UROLOGICAL CANCER

Genetics of mCRPC tracked in ctDNA

Metastatic castration-resistant prostate cancer (mCRPC) has a diverse, dynamic and poorly defined mutational landscape, and tracking genomic changes in patients with this disease can be challenging owing to the need for repeated, invasive biopsy sampling. Now, newly-published research shows that clinically valuable genetic information can be derived from analyses of circulating tumour DNA (ctDNA), which is detectable in blood samples from nearly all patients with mCRPC.

Researchers investigated the clinical potential of ctDNA in 65 men with mCRPC who received enzalutamide for 12 weeks, 38% of whom responded to this drug (defined by assessing changes in serum PSA levels) with a median

progression-free survival duration of 3.5 months. Blood samples were collected prior to, and after 12 weeks of enzalutamide treatment. ctDNA was detected in 122 of 125 samples obtained from these patients, and could be sequenced in 119 of these samples. To reflect the limited availability of the most-sensitive genetic analyses in many clinical practices, researchers used microarray-based comparative genomic hybridization to monitor mutations in 19 different prostate-cancer associated genes, and PCR to detect common androgen receptor (*AR*) mutations.

Overall, 23% of patients had at least one *AR* mutation at baseline, which confirms the clinical validity of the approach — a similar percentage

of patients with mCRPC (10–20%) have *AR* mutations detected in biopsy samples. Patients with *AR* copy-number gains and/or amplifications, multiple *AR* mutations, *RB1* loss, *MET* gain and *MYC* gain all had a higher risk of enzalutamide resistance than patients without these genomic features in ctDNA.

These data indicate that monitoring cancer-associated mutations in ctDNA is a viable strategy in patients with mCRPC, which might, in future, remove the need for repeat biopsy sampling.

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ORIGINAL ARTICLE Wyatt, A. W. *et al.*

Genomic alterations in cell-free DNA and enzalutamide resistance in castration-resistant prostate cancer. *JAMA Oncol.* <http://dx.doi.org/10.1001/jamaoncol.2016.0494> (2016).