Schmid et al\(^1\) report a multi-institutional retrospective evaluation of response rates to platinum chemotherapy in 508 patients with castration-resistant prostate cancer (CRPC). Responses and survival were classified according to biomarker status, specifically the presence or absence of germline or somatic cell variations in the homologous recombination repair (HRR) pathway including $BRCA_1$, $BRCA_2$, and others. The biomarker status defined 3 patient cohorts: (1) HRR gene aberrations detected, (2) HRR gene aberrations not detected, and (3) no molecular testing performed. The cohort with HRR variations showed improved prostate-specific antigen response rates without improvement in survival. Subgroup analysis suggested that the cohort with HRR variations were more likely to respond and to survive longer to multiagent platinum chemotherapy. A limitation of the results is the limited sample size of the group that underwent molecular testing. Further limitations of the study are typical of retrospective analyses and include data integrity, subgroup bias, and the unknown relevance of the group that never had molecular testing performed.

The findings by Schmid et al\(^1\) generate hypotheses for ongoing prospective studies. We suggest that an analogy to triple-negative breast cancer (TNBC) reveals shared genomic pathways, provides a roadmap to test those hypotheses, and that comprehensive molecular characterizations will reveal not only variations but also pathways or circuits that drive phenotype and response or resistance to therapy.

TNBC harbors substantial rates of HRR variations, particularly $BRCA_1$ and $BRCA_2$, and exhibits enhanced sensitivity to synthetic lethality. Synthetic lethality uses 2 different mechanisms of HRR-type DNA repair disruption, the intrinsic BRCA variations and the targeted therapies that inhibit poly(ADP-ribose) polymerase (PARP)–mediated repair.\(^2\)

In breast cancer, 2 clinical trials, OLYMPIAD and EMBRCA, evaluated the PARP inhibitors olaparib and talazoparib in germline BRCA-mutated metastatic breast cancer and demonstrated superiority in progression-free survival (PFS),\(^2\) leading to the FDA approval of both PARP inhibitors in 2018.

Several studies have highlighted that up to 30% of CRPC harbor alterations in HRR genes, and thus could leverage synthetic lethality as well. The PROFOUND trial evaluated olaparib in patients with alterations in the HRR pathway and demonstrated improved PFS compared with patients receiving usual care.\(^3\) Olaparib was FDA approved for patients with HRR-gene variant CRPC in 2020. Similarly, rucaparib received accelerated FDA approval in 2020, based on the TRITON2 trial presented at ESMO 2019, for BRCA-variant CRPC, after preliminary results from this phase 2 single-arm trial showed improvement in objective response rates. The National Comprehensive Cancer Network guidelines, among others, recommends routine testing of CRPC for HRR variations.

Platinum chemotherapy may be another form of synthetic lethality. The TNT trial in breast cancer evaluated carboplatin vs docetaxel in advanced TNBC. A benefit to platinum therapy in PFS was noted in patients who harbored a germline BRCA variation\(^4\) analogous to the findings by Schmid et al\(^1\) in CRPC.

The combination of PARP inhibitors and platinums may enhance response rates in TNBC and CRPC. The BROCADE 3 trial randomized patients with breast cancer with germline BRCA variations to carboplatin and paclitaxel with either a PARP inhibitor, veliparib, or placebo. The trial met its primary end point of PFS in favor of veliparib.\(^5\) In SWOG 1416, TNBC patients received veliparib and cisplatin...
vs cisplatin alone. Analysis was stratified to 1 of 3 cohorts: germline BRCA variant, BRCA-like, or non-BRCA. The BRCA variant and BRCA-like groups that received combined therapy showed a statistically significant improvement in PFS and improved overall survival, although the difference for overall survival was not significant.  

The Hallmarks of Cancer paradigm advances the perspective that understanding the disruption of genomic pathways or circuits is more important than single gene variations. Comprehensive sequencing of human cancers is confirming that view and revealing that seemingly disparate malignant neoplasms may be more similar than not, as exemplified by the many cancers that share HRR pathway disruptions. Clinical trials guided by molecular signatures will refine the prediction of response or resistance in cohorts and individuals. The blurred distinction between clinical research and standards of practice will create new challenges and opportunities to translate research into practice (ie, implementation science) and to improve systems of care that ensure routine adherence to these new standards (ie, improvement science).

**REFERENCES**


