

Olaparib: Why HRD in breast and ovarian cancer goes beyond BRCA

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For years, homologous recombination deficiency (HRD) has been a clear signal for PARP inhibitor efficacy, particularly in patients with germline BRCA1/2 mutations. But what about the substantial population of patients with HRD driven by other mechanisms, those without the familiar germline BRCA1/2 alterations? The phase 2 EMBRACE trial explored olaparib in this less-defined group, specifically in metastatic triple-negative breast cancer (mTNBC) and platinum-sensitive relapsed ovarian cancer (PSROC).

KEY TAKEAWAYS

- ° The Pivot: Olaparib showed activity in HR-deficient mTNBC and PSROC patients lacking germline BRCA1/2 mutations, expanding the potential treatment landscape.
- ° The Data: The objective response rate (ORR) was 29% in mTNBC and 36% in PSROC, indicating clinical benefit in these populations.
- ° The Action: Clinicians should consider broader HRD testing beyond germline BRCA1/2 in mTNBC and PSROC to identify patients who may benefit from PARP inhibitors.

Homologous recombination deficiency (HRD) is a well-established biomarker for sensitivity to PARP inhibitors, particularly in high-grade serous ovarian cancer (HGSOC) and triple-negative breast cancer (TNBC) with germline BRCA1/2 mutations. But HRD can also arise from other genomic alterations, such as promoter methylation of BRCA1 (meBRCA1) or RAD51C (meRAD51C), or mutations in non-BRCA HR genes. The EMBRACE trial aimed to determine if olaparib, a PARP inhibitor, could provide clinical benefit in these non-germline BRCA1/2 HRD-positive populations.¹

The phase 2 EMBRACE trial enrolled patients with either platinum-sensitive relapsed HGSOC (PSROC) or metastatic TNBC (mTNBC) who had evidence of HRD but no germline BRCA1/2 mutations. Patients received olaparib monotherapy at a dose of 300 mg twice daily. The primary endpoints were objective response rate (ORR) and progression-free survival (PFS) in each cohort. The study, led by K.M. Sjoquist from the Australian National University, sought to clarify the role of olaparib in a patient group often excluded from earlier PARP inhibitor trials.¹

Defining the HRD Market Beyond BRCA

The trial's definition of HRD extended beyond germline BRCA1/2 mutations, a significant distinction for identifying a broader patient cohort. Investigators included patients with somatic BRCA1/2 mutations, promoter methylation of BRCA1 or RAD51C, or mutations in other HR pathway genes such as ATM, BARD1, BRIP1, CHEK1, CHEK2, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L. This comprehensive approach to HRD assessment is a step towards

precision oncology that moves beyond the most obvious genetic markers.¹

For the mTNBC cohort, 45 patients were enrolled. The objective response rate (ORR) was 29% (95% CI, 16-42%), with a median duration of response (DOR) of 5.6 months. The median progression-free survival (PFS) in this group was 4.1 months (95% CI, 3.2-5.0 months). These numbers, while not a home run, certainly indicate activity in a disease with limited treatment options, especially for patients who have exhausted standard chemotherapy regimens.¹

The PSROC cohort included 55 patients. Here, olaparib achieved an ORR of 36% (95% CI, 23-49%), with a median DOR of 6.8 months. The median PFS for PSROC patients was 6.7 months (95% CI, 5.1-8.3 months). These results are particularly interesting given the platinum-sensitive nature of the disease, suggesting that HRD, even without germline BRCA1/2 mutations, remains a strong predictor of PARP inhibitor benefit.¹

Still, the trial was a single-arm, open-label phase 2 study, which means it lacked a comparator arm. This design limits the ability to definitively attribute the observed benefits solely to olaparib or to compare its efficacy against other treatments. The absence of a control group means that while activity is clear, the magnitude of benefit relative to standard of care in these specific HRD subgroups remains an open question.¹

Safety Profile and Clinical Considerations

Olaparib's safety profile in the EMBRACE trial was consistent with previous reports for the drug. The most common adverse events (AEs) were nausea (58%), fatigue (49%), and anaemia (38%). Grade 3 or higher AEs occurred in 31% of patients in the mTNBC cohort and 35% in the PSROC cohort. Discontinuation due to AEs occurred in 11% of mTNBC patients and 13% of PSROC patients. These rates are generally manageable, but clinicians must remain vigilant for myelosuppression and gastrointestinal toxicities.¹

The trial did not identify any new safety signals, reinforcing the established tolerability profile of olaparib. But the relatively small cohort sizes in a phase 2 study mean that rare but serious adverse events might not have been fully captured. Long-term safety data, particularly regarding secondary malignancies, remains a consideration for any prolonged PARP inhibitor use.¹

The inclusion of patients with various HRD markers, such as BRCA1 or RAD51C promoter methylation, highlights the evolving understanding of HRD as a complex biological state rather than a simple genetic mutation. This broader definition of HRD could expand the population eligible for PARP inhibitor therapy, moving beyond the traditional germline BRCA1/2 paradigm. For clinicians managing patients with metastatic breast cancer, understanding the nuances of mutational signatures in metastatic ILC could become increasingly important as targeted therapies evolve.¹

But the practical implementation of comprehensive HRD testing in routine clinical practice presents challenges. Access to advanced genomic profiling, including methylation analysis and sequencing of multiple HR genes, is not universally available. This disparity could create inequities in patient access to potentially effective treatments. The advancements in targeted therapies for HER2-expressing breast cancer demonstrate how biomarker-driven treatment can transform outcomes, but only if the biomarkers are accessible.

Where the Data Falls Short

The EMBRACE trial, while providing valuable insights into olaparib's activity in non-germline BRCA1/2 HRD, was not designed to compare different HRD biomarkers head-to-head. It is unclear if certain HRD mechanisms, such as BRCA1 promoter methylation, confer a greater or lesser sensitivity to olaparib compared to, say, a PALB2 mutation.

This granularity is important for refining patient selection and optimizing treatment strategies.¹

The trial's relatively short median follow-up period also limits conclusions about long-term efficacy and survival benefits. While ORR and PFS are important endpoints in oncology, overall survival (OS) data would provide a more definitive measure of clinical impact. Future studies, likely larger phase 3 trials, will need to address these gaps, particularly with a comparative arm to establish a clear benefit over standard of care.¹

The patient populations were also highly selected, focusing on platinum-sensitive relapsed ovarian cancer and metastatic triple-negative breast cancer. Whether these benefits extend to other HRD-positive tumour types or to earlier lines of therapy remains to be investigated. The trials to watch in early breast cancer at ASCO 2026 will likely shed more light on expanding PARP inhibitor indications. For a comprehensive overview of oncology practice, clinicians might find the Oxford Handbook of Oncology (4th ed) a useful reference.

The open-label design is the obvious caveat. While objective response rates are less susceptible to bias than subjective endpoints, the lack of blinding could still influence patient reporting of adverse events or investigator assessments. This is a common limitation in early-phase trials, but it underscores the need for confirmatory studies with more rigorous designs.¹

CLINICAL IMPLICATIONS

The EMBRACE trial pushes the boundaries of PARP inhibitor utility beyond the well-trodden path of germline BRCA1/2 mutations. For clinicians, this means a re-evaluation of HRD testing strategies in mTNBC and PSROC. Relying solely on germline BRCA1/2 status risks missing a substantial cohort of patients who could derive benefit from olaparib, particularly those with BRCA1 or RAD51C promoter methylation.

The data, while from a phase 2 study, provides a clear signal of activity. The objective response rates of 29% in mTNBC and 36% in PSROC are not trivial in these difficult-to-treat populations. This evidence should prompt a discussion about broader genomic profiling to identify these non-germline BRCA1/2 HRD markers, moving towards a more inclusive approach to PARP inhibitor eligibility.

But the challenge lies in the implementation. Comprehensive HRD testing is not yet standard everywhere, and the cost and accessibility of such advanced diagnostics can be a barrier. Payers will need to recognize the clinical value of these expanded HRD definitions to ensure equitable access to testing and, subsequently, to olaparib for eligible patients.

This trial underscores that HRD is a phenotype, not just a genotype. The mechanisms driving it are diverse, and our therapeutic strategies must evolve to match that complexity. The next step is to see if these signals translate into improved overall survival in larger, randomized trials, solidifying olaparib's role in this expanded HRD-positive population.

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REFERENCES

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