PARP Inhibitors in Ovarian Cancer: HRD Status Dictates Maintenance Benefit

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> Ovarian cancer remains a formidable challenge in oncology, often diagnosed at advanced stages with high recurrence rates. For years, clinicians sought therapies to extend remission after initial platinum-based chemotherapy. Poly(ADP-ribose) polymerase inhibitors (PARPis) emerged as a significant advance, particularly in maintenance settings. But their benefit is not universal, and understanding homologous recombination deficiency (HRD) status is paramount for patient selection.1

KEY TAKEAWAYS

- The Pivot: Homologous recombination deficiency (HRD) status fundamentally dictates the efficacy of PARP inhibitor maintenance therapy in ovarian cancer.
- The Data: PARP inhibitors have fundamentally changed the treatment paradigm for patients with ovarian cancer.1
- The Action: Clinicians must assess HRD status to identify patients most likely to derive long-term benefit from PARP inhibitor maintenance, guiding treatment decisions and managing expectations regarding acquired resistance.

Ovarian cancer management has seen substantial evolution, with platinum-based chemotherapy remaining the cornerstone of first-line treatment. But the high rates of recurrence necessitate effective maintenance strategies to prolong progression-free survival. PARP inhibitors entered this space by targeting DNA repair pathways, specifically exploiting deficiencies in homologous recombination repair (HRR) that are common in ovarian cancers, particularly those with BRCA1/2 mutations.1

These agents work by trapping PARP enzymes on DNA, leading to replication fork collapse and DNA double-strand breaks. In cells with intact HRR, these breaks are repaired. But in homologous recombination deficient (HRD) cells, the inability to repair these breaks leads to synthetic lethality, preferentially killing cancer cells while sparing healthy ones. This mechanism underpins the selective efficacy of PARP inhibitors.1

The Evolution of PARP Inhibitors in Ovarian Cancer

The introduction of PARP inhibitors marked a significant shift in ovarian cancer treatment, moving beyond cytotoxic chemotherapy to targeted therapy. Initial trials focused on patients with germline BRCA1/2 mutations, where the benefit was most pronounced. These patients inherently possess a homologous recombination deficiency, making their tumors highly susceptible to PARP inhibition. The success in this subgroup led to broader investigations into other HRD populations.1

Subsequent studies expanded the use of PARP inhibitors to patients with somatic BRCA1/2 mutations and those with other genomic alterations contributing to HRD, often identified through genomic scarring assays. This expansion recognized that HRD is not solely defined by BRCA mutations but encompasses a wider range of defects in DNA repair pathways. The goal was to identify all patients who could benefit from this targeted approach, moving towards a more personalized treatment strategy.1

Understanding Homologous Recombination Deficiency

Homologous recombination deficiency (HRD) is a critical biomarker for predicting response to PARP inhibitors. It describes a tumor's inability to repair DNA double-strand breaks effectively using the homologous recombination pathway. This deficiency can arise from various genetic alterations, including mutations in BRCA1 and BRCA2, but also other genes involved in HRR, such as PALB2, ATM, and CHEK2. Beyond specific gene mutations, HRD can also be indicated by genomic instability patterns, often referred to as 'genomic scars'.1

Testing for HRD involves assessing both BRCA1/2 mutation status and broader genomic instability. Commercial assays evaluate these factors, providing a composite HRD score. A positive HRD status indicates a higher likelihood of response to PARP inhibitors. Conversely, tumors that are homologous recombination proficient (HRP) typically show limited benefit from these agents, highlighting the importance of accurate biomarker testing before initiating maintenance therapy.1

Maintenance Therapy and Acquired Resistance

PARP inhibitors are predominantly used in the maintenance setting for ovarian cancer, following a response to platinum-based chemotherapy. This strategy aims to prolong remission and delay disease progression. For patients with HRD-positive tumors, maintenance PARP inhibition has demonstrated substantial improvements in progression-free survival (PFS). But the long-term benefit is often limited by the development of acquired resistance.1

Resistance mechanisms are complex and varied. One common pathway involves the restoration of HRR function, even in initially HRD tumors. This can occur through secondary mutations in BRCA1/2 that restore protein function, or through upregulation of alternative DNA repair pathways. Efflux pumps, which reduce intracellular drug concentrations, and alterations in PARP trapping mechanisms also contribute to resistance. Understanding these mechanisms is essential for developing strategies to overcome the challenge of resistance.1

The clinical implications of acquired resistance are significant. Patients who initially respond well to PARP inhibitors may eventually experience disease progression, necessitating a change in treatment strategy. This highlights the need for ongoing research into combination therapies and novel agents that can circumvent these resistance pathways. For a deeper understanding of how cancer cells evade therapy, consider reviewing our coverage on why humans don't catch cancer from each other, which touches on fundamental aspects of cancer biology and immune evasion.1

The Clinical Market and Future Directions

Multiple PARP inhibitors, including olaparib, niraparib, and rucaparib, have received regulatory approvals for ovarian cancer. Their use is often stratified by HRD status, with the greatest benefit consistently observed in patients with BRCA-mutated and HRD-positive tumors. For example, in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation, olaparib maintenance significantly extended PFS.1

But for patients with HRD-negative tumors, the benefit is considerably less pronounced, and in some cases, negligible.

This stark difference emphasizes the need for precise patient selection. The Oxford Handbook of Oncology provides a concise reference for navigating these complex treatment algorithms and biomarker-driven decisions in daily practice.1
The ongoing challenge lies in improving outcomes for patients with HRD-negative tumors and those who develop resistance. Combination strategies are under active investigation, pairing PARP inhibitors with anti-angiogenic agents, immunotherapy, or other targeted therapies. The rationale is to exploit multiple vulnerabilities or to overcome resistance mechanisms. For instance, combining PARP inhibitors with bevacizumab has shown promise in certain subgroups, suggesting a synergistic effect.1
Immunotherapy, particularly checkpoint inhibitors, has also been explored in combination with PARP inhibitors. The hypothesis is that PARP inhibition can increase tumor immunogenicity, making cancer cells more susceptible to immune attack. Early data from these combination trials are encouraging, but definitive large-scale studies are still needed to establish their role in standard practice.1
The open-label design of some earlier PARP inhibitor trials is an obvious caveat, potentially introducing bias in subjective endpoints. While progression-free survival is a hard endpoint, patient-reported outcomes and adverse event reporting can be influenced. The trials were also not always powered to detect differences in rare subgroups, and that gap matters when trying to refine treatment for specific patient profiles.1
Another limitation involves the dynamic nature of HRD status. A tumor initially classified as HRD-positive might, over time and treatment, restore HRR function, leading to resistance. This raises questions about the utility of re-testing HRD status at progression and whether sequential or adaptive treatment strategies based on evolving HRD status could improve outcomes. The current standard typically involves a single HRD assessment at diagnosis.1
The heterogeneity of ovarian cancer itself presents a challenge. Different histological subtypes may respond differently to PARP inhibitors, irrespective of HRD status. Most trials have focused on high-grade serous ovarian cancer, which accounts for the majority of cases. Whether the benefits extend to rarer subtypes, such as mucinous or clear cell carcinomas, remains less clear and requires further investigation.1
Finally, the economic burden of PARP inhibitors is substantial. Their high cost necessitates careful consideration of cost-effectiveness, especially in populations where the clinical benefit is marginal. Health economic evaluations are essential to ensure that these valuable therapies are used judiciously and reach the patients who will derive the most meaningful benefit.1

CLINICAL IMPLICATIONS

The data on PARP inhibitors in ovarian cancer are unequivocal: HRD status is not merely a prognostic marker, but a predictive one. For clinicians, this means upfront HRD testing is no longer optional; it is a prerequisite for rational prescribing. Administering these agents to HRD-negative patients offers minimal benefit and exposes them to unnecessary toxicity and cost.
The industry must continue to refine HRD testing methodologies, ensuring accessibility and accuracy across European healthcare systems. The current market of multiple assays and varying cut-offs creates unnecessary complexity. A harmonized approach would streamline patient stratification and improve clinical decision-making.
Patients with ovarian cancer, particularly those with HRD-positive disease, now have a powerful tool to extend

> remission. But they also face the reality of acquired resistance. Managing expectations around long-term efficacy and discussing potential future treatment options, including participation in clinical trials exploring combination therapies, becomes a critical part of patient counseling.
> The challenge now shifts to overcoming resistance. Future research must focus on identifying reliable biomarkers for resistance and developing effective combination strategies or sequential therapies. Without this, the initial gains from PARP inhibitors will remain capped by the inevitable progression of disease.

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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.

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