Next-generation sequencing (NGS) of tissue and cell free DNA (cfDNA) to identify somatic and germline alterations in advanced prostate cancer.

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Background: With the goal of accelerating enrollment onto appropriate clinical trials, we performed prospective genomic characterization of pts with advanced prostate cancer. Given the long natural history and osseous disease predominance, we also analyzed plasma cfDNA to assess the feasibility of identifying targetable alterations in pts for whom adequate tumor tissue was unavailable.

Methods: 1038 tumors from 896 pts along with matched normal DNA were analyzed with a capture-based NGS assay (MSK-IMPACT) targeting 341–468 genes. In 5/2015, the protocol was amended to allow pts to opt-in for a formal germline analysis of 76 genes associated with heritable cancer risk. In select pts, plasma cfDNA was collected and analyzed using the same assay.

Results: Between 2/2014 and 2/2017, 576 primary tumors and 462 metastases were sequenced. The most notable finding was the high frequency of known or likely pathogenic germline and somatic mutations in genes that regulate DNA damage response (DDR). In the subset with both tumor and germline analysis, 28.84% (169/586) had a DDR mutation identified compared to only 10.65% (33/310) of pts with somatic only analysis. In the subset with tumor and germline analysis, 9.39% (55/586) had somatic only DDR mutations and 16.38% (96/586) had germline only DDR mutations, including 8 pts with two germline mutations. 3.07% (18/586) had co-occurring somatic and germline DDR mutations, with only 0.68% (4/586) involving the same DDR gene (all BRCA2). Prostate cancer had the highest tissue failure rate among the overall MSK-IMPACT solid tumor cohort, and bone biopsy-derived tissue was successfully sequenced in only 42% of pts. Profiling of cfDNA did identify somatic DDR or AR mutations in 12.5% (4/32) of pts without adequate tumor for analysis.

Conclusions: This prospective genomic profiling effort identified frequent somatic and germline DDR mutations that may guide PARPi or platinum therapy. Both somatic and germline analyses were required to identify all pts with likely pathogenic DDR alterations. NGS-based cfDNA analysis is feasible in advanced prostate cancer and may identify mutations missed by tumor only sequencing.

Conflict of Interest: None

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