Next generation sequencing of prostate cancer reveals germline and somatic alterations detected at diagnosis and at metastasis that may impact clinical decision making

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Background:
The TCGA and SU2C/PCF projects have allowed for the identification of molecular alterations in primary and metastatic castration-resistant prostate cancer (mCRPC), respectively, through whole exome sequencing of highly curated tissue samples. To explore the frequency of these alteration at clinical scale, we have used a next-generation sequencing assay called MSK-IMPACT that is targeted to 410 cancer-associated genes to profile the tumors and germline of patients (pts) with prostate cancer across the disease spectrum.

Methods:
Prostate cancer pts enrolled on an IRB-approved protocol for tumor genomic profiling, with optional consent for germline DNA analysis. Fresh or archived fixed tumors and matched germline samples underwent targeted DNA sequencing and analysis of somatic mutations and copy number alterations (CNAs) using MSK-IMPACT. Germline analysis was performed according to ACMG guidelines for patients who consented.

Results:
We successfully sequenced 504 tumors from 451 pts, including 276 primary and 228 metastatic samples, evaluated at MSKCC between 2/2014 and 3/2016. We identified actionable somatic alterations in >60% of pts, including in the PI3K/AKT pathway (24% of pts), the MAP kinase pathway (5% of pts) and the Wnt pathway (15% of pts). We found that 22% of pts harbor a tumor somatic alteration in a gene involved in DNA damage repair (DDR). Of the 221 pts who consented to germline DNA analysis, germline pathogenic mutations were identified in BRCA2 (9% of pts), CHEK2 (4% of pts), ATM (2% of pts), and in BRCA1, PALB2 or PMS2 (<1% of pts). Additional germline alterations were identified in BRIP1, NBN, and FH totaling a 19% rate of germline pathogenic mutations. Overall, for patients who underwent germline and tumor somatic analysis, a 26% alteration frequency was identified in BRCA1/2, ATM or CHEK2 either in the germline or somatically. Furthermore, TP53 and BRCA somatic alterations found in men with metastatic disease were also detected in previously sampled matched primary tumors, suggesting that these alterations occur as early events in tumorigenesis.

Conclusions:
In addition to confirming that actionable genomic alterations are common in men with advanced prostate cancer, two additional findings emerge that could influence clinical decision making in patients at the time of diagnosis with primary disease. First, we report a high frequency of germline and somatic pathogenic mutations, including in the DDR genes BRCA2/1, CHEK2 and ATM, that could impact treatment decisions (e.g., with PARP inhibitors) and screening of family members. Second, the fact that somatic TP53 and BRCA alterations are present in matched primary samples of patients who subsequently develop metastatic diseases suggests that early detection of these alterations may be prognostic.

Conflict of Interest: None

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