Increasing targeted therapy options for mCRPC patients using multigene NGS panel.

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Background: Prostate cancer (PCa) represents the second most common malignancy in males, characterized by a high level of clinical and molecular heterogeneity. Eventually, many patients develop metastatic Castration Resistant Prostate Cancer (mCRPC). mCRPC refers to prostate cancer that has spread beyond the prostate gland and is associated with increased morbidity and mortality. Next Generation Sequencing (NGS) has led to the identification of genomic alterations that may represent actionable targets with therapeutic potential in mCRPC. Such alterations can be identified on the somatic or hereditary level and implicate a variety of cell cycle mechanisms, like the DNA repair mechanism (Homologous Recombination Repair genes and Mismatch Repair Genes), as well as the AR, mTOR/AKT/PI3K, PTEN, ERK/MEK/Raf/Ras and WNT signaling pathways. Methods: In this study, 75 samples of patients with mCRPC were successfully processed. An NGS panel, targeting 513 genes associated with molecular and immuno-checkpoint inhibitor therapies, was used for the detection of gene alterations and fusions. In addition, genetic markers such as TMB, MSI and %gLOH were calculated for a subset of patients. Results: At least one mutation was detected in almost 90% of the cases tested, including SNVs, CNVs and gene fusions in a broad spectrum of the tested genes. In our cohort, the most commonly altered gene was CDK12 (9.3%), followed by ATM (6.7%) and PIK3CA (5.3%). Mutations were also found in FANCA (2.7%) and PTEN (2.7%). TMB was calculated in 52 patients, out of which 9.5% were characterized as TMB high ( > 10 muts/Mb). MSI status was high for 4.5% of patients and %gLOH was elevated in 37.5% of the tested cohort. A mutation in an HRR gene was found in 29% of patients, rendering them eligible for therapy with PARP inhibitors. In addition, 18.7% of the patients could benefit from off label treatment. The calculation of genetic biomarkers, like TMB, MSI, and LOH, led to an increase in the cohort of patients who could receive on label therapy, even in cases with no or non-targetable mutation on DNA or RNA level. Moreover, due to the continuous approval of new drug regimens, retrospective evaluation of tumor analysis results led to an increase of the percentage of patients that could benefit from targeted treatment by 20%. Conclusions: Our results indicate that tumor analysis is essential for the identification of actionable biomarkers in mCRPC, since more than half of the patients were positive for a biomarker related to either targeted therapy or immunotherapy. Hence, frequent re-evaluation of NGS results is essential due to continuous drug approvals. Research Sponsor: None.