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European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 562–571 of this issue

Separating the Dreadful from the Merely Bad: Towards Prognostic and Predictive Biomarkers in Metastatic Castration-resistant Prostate Cancer

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Despite the development of novel androgen deprivation therapies (ADTs) such as enzalutamide and abiraterone, metastatic castration-resistant prostate cancer (mCRPC) remains incurable. Developments in massively parallel DNA sequencing and computational biology have allowed unprecedented insights into the molecular alterations underlying prostate tumorigenesis and progression [1–5]. Moreover, prognostic biomarkers of aggressive localized disease have been developed using whole-genome sequencing (WGS) and related technologies [1,6]. However, an unbiased assessment of the link between genome-wide aberrations and clinical outcomes for mCRPC is currently lacking, in large part owing to the lack of well-powered, outcome-matched studies of mCRPC using WGS, which detects coding and noncoding aberrations across multiple mutational classes. Quigley and colleagues [7] recently described the whole-genome landscape of 101 mCRPCs, although they did not address if and how specific aberrations are linked to clinically relevant endpoints.

In this issue of *European Urology*, Chen and colleagues [8] leverage this unique data set and identify for the first time a set of prognostic and predictive biomarkers for mCRPC based on WGS and whole-transcriptome sequencing. Specifically, they show that patients whose metastases harbor two or more aberrations in the *RB1* gene have an approximately threefold lower overall survival time relative to those with zero or one *RB1* mutation. Moreover, expression of WNT/β-catenin pathway genes is significantly elevated in enzalutamide-resistant patients, as are activating single-nucleotide variants (SNVs) in *CTNNB1*. Finally, both *RB1* and *CTNNB1* mutations are independently associated with poor prognosis after controlling for clinicopathological variables.

While these data are compelling, a few important caveats remain. The proportion of patients harboring these aberrations in *RB1* and *CTNNB1* is very low (12/101 with ≥2 *RB1* aberrations; 4/101 with activating *CTNNB1* mutations) and thus careful validation is required to confirm these associations in much larger cohorts. Similarly, the relative paucity of these aberrations suggests that poor prognosis and/or ADT response in mCRPC is multifactorial and likely to involve additional, interdependent molecular pathways. Finally, while evidence suggests that distant metastases are all seeded from a common progenitor clone [9], clonal evolution continues to occur at individual metastatic sites, and thus molecular heterogeneity arising after dissemination may complicate the interpretation of genomic biomarker-based profiling of a single bone or lymph node metastasis. Clearly, there is a need for substantially more data—both genomic and clinical—in this area.

Nevertheless, an intriguing story has begun to emerge regarding the molecular determinants of treatment response in mCRPC. For example, a previous report linked *SPOP* SNVs and *CHD1* allelic loss to better response to abiraterone in mCRPC [10]. Several studies have established that these aberrations are mutually exclusive from *TMPRSS2:ERG* fusions, and thus indirectly imply that *TMPRSS2:ERG* may hold clinical value as a predictive biomarker of ADT response. These findings await robust validation in independent cohorts.

DOI of original article: https://doi.org/10.1016/j.eururo.2019.03.020.
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https://doi.org/10.1016/j.eururo.2019.04.005

A major unanswered question in prostate cancer surrounds the genomic trajectory during progression from localized disease to oligometastases to castration-sensitive distant metastasis and finally to mCRPC. Several studies have established that anatomically distinct distant metastases are derived from a single progenitor clone from the primary tumor and may undergo evolutionary divergence and "metastasis of metastases" [3,9]. While there is some evidence that the highest-grade tumor focus does not always seed distant metastases [11], a comprehensive, longitudinal analysis of the molecular progression of prostate cancer is lacking. Indeed, while clonal heterogeneity in localized prostate cancer is well established [12], a better understanding of the molecular parallels between localized and distant metastatic disease in the same patient would greatly enhance our ability to identify potentially lethal prostate cancer while it remains localized (eg, rare subclones harboring two *RB1* mutations). Similarly, it remains unclear whether the higher burden of driver mutations in mCRPC represents de novo mutation or results from clonal selection during ADT. If clonal selection is the primary mechanism, then, as mentioned, it may be possible to identify lethal disease via deeper and/or more targeted subclonal interrogation of foci within the primary tumor, so that therapy could be intensified in patients harboring these aggressive subclones to prevent metastatic relapse. Conversely, if mutations portending extremely aggressive disease commonly arise de novo during treatment, it might be necessary to profile metastases directly in order to personalize treatment for men with mCRPC.

Unfortunately, mCRPC remains incurable, with median overall survival times for even the most treatment-responsive patient subgroups of $<$5 yr. The vast majority of newly diagnosed prostate cancers are organ-confined, and identification of factors that promote metastatic relapse, despite the use of clinical prognostic factors and precision local therapy, is critical in the drive to reduce prostate cancer-specific mortality. Nevertheless, the evidence presented by Chen and colleagues suggests that it might be possible to personalize treatment for life-threatening mCRPC on the basis of molecular profiles, and thus potentially extend both the quantity and quality of life for these men.

Conflicts of interest: The author has nothing to disclose.

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