Genomic analysis of circulating tumor DNA (ctDNA) in plasma of metastatic castration-resistant prostate cancer (mCRPC) patients (pts) treated with abiraterone acetate (abi) and enzalutamide (enza)

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Background: Collecting ctDNA represents a promising and minimally invasive approach for profiling the cancer genome of mCRPC pts, which may reveal key resistance mechanisms to agents such as abi and enza. Methods: Plasma was collected from 51 mCRPC pts at cessation of abi (n=26), enza (n=17) or other agents (n=8) due to any of biochemical, objective or clinical progression. DNA was extracted and subjected to array Comparative Genomic Hybridization (aCGH) for chromosome copy number analysis and next generation sequencing of exon 8 of the androgen receptor (AR) ligand-binding domain (LBD). Results: Sufficient DNA was available for aCGH in 48 of 51 pts (94%). 8p loss, 8q gain and AR gain were seen in 29% (14/48), 40% (19/48) and 54% (26/48) of pts respectively, with AR amplification status being concordant between ctDNA and fluorescence in situ hybridization (FISH) of concurrent metastatic tumour biopsies in 3 of 4 pts. Other copy number changes detected included high CCND1 and CCNE1 gain (4% each). Correlation of clinical and genomic data showed that AR amplification was significantly more frequent in pts progressing on enza compared to those progressing on abi (76% vs. 39%, p=0.027; Chi-square). In 26 pts switched onto enza after ceasing abi/other agents, those with AR amplification at initiation of enza were significantly more likely to have enza-refractory disease (i.e. no PSA decline on treatment) compared to pts without AR amplification (60% vs. 19%, p=0.046; Chi-square). AR sequencing in 29 pts detected several high frequency mutations including T877A and F876L in 41% (12/29) and 10% (3/29) of pts respectively. The F876L mutation, linked with resistance to enza pre-clinically, was detected in two enza-naïve pts, both of whom progressed within 3 months on subsequent enza therapy. Conclusions: Genomic analysis of ctDNA from mCRPC pts identified key aberrations that may be associated with therapeutic resistance including AR amplification and the F876L AR mutation. Our data illustrate the potential utility of profiling ctDNA to characterize the genomic landscape of mCRPC.