined not only by the presence of a mutation, but by whether the tumor remains biologically dependent on PARP-mediated survival at the time of treatment.

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