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Towards a New Classification for Metastatic Prostate Cancer

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The current system for classifying advanced prostate cancer is based on two landmark events: identification of distant organ infiltration (defining nonmetastatic and metastatic prostate cancer) and progression on androgen deprivation therapy (ADT; transition from hormone-sensitive to castration-resistant disease). Over the last decade, this stratification system has informed prognosis and guided the indication for additional therapies such as taxane-based chemotherapy, abiraterone acetate, enzalutamide, and radium-223. This classification, however, is no longer fit for purpose. Several clinical trials have demonstrated the beneficial effects of docetaxel and abiraterone acetate when administered in the metastatic hormone-sensitive state, before castration resistance [1–3]. In addition, earlier this year, enzalutamide and apalutamide were approved for patients progressing on ADT but with no evidence of metastatic disease according to conventional imaging techniques [4,5]. These paradigm-changing trials have modified clinical guidelines and support the need for a new approach to stratification of advanced prostate cancer.

The improved understanding of localised and metastatic prostate cancer genomics offers the opportunity to develop a new taxonomy for this disease on the basis of molecular profiles. Landscape studies of prostate cancer genomics have led to the identification of disease subsets [6,7]. The clinical value of these subgroups now needs to be proven to advance towards a classification system based on prognostic and predictive genomic biomarkers.

In this issue of *European Urology*, Antonarakis and colleagues [8] report clinical outcome data for a small group of patients with metastatic prostate cancer patients and germline or somatic genomic defects in the DNA mismatch-repair (MMR) machinery. The median progression-free survival to first-line ADT among the 13 patients was 66 mo, compared to 27 mo in a control cohort of 114 patients with no MMR mutations detected. The authors also identified significant antitumour activity of agents targeting the AR axis in this molecularly defined patient subgroup, although only three and five patients in this series were treated with abiraterone and enzalutamide, respectively, so we should interpret the results with some caution. Moreover, 4/13 patients with MMR gene defects received treatment with PD-1 inhibitors, with three of them achieving soft-tissue tumour responses.

Successful development of immune checkpoint inhibitors for other tumour types has led to biomarker-dependent, histology-agnostic approval of pembrolizumab by the US Food and Drug Administration. The spotlight is now on identifying MMR-deficient prostate cancers and evaluating tailored therapeutic options for these patients. The prevalence of MMR defects in metastatic prostate cancer has been reported as 2–12% across different landscape studies. In part, this variability in reported prevalence arises from the lack of an agreed definition of what is a clinically relevant MMR defect in prostate cancer. In this study, the authors report that not all patients with mutations in canonical MMR genes would have been identified according to microsatellite instability (MSI) testing. In a separate recently published study, Nava et al [9] integrated genomics, transcriptomics, pathology, and immune infiltrate studies to characterize MMR function in a larger cohort of metastatic prostate cancer samples. Most, but not all, patients with mutations in canonical MMR genes had higher mutational loads and an MSI-high profile. However, some cases with MMR gene mutations but no accompanying MSI-high profiles or vice versa were identified in the SU2C-PCF advanced prostate cancer data set. Despite the initial disappointment in earlier trials, several

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studies have now identified prostate cancer patients benefiting from treatment with immune checkpoint inhibitors [10]; it is now critical that these multimodal biomarkers are implemented in biology-driven clinical trials to optimally define clinically relevant MMR deficiency for prostate cancer treatment stratification. Of note, in the study by Nava et al [9], MMR deficiency in prostate cancer was associated with faster progression on ADT, contrary to what is reported here. Owing to differences in characteristics of the study population, the type of samples being tested (primary vs metastatic disease, collected either before or after castration resistance), the assays used to define the MMR defect, the gene set selected for interrogation, and regional differences in clinical practice, extreme caution should be applied when comparing data from different retrospective series. A similar scenario is being faced for clinical qualification of homologous recombination–mediated repair mutations as prognostic and predictive markers in advanced prostate cancer.

The small sample size in this retrospective study by Antonarakis et al and the need for a properly designed control cohort hamper the extraction of definitive conclusions from the results, as the authors acknowledge in their discussion. While further studies are needed, this is still a valuable report highlighting some of the challenges for clinical qualification of genomic biomarkers, particularly those with low prevalence, in the context of a rapidly evolving field.

To deliver precision medicine on the basis of prognostic and predictive biomarkers, such as MMR or other DNA repair defects, we need to consider these biomarkers in the specific tumour context, in which other clinically relevant molecular events co-occur. As an example, the authors highlight the relatively high prevalence of *TP53* mutations in this cohort of MMR-mutated tumours, which may also be important in terms of determining patient outcome.

Interrogation of the impact of multiple biomarkers on patient outcomes requires large prospective studies that include tumour evolution and intrapatient genomic heterogeneity concepts. In recent years, collaborative research and cross-institution academic alliances have facilitated huge advances in defining the genomic landscape of prostate cancer. It is likely that this team-science approach will be key in the pursuit of clinical qualification of a new taxonomy for prostate cancer based on genomic stratification, with the ultimate aim of delivering more precise patient care in prostate cancer.

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