Genomic Profiling of Circulating Tumour DNA (ctDNA) and Tumour Tissue for the Evaluation of Rucaparib in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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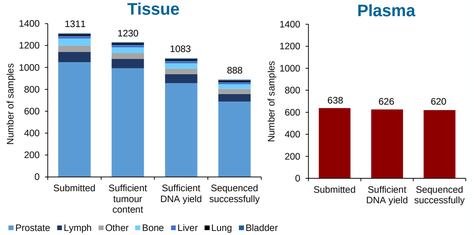
INTRODUCTION

- 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 harbour a deleterious germline and/or somatic alteration in *BRCA1*, *BRCA2*, *ATM*, or other homologous recombination repair (HRR) gene[1] and may benefit from treatment with a PARP inhibitor such as rucaparib
- The phase 2 TRITON2 (NCT02952534) and phase 3 TRITON3 (NCT02975934) studies are investigating rucaparib in patients with mCRPC harbouring an alteration in an HRR gene

METHODS

- A total of 1311 tumour and 638 plasma specimens were collected from 1516 patients to determine patient eligibility for TRITON2 and TRITON3
- HRR-deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*)
- Deleterious alterations include frameshift mutations, nonsense mutations, deleterious missense mutations, protein truncating rearrangements, and (for tissue samples) homozygous loss
- Cell-free circulating tumour DNA (cfDNA) from plasma samples was sequenced by Foundation Medicine, Inc. (FMI), using a next-generation sequencing (NGS) assay[2] to identify deleterious germline or somatic alterations in *BRCA1*, *BRCA2*, *ATM*, or 3 other HRR genes (*CDK12, CHEK2, PALB2*)
- Archival and contemporaneous tissue samples were sequenced by FMI[3] to identify deleterious germline or somatic alterations in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes
- The FMI tissue NGS assay also determines alterations in other prostate cancer–related genes, zygosity of gene mutations, homozygous deletions, and tumour mutational burden (TMB)

Tissue and Plasma Sample Overview



TUMOUR TISSUE

- Tumour tissue testing is often challenging due to insufficient tumour amounts in prostate cancer tumour specimens, but is validated to detect copy number events, including homozygous loss and mutation zygosity
- 1311 archival or recent tissue samples from 1214 patients were submitted for screening, most (88%) with a Gleason score ≥8
- The majority (84%) of samples were core needle biopsies or resections of primary prostate tumours
- The median sample age was 2.8 years (range, 4 days to 21 years)
- The NGS test failure rate was 32%, mainly (18%) due to insufficient tumour content or DNA yield
- The NGS test success rate was higher for metastatic samples (74%) than for primary prostate tumour tissue (56%)
- Tissue from 872 patients was sequenced successfully
- The observed *BRCA1/2* alteration frequency was higher in the later line TRITON2 patients (10.5%) than in the less advanced TRITON3 patients (6.5%)
- The frequency of other HRR gene alterations and prostate cancer–related genomic aberrations, including AR amplifications, was also higher in TRITON2 patients than in TRITON3 patients

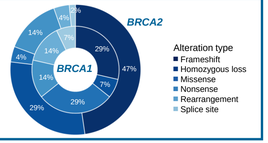
Alteration	Frequency in tissue TRITON2 (n=487)	TRITON3 (n=385)
BRCA1 alteration	1.8%	1.3%
BRCA2 alteration	8.6%	5.5%
ATM alteration	6.6%	5.7%
CDK12 alteration	6.8%	5.4%
TP53 alteration	38.4%	37.1%
AR amplification	9.9%	4.7%
PTEN loss	25.4%	19.5%
ERG-TMPRSS2 fusion	28.3%	28.1%

BRCA1/2 Alterations in Tissue Samples

- 80 *BRCA1/2* alterations were identified in 76 patients
- Biallelic alterations in *BRCA1/2* were observed in 57% (29/51) of TRITON2 patients and 40% (10/25) of TRITON3 patients
- Homozygous loss was observed in 26% (20/76) of patients with *BRCA1/2* alterations

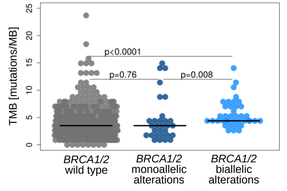
Alteration type	*BRCA1*, n (%)	*BRCA2*, n (%)
Frameshift	4 (29%)	31 (47%)
Homozygous loss	1 (7%)	19 (29%)
Nonsense	2 (14%)	9 (14%)
Missense	4 (29%)	3 (4%)
Rearrangement	2 (14%)	3 (4%)
Splice site	1 (7%)	1 (2%)

Tissue Alteration Types



TUMOUR MUTATIONAL BURDEN

- Tumour mutational burden (TMB) has been shown to be a predictive biomarker of sensitivity to checkpoint inhibitors[4]
- The median TMB determined in 789 tissue samples was 4.6 mutations per megabase (MB)
  - The low TMB observed here is consistent with published reports in prostate cancer[5]
- TMB was significantly higher in samples with biallelic *BRCA1* or *BRCA2* alterations



PLASMA

- Plasma samples from mCRPC patients are easily obtained and generally contain sufficient cfDNA for NGS processing, but the plasma assay is not validated to measure TMB or homozygous loss
- 638 plasma samples from 606 patients progressing on prior therapy were submitted for screening
- The median age of plasma samples was 2 days (range, 1 to 10 days)

Alteration	Frequency in plasma TRITON2 (n=343)[a]	TRITON3 (n=263)[a]
BRCA1 alteration	2.3%	1.9%
BRCA2 alteration	9.6%	6.8%
ATM alteration	14.6%	8.2%
CDK12 alteration	6.1%	3.1%
TP53 alteration	48.1%	44.9%

[a]For *ATM* and *CDK12*, n=246 for TRITON2 and n=194 for TRITON3.

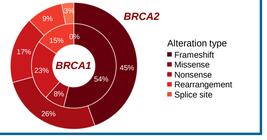
- 620 samples (97%) had sufficient cfDNA for successful NGS
- The *BRCA1/2* alteration frequency in the earlier line TRITON3 patients was 8.0%, compared to 11.7% in the more advanced TRITON2 patients
  - This frequency excludes homozygous loss of *BRCA1/2,* which the assay is not validated to detect
- The *BRCA1/2* alteration frequencies in TRITON2 and TRITON3 were higher in plasma samples than in tissue samples
  - Most of the tissue samples were archival and may be less representative of the metastatic disease state, which has been reported to have an increased frequency of *BRCA1/2* alterations[1]
- The alteration frequencies in *ATM*, *CDK12*, and *TP53* were also lower in the earlier line TRITON3 patients than in the more advanced TRITON2 patients

BRCA1/2 Alterations in Plasma Samples

- 78 *BRCA1/2* alterations were detected in samples from 61 patients
- 46% (36/78) of *BRCA1/2* alterations were frameshift mutations

Alteration type	*BRCA1*, n (%)	*BRCA2*, n (%)
Frameshift	7 (54%)	29 (45%)
Nonsense	3 (23%)	11 (17%)
Missense	1 (8%)	17 (26%)
Rearrangement	2 (15%)	6 (9%)
Splice site	0 (0%)	2 (3%)

Plasma Alteration Types



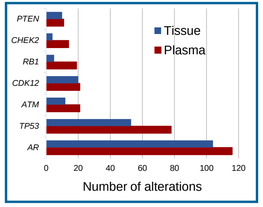
BRCA1/2 CONCORDANCE BETWEEN TISSUE AND PLASMA

- The concordance between *BRCA1/2* mutations in tissue and plasma samples was evaluated in 161 patients with both tissue and plasma samples, 34 of whom had a *BRCA1/2* mutation
- The median time between tissue and plasma sample collection was 2.5 years (range, 4 days to 21 years), with 19% (31/161) of tissue and plasma samples collected within a 30-day window
- 74% (25/34) of patients with a *BRCA1/2* mutation were identified by both tissue and plasma sample

N=161 sample pairs	Plasma *BRCA1/2+*	Plasma *BRCA1/2-*
Tissue *BRCA1/2+*	25/34 (74%)	4/34 (12%)
Tissue *BRCA1/2-*	5/34 (15%)	127/161 (79%)

TISSUE-PLASMA CONCORDANCE IN OTHER GENES

- Several other DNA-repair and prostate cancer–related genes were sequenced by both the tissue and plasma assays
- The frequency of alterations in other genes was evaluated in 106 patients with both tissue and plasma samples
- A greater number of alterations was detected in plasma samples than in tissue samples for all of the genes evaluated, due to the higher sensitivity of the plasma assay[2,3]



CONCLUSIONS

- The TRITON2 and TRITON3 studies are enrolling mCRPC patients with HRR gene alterations to evaluate the potential benefit of treatment with the PARP inhibitor rucaparib
- Both tumour tissue and plasma assays were used to successfully identify patients with an HRR gene alteration
  - There is high concordance between the alterations detected in the tissue and plasma assays
  - Tumour tissue testing has the ability to measure TMB and detect copy number events, such as homozygous loss and zygosity of mutations, but tissue samples often had inadequate amounts of tumour or tumour DNA, resulting in an ≈30% testing failure rate
  - cfDNA plasma sample testing is less invasive to patients and more sensitive than tissue testing and has a low testing failure rate (3%), but it is not validated to detect homozygous loss
- TMB levels are low in patients with mCRPC, but higher in patients positive for biallelic *BRCA1/2* alterations
- Initial results from TRITON2 are being presented at the 2018 ESMO Congress[6]
- Based on initial efficacy and safety data from TRITON2, on 2 October 2018, 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[7]

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Please also see the 2018 ESMO poster presenting initial results from the TRITON2 study, and prior posters on the study designs for TRITON2 and TRITON3 presented at the 2018 ASCO-GU Symposium

Abida et al. ESMO 2018 793PD

Abida et al. ASCO-GU 2018 TPS388

Ryan et al. ASCO-GU 2018 TPS389

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