Two Steps Forward and One Step Back for Precision in Prostate Cancer Treatment

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The recent US Food and Drug Administration approval of two poly (ADP-ribose) polymerase (PARP) inhibitors, rucaparib and olaparib, for men with metastatic castration-resistant prostate cancer (mCRPC) and mutations in homologous recombination (HR) repair genes has finally ushered in the era of precision medicine for advanced prostate cancer.[1-4] These approvals represent the culmination of years of work and are clearly a major step forward for the field. However, the respective labels for rucaparib and olaparib offer stark contrasts, the former restrictive to only *BRCA1*- and *BRCA2*-mutated prostate cancer, and the latter permissive of a larger number of genes directly and indirectly involved in HR repair. The broad approval for olaparib includes several genes that, to date, have not individually been shown to predict for response to PARP inhibition. The unintended consequence of using this permissive biomarker strategy for selecting patients for PARP inhibitor treatment may be that patients who have an unclear chance of benefit are exposed to toxicities and delays in utilizing more effective therapies. In addition, this broad approval could hamper efforts to enroll patients in studies designed to better delineate the ability of relatively rare mutations to predict response to PARP inhibitors.

Rucaparib was granted accelerated approval on the basis of the phase II TRITON2 study.[1,3] In this trial, patients with mCRPC were eligible if they previously experienced progression on a next-generation androgen receptor–signaling inhibitor (eg, abiraterone, enzalutamide, or apalutamide), received one prior line of taxane-based chemotherapy, and who were identified to have a mutation in at least one gene of a larger panel with roles in HR DNA repair. However, only the group consisting of those with *BRCA1* or *BRCA2* mutations clearly seemed to be predictive of response.[5] In total, 115 patients with *BRCA*-mutated mCRPC enrolled, with 62 having measurable disease. Within this group, a confirmed objective radiographic response was observed in 27 patients (44%), with a duration of response 6 months or longer in 56% of responders (range, 1.7 to ≥ 24 months).[1]

Whereas the final TRITON2 results are still anticipated, results of a subgroup analysis evaluating clinical outcomes in those with non–*BRCA*-mutated mCRPC enrolled has recently been reported.[5] Overall, responses in those with *ATM* (n = 49), *CDK12* (n = 15), *CHEK2* (n = 12), or other HR genes (n = 14) were low. The prostrate-specific antigen (PSA) response rate (ie, 50% or greater decline in PSA) was observed in only 4% of *ATM*-mutated cases, 7% of *CDK12*-mutated cases, and 17% of *CHEK2*-mutated cases. Radiographic responses in the subset with measurable disease were similarly low in non-*BRCA* HR repair genes. Small numbers of patients with mutations in *FANCA* (n = 4), *NBN* (n = 4), *BRIP1* (n = 2), *PALB2* (n = 2), *RAD51* (n = 1), *RAD51B* (n = 1), and/or *RAD54L* (n = 1) were also reported. Whereas sample size limitations prevent drawing conclusions about the sensitivity of any given gene, it is notable that responses were observed in those with mutations in genes that directly interact with the BRCA complex (ie, *PALB2*, *FANCA*, and *BRIP1*), which contrasts with the low response rates in genes that either sense DNA damage (eg, *ATM*, *CHEK2*) or indirectly regulate *BRCA* expression (eg, *CDK12*). Finally, it is worth acknowledging that relatively few men with *BRCA1* alterations were included in this study (n = 14), and the true response rate within this population also remains poorly defined.[6]

Olaparib was approved on the basis of the phase III PROfound study, which was a randomized, open-label study evaluating olaparib versus physician's choice of enzalutamide or abiraterone in men with mCRPC and deleterious germline or somatic mutations in HR repair genes.[4] Similar to TRITON2, the PROfound investigators also focused on the subgroup that previously experienced progression on next-generation androgen receptor–directed therapy, and, also similar to TRITON2, enrollment was allowed on the basis of a panel of genes involved in the HR repair pathway. Primary end point was progression-free survival (PFS) in the group with *BRCA1*, *BRCA2*, and/or *ATM* mutations (cohort A). A second cohort consisted of patients with mutations in other HR repair–associated genes (cohort B). Secondary end points were analyzed in a hierarchical fashion to control for trial-wide Type 1 error associated with multiple testing, which occurred in the following order: objective response rate (cohort A),

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PFS (combined cohorts A and B), time to pain progression (cohort A), and overall survival (cohort A).

The primary end point was met, with a PFS of 7.4 months versus 3.6 months ($P < .001$) in the olaparib versus control groups for cohort A. Secondary end points also favored the olaparib group, with an objective response rate in cohort A of 33% versus 2% in control group ($P < .001$), median PFS of 5.8 months versus 3.5 months for combined cohorts A and B ($P < .001$), median overall survival of 18.5 months versus 15.1 months for cohort A ($P = .02$), and median overall survival of 17.5 months versus 14.3 months for combined cohorts A and B ($P = .0063$). These results led the US Food and Drug Administration to approve olaparib for a broad group of patients with mCRPC with somatic or germline alterations in *BRCA1*, *BRCA2*, or any of 12 additional HR repair pathway genes.

Whereas the magnitude of benefit reported for cohort A in PROfound is apparent, the lack of details provided for cohort B leaves more questions than answers. Examining the data more closely, it seems that the observed benefit was largely driven by *BRCA*-mutated patients, which primarily consisted of men with *BRCA2* mutations (> 90%). There is a clear improvement in PFS for the *BRCA*-mutated group (n = 160), whereas no difference in PFS was observed in either *ATM* (n = 86) or *CDK12*-mutated cases (n = 89; Fig 2B and Supplemental Figure S5). Unfortunately, no detailed analysis of outcomes for cohort B—independent of cohort A—are provided, and the small sample size within any given genomic subgroup limits our ability to determine which of these patients may have benefited from olaparib.

The TOPARP-A and -B studies, which preceded PROfound, tested olaparib in a similar patient population.[7,8] In TOPARP-B, the authors found low PSA and radiographic response rates for *ATM* (5.3% and 8.3%, respectively) and *CDK12*-mutated mCRPC (0% for both).[8] In addition, the PROfound investigators acknowledged that the benefits of olaparib are most apparent in *BRCA*-mutated mCRPC. Whereas the design of PROfound was likely informed by the initial TOPARP-A experience, which found that four of five patients with *ATM*-mutatations responded favorably to olaparib (ie, PSA response and/or favorable changes in circulating tumor cell counts), the biologic and clinical rationale for combining *ATM* and *BRCA1/2* mutations into a single cohort is questionable on the basis of our current knowledge.[7] Registries capturing clinical and genomics data are ongoing and may provide important insights into the clinical relevance of rare variants[9]; however, additional prospective studies evaluating outcomes for patients with HR repair–associated mutations receiving PARP inhibitors should be conducted on an individual gene basis.

In the case of PROfound, the *BRCA* group seems to have driven the overall effect size observed between the olaparib and control groups. An important concern is that this experience may motivate the design of future precision medicine trials. The precedent set by the olaparib approval for prostate cancer may incentivize studies that combine molecular subgroups to attain broad indications. This may lead to future study designs that include two groups: one that is expected to benefit (eg, *BRCA2*) and another that is more exploratory and permissive (eg, *ATM*/*CDK12*). The consequence, intended or not, may be that a *P* value less than .05 could be reached in the combined group as long as the sample size is sufficient to detect a diluted treatment effect. This approach would ultimately run counter to the idea of precision oncology.

As discussed above, the clinical data supporting the use of PARP inhibitors in non–*BRCA2*-mutated cases remain scant; however, there is a rationale for their routine use in men with mutations in a handful of other HR repair–associated genes. Whereas some data suggest lower response rates in men with *BRCA1*- compared with *BRCA2*-mutated prostate cancer (eg, PSA response rate of 29% *v* 56% per TRITON2) and no clear difference in PFS was observed in men with *BRCA1* mutations receiving olaparib versus abiraterone/enzalutamide in PROfound, the small number of patients with *BRCA1* mutations included in prospective studies make drawing conclusions regarding differences in activity impossible.[4,6] Overall, the known biologic role of *BRCA1* in HR repair, along with available clinical data, generally supports the use of both olaparib and rucaparib in these patients. Likewise, there is also evidence that PARP inhibitors may afford benefits to those with *PALB2* mutations, with responses to olaparib documented in approximately one third of *PALB2*-mutated prostate cancers.[8] In addition, because *PALB2* also plays a critical role in HR repair—directly interacting with the BRCA complex—there is a strong biologic rationale for using PARP inhibitors in patients with prostate cancer with inactivating *PALB2* mutations.[5,8,10,11]

The primary advantage of olaparib's broad approval is that providers will have the latitude to use this drug in men with mutations in less common HR repair genes (eg, *PALB2*) that are likely predictive for response. However, approving olaparib for such a large genomic subgroup could prove detrimental to some patients and the field if not used judiciously. To qualify for olaparib, patients must have already experienced progression on a next-generation hormonal agent (eg, abiraterone or enzalutamide) and owing to the heavily pretreated state of their disease, this population often has rapid disease progression with a short overall survival. On the basis of the published studies, there are limited data to support use of olaparib in the absence of *BRCA1/2* mutations, and without other indications of HR repair deficiency, these patients would be better served by participating in clinical trials or receiving a therapy that is beneficial in unselected patients (eg, taxane-based chemotherapy).[12] Using standard-of-care PARP inhibitors in those with uncertain or little chance of

benefit could mean missing a window of opportunity for more effective therapy. This may result in decreased survival and hamper clinical trial enrollment to the very studies that could define the predictive utility of individual genes. Cumulative experience should matter, and given our understanding of which genes predict response to PARP inhibitors, the use of rucaparib and olaparib should be primarily limited to those with *BRCA1/2* mutations until the development of additional biomarkers that are more predictive of benefit.

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