Comprehensive Genomic Profiling of >1000 Plasma and Tumor Tissue Samples from Metastatic Castration-Resistant Prostate Cancer (mCRPC) Patients Gives Insight into Targeted Treatment Strategies

Abstract 727

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INTRODUCTION

- There are limited treatment options available for patients with mCRPC following androgen receptor (AR)-directed and taxane treatment
- However, up to 25% of patients with mCRPC harbor a deleterious germline and/or somatic alteration in *BRCA1*, *BRCA2*, *ATM*, or other DNA damage repair (DDR) gene[1] and may benefit from treatment with a PARP inhibitor such as rucaparib
- The phase 2 TRITON2 (NCT02952534) study is investigating rucaparib in patients with mCRPC harboring an alteration in a DDR gene

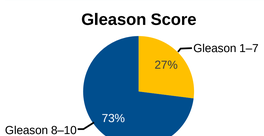
METHODS

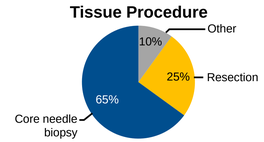
- A total of 1155 tumor and 709 plasma specimens were collected from 1330 patients to determine patient eligibility for TRITON2
- DDR deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other DDR genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*)
- Deleterious alterations include frameshift mutations, nonsense mutations, deleterious missense mutations, protein-truncating rearrangements, and homozygous loss

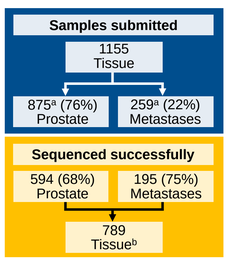
TISSUE SAMPLE OVERVIEW

- 1155 archival or recent tissue samples from 1050 patients were sequenced by Foundation Medicine, Inc. (FMI), using a next-generation sequencing (NGS) assay[2]
- Some patients submitted multiple specimens

Specimen site	Sample age, median (range)
All tissue	1.1 years (4 days–22.2 years)
Prostate	3.8 years (4 days–22.2 years)
Metastases	2.0 months (4 days–19.0 years)

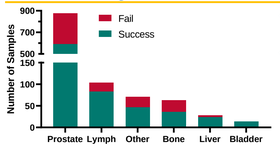






[a]Specimen site was not available for 21 samples.
[b]Sequencing results were available from 774 patients (some patients submitted multiple specimens).

TISSUE SEQUENCING METRICS



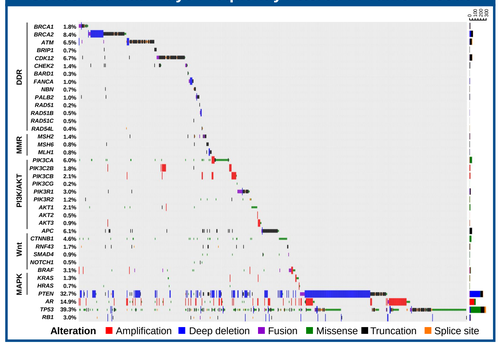
- The overall tissue test failure rate was 31%
- The sequencing success rate was higher for samples from metastases (75%) than for prostate tumor tissue (68%)

GENE ALTERATIONS IN TISSUE

Gene or pathway	Alteration frequency, % (n) All tissue (n=774)[a]	Prostate (n=576)	Metastases (n=190)
DNA repair related alterations			
DNA repair pathway	26.6% (206)	27.6% (159)	23.7% (45)
BRCA2 alteration	8.4% (65)	9.5% (55)	4.7% (9)
ATM alteration	6.5% (50)	6.6% (38)	5.8% (11)
BRCA1 alteration	1.8% (14)	1.9% (11)	1.6% (3)
Cancer related alterations			
TP53 alteration	39.3% (304)	39.9% (230)	37.9% (72)
ERG-TMPRSS2 fusion	30.1% (233)	31.1% (179)	26.8% (51)
PTEN loss	24.8% (192)	22.6% (130)	30.5% (58)
PI3K pathway	15.6% (121)	15.1% (87)	17.4% (33)
Wnt pathway	15.0% (116)	14.9% (86)	15.8% (30)
AR amplification	11.5% (89)	5.7% (33)	29.5% (56)
MAPK pathway	4.9% (38)	3.8% (22)	8.4% (16)
RB1 alteration	3.0% (23)	1.7% (10)	6.8% (13)

[a]Specimen site was not available for 8 samples.

Genes and Pathways Frequently Altered in Tumor Tissue



PLASMA SAMPLE OVERVIEW

- Plasma samples were sequenced using a cell-free DNA FMI NGS assay[3] to identify deleterious germline or somatic alterations in *BRCA1*, *BRCA2*, *ATM*, or 3 other DDR genes (*CDK12*, *CHEK2*, and *PALB2*)
- 709 plasma samples from 654 patients (some submitted multiple samples) were collected upon progression on prior therapy
- The median sample age was 2 days (range, 1–10 days)
- The plasma test failure rate was 4%

709 samples submitted → 679 (96%) samples successfully sequenced

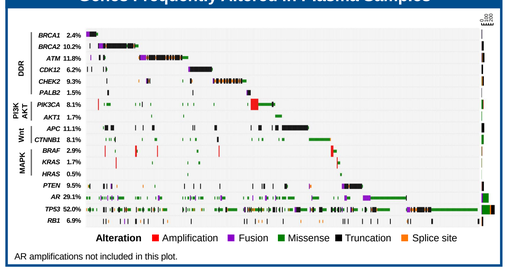
GENE ALTERATIONS IN PLASMA

- The plasma assay queries 70 cancer-related genes, including 6 DDR genes
  - Alteration frequencies in selected genes are shown below
  - The plasma assay is not validated to detect homozygous loss

Gene or pathway	Alteration frequency, % (n)[a] All plasma
DNA repair related alterations	
ATM alteration	11.8% (65)
BRCA2 alteration	10.2% (67)
CHEK2 alteration	9.3% (51)
CDK12 alteration	6.2% (34)
BRCA1 alteration	2.4% (16)
PALB2 alteration	1.5% (8)
Cancer related alterations	
TP53 alteration	52.0% (340)
RB1 alteration	6.9% (38)
MAPK pathway	4.9% (32)

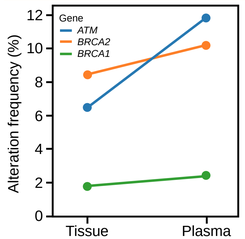
[a]n=654, with the exception of *ATM*, *CHEK2*, *CDK12*, *PALB2*, and *RB1*, for which n=550.

Genes Frequently Altered in Plasma Samples



AR amplifications not included in this plot.

TISSUE AND PLASMA DDR GENE ALTERATIONS



- The *BRCA1/2* alteration frequency was 12.6% in plasma, compared to 10.2% in tumor tissue
- The plasma assay detected more alterations in *BRCA1/2* or *ATM* than the tissue assay
  - Most of the tissue samples were archival and may be less representative of the metastatic disease state

TISSUE-PLASMA CONCORDANCE

- Both tissue and plasma samples were available for 269 patients and used to evaluate the concordance between these assays
- Tissue and plasma sample pairs were not always collected simultaneously
  - 68% of tissue samples were archival prostate tissues
  - Only 14% of the tissue and plasma sample pairs were collected within a 31-day window[a]
  - The median time between tissue and plasma sample collection was 2.9 years (range, 3 days–17.8 years)[a]
- Here, we determined if deleterious alterations[b] detected in tissue samples were also observed with the plasma assay
- The plasma assay detected 56%–91% of pathogenic alterations observed in tissue for the 8 genes interrogated; for example:
  - In 91% of patients, the plasma assay detected the same *TP53* alteration present in tissue
  - In 86% of patients, the plasma assay detected the same *BRCA2* alteration present in tissue

Gene	Tissue GA also detected in subsequent plasma test, %	Patients with GA in tissue, n
TP53	91%	95
BRCA2	86%	28
ATM	77%	18
BRCA1	71%	7
CDK12	67%	24
PALB2	67%	3
RB1	60%	18
CHEK2	56%	21

[a]Included samples with confirmed collection data.
[b]Homozygous loss excluded.

CONCLUSIONS

- The TRITON2 study is enrolling mCRPC patients with a deleterious DDR gene alteration to evaluate the potential benefit of treatment with the PARP inhibitor rucaparib
- Tumor tissue and plasma assays were both used to successfully identify patients with a DDR gene alteration
- Alterations were frequently observed in several cancer related pathways, including DDR, PI3K/AKT, MAPK, and Wnt
- There was high concordance between the alterations detected with the plasma and tissue assays
  - The plasma assay detected the same *BRCA2* and *BRCA1* alteration present in tissue for 86% and 71% of patients, respectively
- Based on initial efficacy and safety data from TRITON2, Clovis announced on October 2, 2018, that the U.S. Food and Drug Administration granted Clovis Oncology Breakthrough Therapy designation for rucaparib as a monotherapy treatment of adult patients with *BRCA1/2*-mutated mCRPC who have received at least 1 prior AR-directed therapy and taxane-based chemotherapy[4-6]

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