Genomic profiling of circulating tumor DNA (ctDNA) and tumor tissue for the evaluation of rucaparib in metastatic castration-resistant prostate cancer (mCRPC)

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Background: The phase 2 TRITON2 (NCT02952534) and phase 3 TRITON3 (NCT02975934) studies are evaluating the poly(ADP-ribose) polymerase inhibitor rucaparib in patients with mCRPC who have a deleterious germline or somatic mutation in BRCA1, BRCA2, ATM, or other homologous recombination repair (HRR) gene. Here we present initial results from central genomic screening of plasma ctDNA and tissue samples in TRITON2 and TRITON3.

Methods: Plasma samples were profiled for genomic alterations in 64 genes using a Foundation Medicine, Inc. (FMI), next-generation sequencing (NGS) assay. FFPE tumor tissue samples were profiled for genomic alteration in 395 genes, genome-wide loss of heterozygosity (LOH), and tumor mutational burden (TMB) using an FMI NGS assay.

Results: As of July 2, 2018, ctDNA samples from 606 patients with mCRPC and disease progression were sequenced. Cell free DNA burden was significantly higher (P<0.0001) in patients who had progressed on prior androgen receptor (AR)-directed therapy and taxane-based chemotherapy (TRITON2) than in those on AR-directed therapy alone (TRITON3). Prevalence of TP53 genomic alterations in ctDNA was similar in TRITON2 (48%) and TRITON3 (44%). A deleterious genomic alteration was detected in BRCA1 (2.1%), BRCA2 (8.4%), or ATM (11.8%). We also sequenced 1214 patients' tissue samples (Gleason score ≥8, 88%) from primary prostate cancer tumors (84%) or metastases (16%). A deleterious genomic alteration in BRCA1 (1.6%), BRCA2 (7.2%), or ATM (6.2%) was observed in 14.6% of samples; of these genomic alterations, 39% were biallelic. A deleterious genomic alteration in CDK12 or 1 of 11 other HRR genes was detected in 6.2% and 6.0% of patients. Genome-wide LOH was determined for 535 BRCA1 tissue samples and was significantly higher (P<0.0001) in metastatic (median, 9.1%) than in primary (median, 7.6%) samples, suggesting a higher degree of DNA damage in more advanced disease. Median TMB observed in 789 tumor samples was 3.5 mutations per megabase, with 83% having low, 16% intermediate, and 1% high TMB. A tissue and plasma sample was available for 161 patients, 34 of which had a BRCA1 or BRCA2 alteration. The BRCA1 or BRCA2 mutations were detected in both the tissue and plasma sample in 74% (25/34) of cases.
Conclusions: Genomic profiling of both ctDNA and FFPE tumor tissue samples using NGS successfully identified patients with a genomic alteration in an HRR gene for the evaluation of rucaparib in mCRPC. Additional and updated genomic analyses will be presented.

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