Clinical Cancer Research

The *HRD* Decision—Which PARP Inhibitor to Use for Whom and When

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Rucaparib, a polyADPribose polymerase inhibitor (PARPi), was approved recently for use in women with high-grade serous ovarian cancer (HGSOC). It is now one of three approved PARPi for use in recurrent ovarian cancer, a family of agents that has changed the HGSOC treatment landscape and outcome. *Clin Cancer Res; 23(23); 7155–7.* ©*2017 AACR.*

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In this issue of *Clinical Cancer Research*, Balasubramaniam and colleagues discuss the details that led to the FDA approval of the polyADPribose polymerase inhibitor (PARPi) rucaparib for the treatment of patients with deleterious *BRCA* mutation–associated advanced high-grade serous ovarian cancer (HGSOC; ref. 1). Rucaparib, the second of three approved PARPi, is licensed for use in patients with germline or somatic *BRCA* mutation–associated HGSOC (g or s*BRCA*m) for third- or later-line treatment.

Ovarian cancer incidence remains relatively stable in the United States, with 24,000+ new cases and over 14,000 women dying of disease each year; despite these concerning numbers, women are living longer and having improved quality of life (2). Continuing this advance requires new therapeutic opportunities. PARPi are the first new class of agents to be approved uniquely for ovarian cancer in over two decades. Their potential clinical utility was identified as the biochemical effects of deleterious germline mutations in *BRCA1* and *BRCA2* demonstrated their integral role in maintaining functional high-fidelity DNA repair through homologous recombination (3). The single-agent activity in several aspects of HGSOC treatment suggests untapped potential for this new class. Concomitant with progress comes the conundrum of how, when, for whom, and in what combinations to use these agents in the treatment of ovarian cancer.

Five PARPi are in clinical development: olaparib, rucaparib, niraparib, talazoparib, and veliparib. The first three listed are licensed for specific indications in HGSOC (Fig. 1). PARPi are divided into two classes: weak PARP trappers (veliparib) and strong PARP trappers (all others; ref. 4). The ability to trap PARP enzyme on damaged DNA prevents DNA repair, stabilizes toxic PARP1/2–DNA complexes, and allows degeneration of stalled replication forks into double-stranded DNA breaks. PARP enzyme inhibition in the absence of intact homologous recombination promotes poor fidelity repair through alternative end joining. This results in increased cancer cell susceptibility to catastrophic repair events. Trapping comes at the cost of enhanced toxicity, most often myelosuppression and thrombocytopenia; equitoxic doses of trapping PARPi result in relatively similar clinical activity.

Three PARPi are now approved: rucaparib, olaparib, and niraparib (Fig. 1). The phase II ARIEL2 study, for which the approval was given, examined rucaparib 600 mg twice daily in patients with HGSOC or high-grade endometrioid ovarian cancer (HGEOC) after $\geq$1 prior platinum-based chemotherapy regimen and whose last treatment was platinum based (5). The study evaluated rucaparib activity as a function of potential predictive biomarkers: g/s*BRCA*m, a signature of homologous recombination dysfunction (HRD) by a loss-of-heterozygosity assay (LOH high; Foundation Medicine, Inc.) and no mutation, and neither mutation nor HRD (LOH low). RECIST response rate and progression-free survival (PFS) were monitored, with greatest activity in g/s*BRCA*m patients (80%, 12.8 months), reduced response rate in LOH high (29%, 5.7 months), and least activity in LOH low (10%, 5.2 months). Liver enzyme elevation, anemia, and fatigue were the most common grade 3 events occurring in $\geq$9% of patients. The phase III ARIEL3 study, just reported at ESMO 2017, examined maintenance therapy with rucaparib 600 mg twice daily in patients with platinum-sensitive (platS) HGSOC after 1 or 2 prior platinum-based chemotherapy regimens. PFS was the primary endpoint. Results showed an improvement from 5.4 months to 16.6 months in g/s*BRCA*m patients (HR = 0.23), 13.6 months in LOH high (HR = 0.32), and 10.8 months in the full intent-to-treat group (HR = 0.36).

Olaparib 300 mg twice-daily tablet formulation, the first approved PARPi, now is approved for treatment of women with HGSOC, independent of g*BRCA* status, with $\geq$3 recurrences, and for maintenance of first-recurrence treatment response for platS HGSOC (6). SOLO1, maturing, evaluates olaparib in maintenance of primary treatment response (NCT01844986). Retrospective studies have shown that prior exposure to olaparib does not abrogate platinum sensitivity in subsequent lines of therapy (7). Niraparib is approved for maintenance of first-recurrence treatment response in unselected recurrent platS HGSOC. Niraparib 300 mg twice daily improved PFS for all tested patient subsets, with best response in g*BRCA* HGSOC patients (21 vs. 5.5 months; HR = 0.27, $P < 0.0001$). The exploratory population of HRD-negative *BRCA* wild-type (*BRCA*wt) patients derived benefit with niraparib (6.9 vs. 3.8 months; HR = 0.58, $P = 0.02$). The impact of niraparib (PARPi) exposure on response and PFS to subsequent

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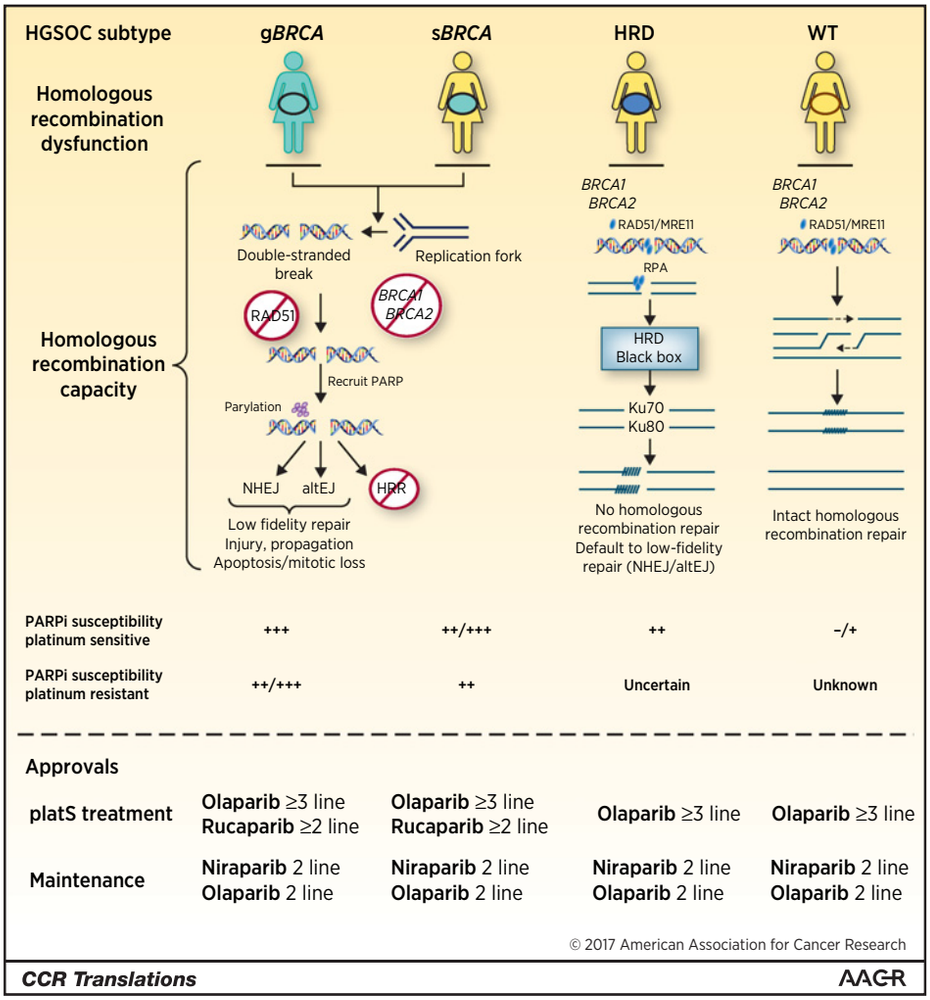

Figure 1.
PARPi application and pathway events as a function of homologous recombination capacity. HGSOC subtypes are designated as germline deleterious (g*BRCA*) or somatic (s*BRCA*) mutation of *BRCA1/2*, or HRD, homologous recombination deficient, as determined by HRD testing, or wild type (WT). DNA double-stranded breaks (DSB) occur directly or as a result of stalled replication fork degeneration. Inability to repair due to loss of homologous recombination capacity in g/s*BRCA* and HRD play out using different mechanisms. s/g*BRCA* have homologous recombination dysfunction caused by the inability to recruit and load RAD51 at DNA DSBs, as occurs in WT homologous recombination. Absent homologous recombination, PARP is recruited and PARylation of DNA ends occurs followed by activation of nonhomologous end joining (NHEJ) or alternative end joining (altEJ), both low-fidelity repair mechanisms, ultimately leading to cell injury, apoptosis, or mitotic arrest or catastrophe. HRD may also occur in the absence of defined mutations; in such cases, the causative event may not be known, hence the "black box." In HRD without known mutation, recruitment of *BRCA1/2* and downstream partners may occur, but normal homologous recombination repair does not; similar to g/s*BRCA*, low-fidelity repair occurs and PARP susceptibility is observed. PARPi susceptibility is a function of homologous recombination capacity and of platinum sensitivity, as shown. Current FDA approvals are outlined.

therapy, whether PARPi induce cross-resistance to the subsequent chemotherapy, such as platinums, and the long-term risks and benefits, remain unknown.

The most compelling questions in PARPi incorporation into the treatment lifecycle of HGSOC/HGEOC remain—for whom are these agents most active, and when should they be used? Complicating whom to treat, beyond g/s*BRCA* and HRD$^+$ patients, is the issue of variants of undetermined significance (VUS). Validation of the different HRD assays as predictive for benefit to PARPi awaits. Germline VUS raise a different flag. VUS determinations are now being made based upon *in silico* determination of deleterious function of the putative mutated protein; this need may be abrogated by a reliable, accurate HRD assay. Lastly, reclassification of patients previously described as having a VUS may be required upon receipt of new information; however, this requires due diligence on the part of providers and genetic testing entities, with timely follow-up of patients with VUS.

Benefits of PARPi appear strongest in women with g*BRCA*m with platS disease. An incremental reduction in responsiveness occurs with progression to s*BRCA*, HRD, and then *BRCA*wt genomics. Similarly, there is incremental loss of responsiveness with platinum-resistant (platR) disease. This would suggest better outcome with earlier use. However, we have no guidance as to when along the treatment timeline to best use PARPi or if combinations will change such recommendations. There is risk that these studies may be biased by access to PARPi in postprogression therapy, complicating overall survival (OS) endpoints. The question remains open as to the best timing to introduce these agents.

The future of PARPi use in HGSOC/HGEOC and in other cancers is wide open. The renaissance of the cellular DNA damage response as a therapeutic target has advanced our understanding of complex DNA repair and resistance mechanisms in general and those that arise with PARP inhibition in particular (8). PARPi are intriguing combination therapy partners to combine with other DNA repair, angiogenesis, cell-cycle, and signaling inhibitors. These combinations provide the opportunity to leverage clinical synthetic lethality where the combined effects of the agents may be far more active than either single agent (9). Initial proof of concept comes from the activity of olaparib in combination with the VEGFR1-3 inhibitor cediranib. This combination, now in phase III, demonstrated unexpected and striking activity in women with *BRCA*wt HGSOC, with >2-fold improvement in PFS (10). Other combination partners include small-molecule and antibody inhibitors of angiogenesis, cyclin-dependent kinases, phosphatidylinositol-3′kinase inhibitors, DNA repair/cell-cycle

regulation enzymes (ATM, ATR, and CHK 1/2), and perhaps immune and cell-cycle checkpoint modulation. Studies of most of these combinations are underway. We have entered an era of HGSOC treatment change yielding improvements in PFS and overall survival, and broadening applicability of PARPi to more women with ovarian cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E.C. Kohn, J.-m. Lee, S.P. Ivy
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E.C. Kohn
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Other (design of figure/table): E.C. Kohn, J.-m. Lee, S.P. Ivy

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