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Platinum Priority – Editorial

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PARP Inhibitors for Advanced Prostate Cancer: Validating Predictive Biomarkers

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Prostate cancer (PC) is a highly heterogeneous disease. Many PCs have DNA repair gene aberrations in germline DNA or, more commonly, tumour DNA, usually as early truncal events in prostate carcinogenesis. In advanced PC, *BRCA2* is the most commonly aberrant gene; other reported defects involve *ATM* and *CDK12* [1]. Unlike *BRCA2*, loss of *ATM* or *CDK12* does not generate typical genomic signatures of homologous recombination DNA repair (HRD) defects [2], although other HRD genes are deleteriously aberrant in PC, including *BRCA1*, *PALB2*, *RAD51*, and *FANCA*. Preclinical studies have shown that total loss of function (biallelic loss) of one of these genes sensitises to PARP inhibition (PARPi). The degree of sensitisation differs from one gene to another, with loss of *BRCA2* being the most sensitising [3]. Multiple PARP inhibitors are being evaluated in PC clinical trials, including olaparib, niraparib, talazoparib, and rucaparib. An analytically valid and clinically qualified predictive biomarker identifying tumours sensitive to these agents is urgently needed, as some tumours are sensitive and have evidence of HRD loss through genomic scar detection (high HRD score) without identifiable gene aberrations.

In this issue of *European Urology*, Marshall et al. [4] report on 23 men with metastatic castration-resistant PC with *BRCA2* or *ATM* alterations treated with off-label olaparib 300 mg twice daily (BID), although 46 patients overall received off-label olaparib. Thirteen of 17 men with germline or somatic *BRCA* defects had a 50% prostate-specific antigen (PSA) decline following olaparib, with median progression-free survival of >1 yr, while none of six men with *ATM* alterations had a >50% PSA fall. These *BRCA1/2* results are in keeping with published data and support the use of PARPi for this subgroup. The olaparib dose used in this retrospective analysis was 300 mg BID, the dose approved for ovarian cancer, which is lower than the dose of 400 mg BID used in the TOPARP-A trial [5]. While the antitumour activity of olaparib is highly dose-dependent (in ovarian cancer with *BRCA1/2* aberrations the response rate to the maximum tolerated dose of 400 mg BID was 33%, but only 13% at the minimum biologically active dose of 100 mg BID) [6], these data indicate that a dose of 300 mg BID may be sufficient to impact PC outcomes, although it is impossible to determine if their durations of benefit differ. The lack of biochemical responses in these six patients with *ATM* alterations differs from the data we reported in TOPARP-A with olaparib 400 mg BID, in which *ATM* deleterious aberrations were detected in five different tumours, with a sixth patient having an *ATM* mutation in plasma cell-free DNA not detectable in biopsies [7]. Overall, two patients (33%) had a 50% PSA response, two had a decrease in circulating tumour cell count but no PSA decrease, and two had no discernible benefit in TOPARP-A [5]. A preliminary analysis of a phase 2 trial of rucaparib [8] recently reported no confirmed responses among 18 men classified as having tumours with *ATM* alterations, although a few had some PSA declines. Overall, however, no Response Evaluation Criteria in Solid Tumours responses were reported for any of these three series of patients with cancers with *ATM* alterations, although most had bone-only disease.

ATM is a large gene on chromosome 11 encoding ATM serine/threonine kinase, a 350-kDa protein of 3056 amino acids found in its inactive form as a homodimer. ATM activation occurs primarily after the recognition of a

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double-strand break (DSB) by the MRE11-RAD50-Nbs1 (MRN) complex; ATM activation after DSB sensing involves autophosphorylation of serine 1981 and dissociation into active monomers, with ATM-dependent stabilisation of p53 regulating pro/anti-apoptotic signalling responses to DNA damage. ATM protein loss impacts DNA damage response quite differently to dysfunctional ATM protein as a result of a truncating mutation encoding a kinase-dead protein; mouse models with *ATM* loss are viable, but mouse embryos expressing kinase-dead ATM are not [9]. *ATM* loss of function induces PARPi sensitivity in multiple preclinical models, including chronic lymphocytic leukaemia, lung, and breast models, although most of these have dual *ATM* and *p53* loss [10]. *ATM* loss can also result in sensitivity to platinum-based chemotherapy, but is associated with a different mutational signature to *BRCA2* HRD tumours, reflecting differing biological functions. Unlike *BRCA2*, the genomic mutation landscape of the large *ATM* gene remains poorly mapped and interpretation of the genomic assays being used to report these alterations remains challenging. Interestingly, in the series reported by Marshall et al. [4], one of six *ATM* alterations, compared to 12 of 17 *BRCA* aberrations, was of germline origin. Patient selection for off-label olaparib 300 mg BID used germline or somatic DNA sequencing data, different sequencing platforms (including either panel testing or exome sequencing), and either plasma cell-free DNA or tumour biopsy DNA. Moreover, the mutation allele frequency and loss-of-heterozygosity status helps understanding if gene loss is mono- or biallelic. The assay performance may therefore have impacted these data; it remains critical to identify loss of *ATM* function, that is, the absence of functional protein, and the optimal way to do this may involve immunohistochemistry assays complementing genomics data.

In conclusion, how do these data impact the field? They clearly confirm that olaparib, even at the lower dose of 300 mg BID, has impressive antitumour activity against PC with *BRCA2* loss. The jury, however, is still out on *ATM* loss. Future trials studying loss of *ATM*, and indeed of other key DNA repair genes, need to analyse this separately to *BRCA2* with validated and preferably multiple orthogonal assays such as next-generation sequencing (of both germline and tumour DNA) and immunohistochemistry. Overall, however, it is clear that loss of *ATM* has a major role in prostate carcinogenesis. Studies are now warranted on the biology of these *ATM* aberrations in prostate cancer, and how biological and genomic contexts alter their impact on sensitivity to DNA repair inhibitors and platinum chemotherapy.

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