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PARP inhibition — not all gene mutations are created equal

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Abstract

Preliminary results from TRITON2 demonstrate efficacy of the poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib in ~50% of patients with metastatic castration-resistant prostate cancer and inactivation of *BRCA1/BRCA2*. However, those with *ATM* and *CDK12* mutations do not seem to benefit. An improved homologous recombination deficiency test must be developed and alternative treatments defined for these subsets of patients.

In 2015, a genome-wide study detected biallelic mutational loss of DNA damage repair (DDR) genes in 22.7% (34/150) of patients with metastatic castration-resistant prostate cancer (mCRPC)[1], a disease with lethal potential that can be managed with sequential systemic therapies, yielding survival benefits. A subsequent study found that 11.8% (82/692) of patients with metastatic prostate cancer harbour a deleterious germline DDR alteration[2], suggesting that germline analysis alone can detect about half of these oncogenic DDR gene drivers. Affected DDR genes in prostate cancer include *BRCA2, ATM, BRCA1, CDK12*, and many of the Fanconi anaemia (*FANC*) genes that are implicated in homologous recombination (HR) DNA repair. Importantly, HR deficiency (HRD) due to biallellic loss of HR genes is ‘synthetic lethal’ with poly(ADP-ribose) polymerase (PARP) inhibition. Thus, detection of HRD might be therapeutically actionable. PARP inhibitors such as olaparib, rucaparib, niraparib, and talazoparib have received FDA approval for ovarian and breast cancer. Although no PARP inhibitor has yet received regulatory approval in prostate cancer, multiple biomarker-driven trials are currently underway to evaluate PARP inhibitors in patients with mCRPC who have HRD mutations.

To address the unmet clinical need in patients with mCRPC who have limited treatment options, such biomarker-driven trials generally target patients who have failed at least one novel hormonal therapy (abiraterone or enzalutamide) and up to one taxane chemotherapy. At the 2018 European Society for Medical Oncology (ESMO) conference, preliminary results from one such trial, TRITON2, were reported[3]. This phase II, single-arm study

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Competing interests

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(ClinicalTrials.gov identifier: NCT02952534) is investigating the PARP inhibitor, rucaparib, in patients with mCRPC and HR gene mutations who have failed to respond to at least one novel hormonal therapy and one taxane chemotherapy. In an interim analysis after the first 85 patients had been enrolled, 45 had *BRCA1/BRCA2* mutations (predominantly *BRCA2*), 18 had *ATM* mutations, 13 had *CDK12* mutations, and 9 had other HR mutations. The median follow-up duration was 5.7 months (range, 2.6–16.4 months). Encouragingly, among the 45 patients with a *BRCA1/BRCA2* alteration, 51.1% (23/45) had a confirmed ≥50% PSA response, and among those who also had measurable disease, 44.0% (11/25) had a confirmed partial objective response using RECIST criteria. By contrast, none of the measurable-disease patients with *ATM* ($n = 5$) or *CDK12* ($n = 12$) alterations achieved objective responses, and the majority of patients with *ATM* and *CDK12* mutations also failed to demonstrate a PSA response[3].

The TRITON2 results are promising, but also suggest that a substantial proportion of patients with HR mutations are unlikely to benefit from PARP inhibition. This differential response seems to be gene related: for example, none of the patients with *ATM* or *CDK12* mutations responded favourably to rucaparib, whereas a large subset of patients (but by no means all) with *BRCA1/BRCA2* mutations did respond to PARP inhibitor treatment. Perhaps lack of response in *CDK12*-mutated patients is expected, given the data demonstrating that *CDK12*-mutant tumours are genetically, transcriptionally, and phenotypically distinct from HRD cancers[4], in spite of original data linking CDK12 to HRD. No germline *CDK12* alterations have been detected, and somatic-only *CDK12* biallelic loss was detected in 6.9% of patients with mCRPC who might benefit from immune checkpoint inhibitors[4,5].

The lack of response to rucaparib in virtually all patients with *ATM* mutations (and in a considerable number with *BRCA1/BRCA2* mutations) is seemingly at odds with a report from Mateo et al.[6], in which another PARP inhibitor (olaparib) was shown to be effective in the majority of patients with *BRCA1/BRCA2* and *ATM* mutations in a 49-patient phase II trial. This discrepancy might be explained by the different methods used in the two studies to detect HR mutations: whereas Mateo et al.[6] characterized the germline or somatic and biallelic status of the *BRCA2, BRCA1*, and *ATM* genes, the mutation test (conducted by Foundation Medicine using archival tissue or plasma-derived DNA samples) in the TRITON2 trial did not differentiate the biallelic status or the germline or somatic status. Thus, that some of the rucaparib nonresponders in the TRITON2 trial might have an intact wild-type allele cannot be ruled out, and, therefore, the tumour might not have had true HRD at the functional level.

Furthermore, detection of a germline *BRCA2* mutation in patients with mCRPC often indicates biallelic mutational loss in the tumour cells. However, the reverse might not be true and detection of a somatic-only mutation without information on biallelic status might not indicate HRD or the presence or absence of a germline event. Thus, one could classify HR mutations into three distinct functional groups: those with germline plus somatic mutations; somatic-only monoallelic mutations; and somatic-only, biallelic mutations. These subgroups could be further subdivided according to the type of mutation involved. Currently, whether response to PARP inhibition is different among the different groups (or subgroups) is

unknown, although a less robust response can be reasonably expected in the somatic-only, monoallelic group, because the tumour does not have functional HRD (FIG. 1). However, the test employed in the TRITON2 trial cannot accurately differentiate the different mutation groups for all patients enrolled.

For *ATM*, deleterious germline mutations occur in ~2% of patients with mCRPC[7] with few accompanied by a somatic second hit, whereas somatic *ATM* alterations (without a germline event) are detected at greater frequency (5–10%) in mCRPC tumours[7]. With the small sample size of the TRITON2 study, establishing the accurate frequencies of *ATM* germline-only, germline/somatic, or somatic-only alterations and their precise clinical implications is challenging. Whether detection of *ATM* mutations in the TRITON2 trial implies HRD remains unknown. Additionally, a 2018 study suggests a genomic signature of *ATM* loss that is distinct from *BRCA1/BRCA2* loss, suggesting a possible distinction in their genomic and clinical implications[8].

Overall, the preliminary TRITON2 results[3] are promising and also reveal several important findings to guide future clinical development. First, patients with *BRCA2* (and perhaps *BRCA1*) loss seem to be responsible for the overall clinical benefit of PARP inhibition, perhaps owing to the central role of these proteins in the homologous recombination process. Second, patients with *ATM* and *CDK12* mutations do not seem to derive benefit from rucaparib, and alternative therapies might be needed for such patients. Third, a substantial proportion of patients, even with a *BRCA2* mutation, do not respond favourably to rucaparib. These results could potentially be explained by lack of HRD, rapid development of resistance owing to reversion mutations that restore the open-reading frame, or presence of heterogeneous clones that do not harbour HRD. Thus, a better HRD test must be developed and alternative treatments need to be defined for the subset of patients that might not draw benefit. Notably, both germline and somatic analyses should be performed to identify patients with true DDR gene deficiency Finally, studies suggest that patients with HRD might also respond to androgen receptor (AR)-targeting therapies[9,10], although the literature has been conflicting. As PARP inhibitors are not yet approved in prostate cancer, patients with mCRPC who have not developed resistance to novel AR targeting therapies might benefit from such PARP-sparing therapies. The treatment options for HRD prostate cancer might, therefore, be more abundant than previously thought.

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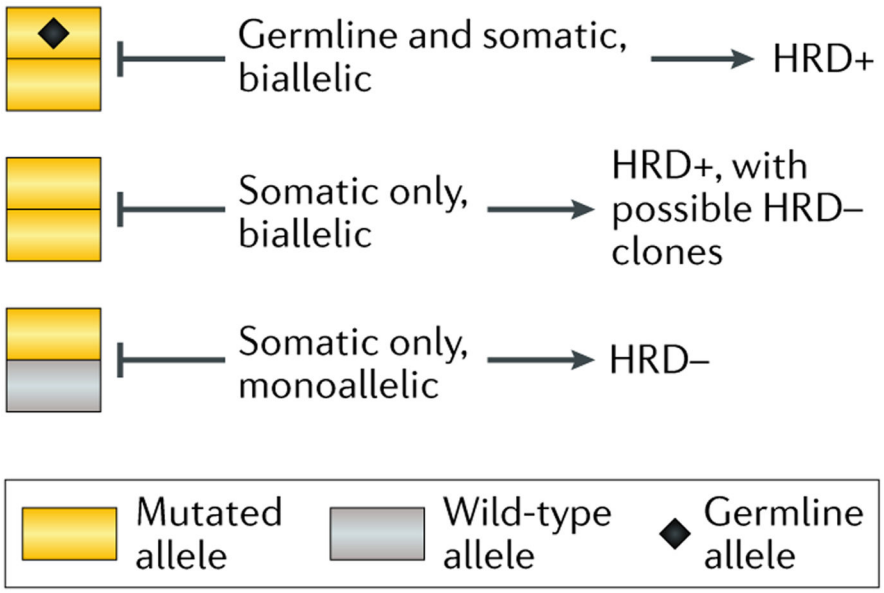

Fig. 1 |. Clinical benefit of PARP inhibition might differ by mutation patterns of genes implicated in HR DNA repair.

Homologous recombination (HR) mutations can be classified into three distinct functional groups: those with germline plus somatic mutations; somatic-only, biallelic mutations; and somatic-only, monoallelic mutations. Subgroups could be further subdivided according to the type of mutation involved (frameshift, nonsense, missense, and copy loss), leading to different HR deficiency (HRD) status and clinical benefit of PARP inhibition. A less robust response can be reasonably expected in the somatic-only, monoallelic group, as well as in the somatic-only, biallelic group if somatic alterations are heterogeneous. PARP, poly(ADP-ribose) polymerase.