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Genomic Profiling of Metastatic Castration-Resistant Prostate Cancer Patients for Treatment With Rucaparib: Next-Generation Sequencing of Cell-free Tumor DNA (ctDNA) and Tumor Tissue

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SUMMARY

- **The PARP inhibitor rucaparib was approved by the US FDA for the treatment of patients with mCRPC and a deleterious *BRCA1* or *BRCA2* (BRCA) alteration**
- **Both tumor tissue and plasma assays were used to successfully identify patients with a BRCA gene alteration for the TRITON2 study**
- **BRCA alterations were identified in 9.7% of patients' tissues and 10.7% of patients' plasma samples**
- **Tumor tissue is more invasive to collect and has a higher sequencing failure rate (≈30%) than plasma**
  - **Sequencing success depended on the biopsy site and decreased with sample age**
- **Plasma samples are less invasive to collect than tissue and have a low sequencing failure rate (6%)**
- **Among patients with a BRCA alteration, the confirmed objective and PSA response rates were 43.5% and 54.8%**

INTRODUCTION

- The poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib is approved by the US Food and Drug Administration (FDA) for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) and a deleterious *BRCA1* or *BRCA2* (BRCA) alteration[1]
- Approval was based on interim results from the phase 2 TRITON2 study (NCT02952534)[2]
- Approximately 12% of patients with mCRPC harbor a deleterious mutation in *BRCA1* or *BRCA2*[3,4] and may benefit from treatment with rucaparib
- Here, we present BRCA alteration frequencies from genomic screening of tissue and plasma samples for TRITON2

Genomic Testing in mCRPC

- The National Comprehensive Cancer Network (NCCN) recently updated their guidelines[5] to recommend consideration of genetic testing for DNA damage repair (DDR) gene mutations in men with regional or metastatic prostate cancer
  - Germline genetic testing is recommended for all men with high-risk, very high-risk, regional, or metastatic prostate cancer
  - Somatic testing is recommended for men with metastatic prostate cancer
  - Somatic testing can be considered in men with regional prostate cancer
  - Somatic testing may require repetition when prostate cancer progresses after treatment
- Several commercially available tests can detect germline and somatic DDR gene mutations

	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	≈150–500	≈50–500
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* • 10–30 other DDR genes
Advantages	• Minimally invasive • Very low cost	• More comprehensive (eg, alteration zygosity, 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.

METHODS

Genomic Assays

- Comprehensive genomic profiling was performed using Foundation Medicine next-generation sequencing (NGS) assays
- The tissue-based FoundationOne assay[6] analyzes 324 cancer-related genes and identifies all classes of BRCA alterations, including homozygous deletions
- The plasma-based FoundationOne Liquid assay[7] was used to analyze 70 cancer-related genes but was not validated to detect homozygous deletions
- Both tissue and plasma assays report germline and somatic alterations but do not distinguish between them

Efficacy Assessment

- Objective response rate (ORR) by independent radiographic review was determined per modified Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST)/Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria in patients with measurable disease at baseline
- Prostate-specific antigen (PSA) response was assessed in all patients and defined as ≥50% reduction in PSA from baseline, confirmed by an assessment at least 3 weeks later

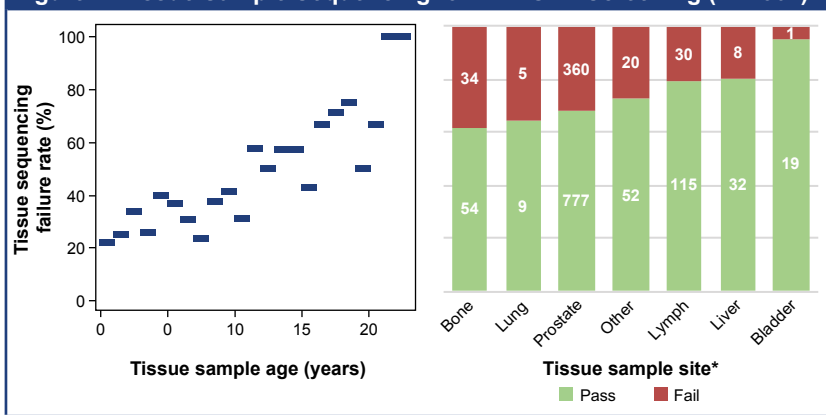
RESULTS

- As of January 30, 2020, a total of 1564 tumor and 1407 plasma specimens were collected from patients with mCRPC to identify BRCA alterations and determine eligibility for TRITON2

Tumor Tissue Testing

- In patients with mCRPC, obtaining a metastatic tumor tissue sample is invasive and often challenging
- Primary prostate tumor samples are frequently taken at the time of diagnosis and it may be years before they are submitted for genomic testing
  - Archival tissue samples may be less representative of the metastatic disease state
  - Older samples have a lower NGS testing success rate
  - Metastatic samples have a higher density of tumor cells and are usually more recently obtained
- Overall, 1564 archival or recent tissue samples from 1426 patients were submitted for TRITON2 screening
- The majority of samples (75%) were core needle biopsies or resections of primary prostate tumors; 25% were samples from metastatic sites
- Median age of prostate samples was 3.9 years (range, 4 days–22.2 years), compared with 2.6 months for metastatic samples (range, 2 days–19 years)
- The overall NGS test failure rate was 31%, but was lower for more recently collected samples and depended on the sample site (**Figure 1**)
- The observed BRCA alteration frequency in tissue samples was 9.7%

Figure 1. Tissue Sample Sequencing for TRITON2 Screening (N=1564)

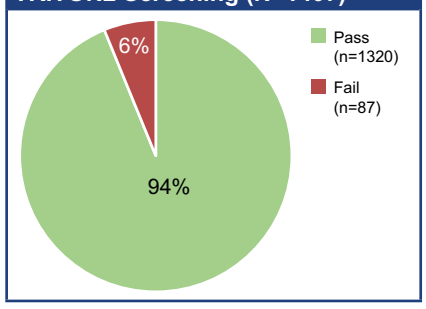


*Values in bars represent the number of samples.

Plasma Testing

- Compared with invasive tissue sample procedures, plasma samples can be more easily obtained
  - Samples can be readily collected at multiple time points
- Plasma samples taken at the metastatic disease stage may be more representative of the patients' current genomics
  - The assay queries DNA from multiple lesions
- The plasma assay is analytically validated to detect several classes of alterations: insertions, deletions, rearrangements, and amplifications
- 1407 plasma samples from 1343 patients progressing on prior therapy were submitted for TRITON2 screening
- The median age of plasma samples was 2 days (range, 1–11 days)
- The sequencing success rate was 94% (**Figure 2**)
- The observed BRCA alteration frequency in plasma samples was 10.6%

Figure 2. Plasma Sequencing for TRITON2 Screening (N=1407)



Alteration	Frequency	
	Tissue testing	Plasma testing
BRCA alteration	9.7%	10.6%
BRCA1 alteration	1.5%	2.2%
BRCA2 alteration	8.2%	8.6%

Rucaparib Efficacy

- TRITON2 is a fully enrolled, ongoing, international, open-label, phase 2 study evaluating rucaparib in patients with mCRPC associated with DDR deficiency
- Eligible patients had to have progressed on 1–2 lines of androgen receptor-directed therapy and 1 taxane-based chemotherapy
- As of May 8, 2019, 115 patients with a BRCA alteration were enrolled in TRITON2 and treated with rucaparib 600 mg BID[2]
- In total, 62 patients had measurable disease and were evaluated for ORR

Response	*BRCA1*	*BRCA2*	Overall BRCA
Confirmed ORR by IRR, n/N (%) [95% CI]	3/9 (33.3%) [7.5–70.1%]	24/53 (45.3%) [31.6–59.6%]	25/62 (43.5%) [31.0–56.7%]
Confirmed PSA response, n/N (%) [95% CI]	2/13 (15.4%) [1.9–45.4%]	61/102 (59.8%) [49.6–69.4%]	63/115 (54.8%) [45.2–64.1%]

Visit cutoff date: December 23, 2019.
Adapted from Abida et al. *J Clin Oncol*. 2020.[2]
IRR, independent radiographic review; ORR, objective response rate; PSA, prostate-specific antigen.

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