PARP Inhibitors in Ovarian Cancer: HRD Status Dictates Maintenance Benefit

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> Ovarian cancer remains a significant challenge in oncology, often presenting at advanced stages with high recurrence rates. For years, clinicians sought therapies to extend remission following initial platinum-based chemotherapy. Poly(ADP-ribose) polymerase inhibitors (PARPis) emerged as a key strategy, fundamentally altering the treatment market for these patients.1
> But the benefit of these agents is not universal; homologous recombination deficiency (HRD) status dictates which patients truly gain from maintenance therapy. Understanding this distinction is important for optimal patient selection and managing expectations regarding long-term outcomes.1

KEY TAKEAWAYS

- The Pivot: Homologous recombination deficiency (HRD) status is the primary determinant of PARP inhibitor efficacy in ovarian cancer maintenance.
- The Data: Patients with HRD tumors derive substantial benefit from PARP inhibitors, while those with homologous recombination proficiency (HRP) show limited or no significant improvement.
- The Action: Routine HRD testing is essential to guide PARP inhibitor maintenance therapy decisions in ovarian cancer, ensuring appropriate patient selection and resource allocation.

Ovarian cancer treatment has evolved considerably, but the disease's aggressive nature and propensity for recurrence mean that extending progression-free survival (PFS) remains a central goal. Platinum-based chemotherapy achieves high initial response rates, yet many patients relapse. Maintenance therapy, particularly with PARP inhibitors, aims to prolong the duration of response and delay disease progression.1
The mechanism of PARP inhibitors relies on synthetic lethality, a concept where two non-lethal defects become lethal when combined. In cancer cells with defects in homologous recombination repair (HRR), PARP inhibitors prevent single-strand break repair, leading to an accumulation of DNA damage that overwhelms the cell's ability to repair itself, causing cell death. This makes HRD a key biomarker for predicting PARP inhibitor sensitivity.1

The Role of Homologous Recombination Deficiency

Homologous recombination deficiency (HRD) describes a cell's impaired ability to repair double-strand DNA breaks through the high-fidelity homologous recombination pathway. This deficiency can arise from mutations in genes like BRCA1 or BRCA2, or from other genomic alterations that compromise HRR. Ovarian cancers frequently exhibit HRD, making them prime candidates for PARP inhibitor therapy.1
Wang, Li, and Yang, in their 2026 narrative review published in Translational Cancer Research, described the

fundamental impact of PARP inhibitors on ovarian cancer treatment.1 They highlighted that these agents have fundamentally changed the treatment paradigm, particularly for patients whose tumors exhibit HRD. This review provides a comprehensive synthesis of the scientific and clinical evolution of PARP inhibitors, critically analyzing resistance mechanisms and evaluating emerging strategies to overcome these challenges.1

Clinical Efficacy and Patient Selection

Multiple clinical trials have established the efficacy of PARP inhibitors as maintenance therapy in ovarian cancer following a response to platinum-based chemotherapy. But the benefit is not uniform across all patient populations. Patients with germline or somatic BRCA mutations, a direct cause of HRD, consistently show the most pronounced and durable responses to PARP inhibitors. For these patients, PARP inhibitor maintenance therapy significantly extends PFS.1

Beyond BRCA mutations, broader HRD status, often assessed by genomic scar scores, also predicts response. Patients with HRD-positive, non-BRCA mutated tumors also derive substantial benefit, albeit sometimes less than those with BRCA mutations. This expanded indication has broadened the population eligible for PARP inhibitor therapy, moving beyond just BRCA carriers.1

But for patients with homologous recombination proficient (HRP) tumors, the picture is less clear. While some trials have shown a modest benefit in certain HRP subgroups, the magnitude of effect is considerably smaller, and in many cases, not clinically meaningful. This distinction is essential for guiding treatment decisions and avoiding unnecessary exposure to potential toxicities and costs in patients unlikely to benefit.1

Mechanisms of Resistance and Emerging Strategies

Despite their initial efficacy, acquired resistance to PARP inhibitors remains a significant challenge, limiting their long-term benefit. Wang, Li, and Yang meticulously detailed several mechanisms of resistance.1 These include secondary mutations in BRCA1/2 that restore HRR function, upregulation of drug efflux pumps, and alterations in other DNA repair pathways that compensate for PARP inhibition. Understanding these mechanisms is paramount for developing strategies to overcome resistance.1

One emerging strategy involves combining PARP inhibitors with other agents that target different aspects of DNA repair or cell cycle control. For instance, combining PARP inhibitors with anti-angiogenic agents or immune checkpoint inhibitors has shown promise in preclinical and early clinical studies. These combinations aim to exploit additional vulnerabilities in cancer cells, potentially overcoming resistance mechanisms and enhancing therapeutic efficacy.1

Another approach focuses on identifying novel biomarkers that can better predict response and resistance. Beyond HRD, researchers are investigating other genomic and transcriptomic signatures that might indicate sensitivity to PARP inhibitors or specific combination therapies. This precision medicine approach aims to tailor treatment more effectively, ensuring that patients receive the most appropriate therapy for their tumor biology. For more on how genomic markers are changing cancer screening, see our article on IBD overlap and colorectal cancer screening.

The Clinical Imperative for HRD Testing

The differential benefit of PARP inhibitors based on HRD status highlights the clinical imperative for routine HRD testing in all patients with ovarian cancer. This testing should ideally occur at diagnosis to inform initial treatment planning, including the potential for PARP inhibitor maintenance. Without this information, clinicians risk either under-treating

patients who would benefit significantly or over-treating those who would not, exposing them to unnecessary adverse events and financial burden.1

HRD testing involves assessing for BRCA1/2 mutations and evaluating genomic scar scores. Various commercial assays are available, each with its own methodology and interpretation. Standardizing these assays and ensuring their accessibility are important considerations for widespread clinical implementation. The Oxford Handbook of Oncology provides a concise overview of current diagnostic approaches in cancer.

Adverse Events and Management

While generally well-tolerated, PARP inhibitors do carry a risk of adverse events. The most common toxicities include myelosuppression (anemia, neutropenia, thrombocytopenia), fatigue, nausea, and vomiting. These adverse events are typically manageable with dose modifications, interruptions, or supportive care. However, clinicians must monitor patients closely, especially during the initial cycles of therapy.1

Rare but serious adverse events, such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), have been reported with long-term PARP inhibitor use. The incidence of these secondary malignancies is low, but the risk must be weighed against the potential survival benefit, particularly in patients with HRP tumors where the benefit is marginal. This careful risk-benefit assessment is a cornerstone of oncology practice, similar to considerations in intensified blockade for prostate cancer.

Limitations and Future Directions

The narrative review by Wang, Li, and Yang, while comprehensive, highlights areas where further research is needed.1 One limitation of current PARP inhibitor therapy is the lack of effective strategies for patients who develop acquired resistance. The review emphasizes the need for novel therapeutic approaches to overcome these resistance mechanisms, including combination therapies and next-generation PARP inhibitors.1

Another area for development involves refining HRD testing. Current assays are not perfect, and some patients with HRD-negative tumors still respond to PARP inhibitors, while others with HRD-positive tumors do not. This suggests that other, as yet unidentified, biomarkers or mechanisms may influence response. Future research should focus on developing more precise predictive biomarkers to optimize patient selection further.1

The optimal sequencing of PARP inhibitors with other agents, such as immune checkpoint inhibitors or anti-angiogenic drugs, also requires further investigation. Clinical trials are ongoing to determine the most effective combinations and treatment schedules. These studies will help define the role of PARP inhibitors in the evolving guidelines of ovarian cancer therapy, ensuring that patients receive the most effective and least toxic treatments available.1

> **CLINICAL IMPLICATIONS**
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> The message from the latest review is unequivocal: HRD status is not merely a prognostic marker, but a predictive one for PARP inhibitor maintenance in ovarian cancer. Clinicians who continue to prescribe these agents without robust HRD testing are operating on an outdated understanding of the evidence, potentially exposing patients to unnecessary toxicity and cost without commensurate benefit.
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> For patients with HRD-positive tumors, PARP inhibitors offer a genuine extension of progression-free survival, a critical endpoint in a disease notorious for recurrence. But for those with HRP tumors, the data simply do

> not support widespread use. This distinction demands a rigorous approach to molecular testing at diagnosis, integrating it into standard clinical pathways.
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> The industry, too, must adapt. The focus should shift from broad-spectrum marketing to precision targeting, emphasizing the HRD-positive population where these drugs truly shine. Investment in overcoming acquired resistance mechanisms and developing more refined biomarkers will be vital for the next generation of PARP inhibitor strategies.
>
> The goal is to maximize benefit while minimizing harm. HRD testing provides the roadmap for achieving this balance with PARP inhibitors in ovarian cancer. Ignoring it is no longer defensible.

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REFERENCES

1. 1. Wang Y, Li X, Yang Y. PARP inhibitors in the treatment of ovarian cancer: a narrative review. Transl Cancer Res. 2026;15(1):421-435. doi:10.21037/tcr-25-200

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