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TARGETING DNA REPAIR IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC): GENOMIC SCREENING FOR A CLINICAL TRIAL OF RUCAPARIB

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Objectives: The high prevalence of men with mCRPC carrying pathogenic mutations in DNA damage repair (DDR) genes may have implications for clinical treatment, as poly(ADP-ribose) polymerase (PARP) inhibitors, such as rucaparib, have shown preliminary evidence of activity in these patients. The ongoing phase 2 TRITON2 study (NCT02952534) is evaluating rucaparib in mCRPC patients harboring a deleterious germline or somatic mutation in *BRCA1*, *BRCA2*, *ATM*, or other DDR gene. Here we present results from genomic screening of tissue and plasma samples from mCRPC patients.

Methods: Comprehensive genomic profiling was performed by Foundation Medicine, Inc., using FFPE tumor tissue and plasma circulating cell-free DNA (cfDNA) samples. These next-generation sequencing (NGS) assays detect germline and somatic genomic alterations (GAs), but do not distinguish between them.

Results: By Jan 15, 2019, prostate or metastatic tumor tissue samples from 1050 mCRPC patients were processed. Sequencing was successful for 68% of prostate samples, 82% of soft-tissue metastatic samples, and 57% of bone metastatic samples. In total, tissue sequencing results were obtained for 774 (74%) patients. GAs in *BRCA1*, *BRCA2*, or *ATM* were observed in 16.7% of patients' tissue. In parallel, plasma from 654 mCRPC patients was collected and sequenced: 96% of plasma samples had sufficient cfDNA to obtain sequencing results, and sequencing success was independent of the location of metastases (visceral, nodal, or bone). GAs in *BRCA1*, *BRCA2*, or *ATM* were observed in 21.4% of patients' plasma. There was high concordance between the alterations detected by the tissue and plasma assays. For example, in 86% of patients the plasma assay detected the same *BRCA2* alteration present in tissue.

Conclusions: Genomic profiling may help guide clinical decision-making for mCRPC patients. Tumor and plasma testing successfully identified patients with eligible somatic or germline GAs for enrollment into TRITON2. These data continue to support the utilization of plasma genomic testing, particularly in patients without a lesion that can be biopsied.

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