



# PARP inhibitors beyond *BRCA*-mutated cancers: precision medicine at the crossroads

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Precision oncology is a rapidly evolving concept that considers the individual molecular and cellular features of a tumor. This paradigm is based on the possibility to precisely characterize specific targetable alterations and define the subpopulations that are most likely to benefit from personalized therapeutic interventions. Discovery of the tyrosine kinase inhibitor imatinib in 1996 marked the beginning of the “precision oncology” era and sparked hope for patients with cancer (1). Indeed, several biomarker-based therapies have allowed for unprecedented survival gains in patients with specific molecular alterations (2). One of the most promising agents are the inhibitors of poly (ADP-ribose) polymerase (PARP), a family of proteins that constitutes a crucial element of the complex machinery involved in response to DNA damage.

PARP inhibitors (PARPi) are considered the first clinically approved medicine designed to exploit synthetic lethality, a genetic phenomenon that was first described almost 100 years ago, perfectly matching the assumptions of precision oncology. This term describes the situation in which a defect in a single gene or protein does not result in cell death, unless combined with another altered gene or protein, also nonlethal, as a standalone abnormality. In the context of anticancer therapy, the most prominent examples are *BRCA1*- and *BRCA2*-deficient tumors. These genes are well-known tumor suppressors that are involved in the repair of DNA double-strand breaks via a homologous recombination repair (HRR) mechanism. Cells with defective *BRCA1* or *BRCA2* cannot perform HRR efficiently. This is partially compensated by other

DNA repair pathways, such as nonhomologous end joining, which is less effective and more prone to error than HRR. The cytotoxic mechanism underlying synthetic lethality is that PARPi trap PARP1 on the DNA, creating a lesion that is repairable via the HRR pathway in normal but not in *BRCA1*- or *BRCA2*-deficient cells (3).

For a long time, PARPi have been approved only for breast and ovarian *BRCA*-associated cancers: olaparib, niraparib, and rucaparib in high-grade serous ovarian cancer and olaparib and talazoparib in metastatic breast cancer (4). In May 2020, two PARPi were approved by the Food and Drug Administration (FDA) for men with metastatic castration-resistant prostate cancer (mCRPC). The first, accelerated, approval was granted to rucaparib for patients with mCRPC with a deleterious *BRCA1/2* mutation (germline or somatic). This approval was based solely on the results of TRITON2 (NCT02952534), an ongoing phase 2, single-arm study without a control group, with objective response rate and prostate-specific antigen response as co-primary end points (5). Even more controversial was the second approval, which was granted to olaparib for men with mCRPC and mutations not only in *BRCA1/2*, but also in 12 other “HRR-related” genes. The primary end point of the PROfound registration study was imaging-based progression-free survival (iPFS) evaluated in two groups of patients: cohort A (patients who had at least one alteration in *BRCA1*, *BRCA2*, or *ATM*) and the overall population (cohort A and a smaller cohort B combined, including patients with alterations in any of the other 12 prespecified genes involved in HRR, i.e., *BRIP1*, *BARD1*,

*CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*) but not cohort B alone (6). This approval, for the first time, extended the applications of PARPi beyond *BRCA1/2*-mutated cancers, beginning a new chapter in the history of these drugs.

However, this decision may be considered debatable. For instance, the median iPFS in the merged cohorts, cohorts A and B, was 5.8 months, compared to 7.4 months in cohort A alone, which causes doubt regarding any benefit from olaparib in cohort B. In fact, this presumption is supported by the data presented in the Supplementary Appendix of the PROfound study: no significant differences were found between both study arms in this subset (hazard ratio: 0.88, no data on the 95% confidence interval), with crossing survival curves. Thus, it may be inferred that the benefit of olaparib in cohorts A and B (“overall population”) resulted entirely from its effect in cohort A, partially diluted by the twice-smaller cohort B. One might even consider going further; that is, if cohort B had instead comprised an equinumerous group of unselected patients with prostate cancer, their negative result would not have completely undermined the claim of “benefit” in the merged population.

In addition, deficiencies in HRR-related genes cannot be considered as one consistent group. In fact, this assumption is supported by the data presented by the authors of the PROfound trial. According to the Supplementary Appendix, among patients with alterations in *BRCA1/2* and/or *ATM*, the benefit was limited to the *BRCA2*-deficient group. However, patients with alterations in some of the other HRR-related genes (e.g., *RAD51B* or *RAD54L*) seemed to derive benefit from olaparib, but these alterations are rare. These results suggest that PARPi seem to be highly effective in *BRCA2*-mutated mCRPC, while the responses in cases with alterations in less common HRR-related genes are anecdotal (7). Therefore, the activity of PARPi in this group should be verified in a large trial with an adequate sample size and statistical power. In fact, such an approach was proposed by the authors of the TRITON2 trial, who presented a separate analysis including a subset of 78 patients with non-*BRCA* HRR-related gene alterations enrolled in the study (8). They concluded that alterations in *FANCA*, *PALB2*, *BRIP1*, and *RAD51B* induce a tumor response and warrant further investigation. However, these results again do not provide definitive conclusions and rather generate hypotheses. The same approach applies to breast and ovarian cancer, wherein case reports describing spectacular responses in non-*BRCA*-deficient patients are considered anecdotal

and warrant further investigation (9-11).

With regard to the more common alterations, numerous questions also remain to be answered. Although olaparib seems to be effective in the majority of patients with *BRCA2*-mutated mCRPC, the magnitude of its benefit in *BRCA1*-mutated patients remains unclear (12). Indeed, both TRITON2 and PROfound have shown better outcomes for patients with mCRPC harboring *BRCA2* mutations than for those with *BRCA1* mutations. Several hypotheses explaining this discrepancy were proposed, including differences in germline lesions, biallelic mutations, or existence of co-alterations (12). Alternatively, this discrepancy may simply be due to the much lower prevalence of both germline and somatic *BRCA1* alterations in mCRPC, hampering the evaluation of the differences in PARPi activity between particular subgroups (13). Notably, the PROfound trial and all phase II trials, including TRITON2, have shown little, if any, benefit of PARPi in the *ATM*-mutated subgroup (5,6). This observation indicates that, instead of being grouped together with *BRCA1/2* cases, this cohort warrants alternative testing strategies (7).

It should be noted, however, that some patients without detectable HRR deficiencies still respond to PARPi. Therefore, given the inconsistent results of clinical trials, there is a need for a more precise definition of PARPi sensitivity and identification of predictive biomarkers. Indeed, a substantial proportion of HRR deficiencies may be missed by gene sequencing, as the inactivation may be related to other mechanisms, for example, epigenetic alterations, such as methylation or noncoding RNAs. Several potential approaches exist for addressing this issue, including scores capturing large genomic aberrations, also called “genomic scars,” or RAD51 assays (14). However, companion diagnostics evaluating homologous repair deficiency (HRD) via loss of heterozygosity and global genomic alterations have not allowed for selecting patients with non-*BRCA*-mutated tumors who might benefit from PARPi (15). Likewise, a recent meta-analysis of individual patient data evaluating *BRCA1* promoter methylation in ovarian cancer has shown no favorable prognostic impact of methylation (16). However, the meta-analysis showed a remarkable heterogeneity in the methylation assays utilized across particular studies; for example, many of them considered methylation in a binary manner, without considering CpG sites, which are likely more relevant for clinical purposes.

To tackle the aforementioned issues, the Translational Research and Precision Medicine Working Group of

the European Society for Medical Oncology recently defined the best practices for predictive biomarker testing for HRD and PARPi benefit (17). According to these recommendations, there is no strong clinical evidence for the validity of individual genes or panels of non-*BRCA* HRR-related genes in predicting a PARPi response, although more data need to be collected in a prospective manner. Possibly, one of the most important issues raised is developing a test that provides a dynamic readout and addresses the continuous evolution of the cancer genome. Currently, in most cases, the snapshot derived from the archival material may not be sufficiently reliable, as it does not reflect the current status of the tumor. Such material is often of low quality; for example, in the PROfound trial, around 30% of the tissue blocks submitted for testing did not pass quality control (7). A possible solution to overcome these issues might be to use liquid biopsies. This approach has been prospectively tested in the TRITON2 study, in which next-generation sequencing of circulating cell-free DNA (cfDNA) has been shown to exhibit a high level of concordance with tissue biopsies. Soon after this trial was published, the test, provided by FoundationOne, was approved by the FDA. Most recently, this company confirmed the previous findings using more than 3,000 plasma samples of patients with mCRPC (18). However, it should be noted that, in some scenarios, cfDNA may be characterized by an inferior sensitivity when compared to tumor tissue testing, in particular when detecting copy-number losses (19).

Given that germline *BRCA1/2* mutations are present in less than 2% of prostate cancers, it is not surprising that the development of PARPi in this indication has been slower than for breast or ovarian cancer. At the same time, germline and somatic inactivating mutations in HRR-related genes occur in approximately 10–15% and 20–25% of patients with metastatic prostate cancer, respectively (4). Therefore, in view of the growing number of reports suggesting a potential activity of PARPi in a broader molecular background (11), it is tempting to evaluate them not only in *BRCA1/2*-deficient prostate cancer. Consequently, there is a growing tendency to broaden the inclusion criteria in the hope of allowing more patients to benefit, even marginally, from particular targeting agents. These practices may undermine the core principles of precision oncology and carry considerable adverse consequences with nonnegligible physical and financial toxicity (20,21). Notably, it has been estimated that, among the whole population of patients with cancer, the percentages of those who are eligible to receive

these therapies and those who achieve clinical benefit are merely around 9% and 5%, respectively (22). Therefore, it can be concluded that precision oncology necessitates precise clinical testing.

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