IPCU
INTERNATIONAL PROSTATE CANCER UPDATE

Genomic Profiling of Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) for the Evaluation of Rucaparib: Next-Generation Sequencing (NGS) of Tumor Tissue and Cell-Free DNA (cfDNA)

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Background and Methods

- The TRITON2 and TRITON3 studies are enrolling mCRPC patients with a deleterious alteration in a DDR gene (eg, *BRCA1/2*) to evaluate treatment with the PARP inhibitor rucaparib
  - Both studies are enrolling patients at sites in the United States and throughout the world
- The DDR alteration may be identified by local testing or central screening of tissue or plasma using NGS assays by Foundation Medicine, Inc.

	Saliva / blood	Tissue	Plasma
Collected from patient	Buccal swab / whole blood	Contemporaneous or archival tumor tissue	Whole blood
Components analyzed	Tissue cells / leukocytes	FFPE tumor tissue	ctDNA
Alteration types detected	Germline	Germline & somatic	Germline & somatic
Number of genes typically assessed	≈2–45	≈150–400	≈50–100
Genes typically included	• Cancer-related genes • *BRCA1*, *BRCA2* • 5–10 other DDR genes	• Cancer-related genes • *BRCA1*, *BRCA2* • 10–30 other DDR genes	• Cancer-related genes • *BRCA1*, *BRCA2* • 2–10 other DDR genes
Advantages	• Minimally invasive • Low cost	• More comprehensive (eg, MSI, TMB, LOH)	• Minimally invasive • Queries DNA from multiple tumor lesions
Disadvantages	• Limited to inherited mutations • Fewer genes	• Challenging to collect metastatic tissue • High assay-failure rate	• Technical challenges to detect certain alteration types

ctDNA, cell-free tumor DNA; DDR, DNA damage repair; FFPE, formalin-fixed paraffin-embedded; LOH, loss of heterozygosity; MSI, microsatellite instability; PARP, poly(ADP-ribose) polymerase; TMB, tumor mutational burden.

Results and Conclusions

- The frequency of deleterious *BRCA1/2* alterations was higher in plasma (10.6%) than in the predominantly archival tissue samples (8.8%)
  - Consistent with higher frequencies of DDR alterations in mCRPC patients with more advanced disease
- Both tumor tissue and ctDNA plasma assays were used to successfully identify patients with a DDR gene alteration for treatment with rucaparib
  - Plasma is less invasive to collect and has a higher success rate than tumor tissue (97% vs ≈70%)
  - However, the tissue test is more comprehensive regarding number of genes, alteration types, and other genomic features queried
- There was high concordance between the tissue and plasma assays
  - 74% (25/34) of patients with a *BRCA1/2* mutation were identified by both tissue and plasma sample
- The TRITON2 and TRITON3 studies are evaluating the activity of rucaparib in mCRPC patients with a deleterious alteration in a DDR gene
  - Rucaparib received Breakthrough Therapy designation from the U.S. FDA on October 2, 2018, based on the initial efficacy and safety data from TRITON2
  - Rucaparib is approved in the United States for patients with recurrent ovarian cancer

FDA, Food and Drug Administration.