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 *BRCA*^{wt} 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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Andrea Loehr, Andy D. Simmons, and **Simon P. Watkins** are employees of Clovis Oncology and may own stock or have stock options in that company.

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