Genomic Characteristics of Deleterious *BRCA1* and *BRCA2* Alterations and Associations with Baseline Clinical Factors in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Enrolled in TRITON2

Abstract 5031

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INTRODUCTION

- There are limited treatment options available for patients with mCRPC following androgen receptor (AR)-directed therapy and taxane chemotherapy[1,2]
- Up to 12% of patients with mCRPC harbor a deleterious germline and/or somatic alteration in the DNA damage repair (DDR) genes *BRCA1* and *BRCA2*[3,4]
- Data from the international, multicenter, open-label, phase 2 study TRITON2 (CO-338-052; NCT02952534) have shown that the poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib has antitumor activity in *BRCA1/2*-deficient mCRPC[5]
- Here we present associations of genomic characteristics and baseline clinical factors in 45 mCRPC patients with *BRCA1/2* deficiency enrolled in the ongoing TRITON2 study (enrollment cutoff: April 16, 2018; visit cutoff: June 29, 2018)

METHODS

- For the TRITON2 study, eligible patients were screened for the presence of a deleterious germline or somatic alteration in *BRCA1*, *BRCA2,* or other prespecified DDR gene alteration[3,4]
- Central screening of tumor tissue or plasma was performed using next-generation sequencing assays by Foundation Medicine, Inc.[6,7]
  - Both assays detect somatic and germline alterations but do not distinguish between them
  - Patients with a deleterious alteration from local testing were also eligible
- Germline testing was performed for all patients using a Color Genomics assay[8]

DEMOGRAPHICS

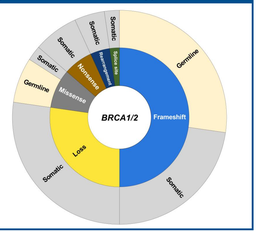
Baseline demographics	Gene		Overall (N=45)
	BRCA1 (n=5)	*BRCA2* (n=40)	
Age, median (range), y	68.0 (62–78)	72.5 (50–88)	71.0 (50–88)
Time since cancer diagnosis, median (range), mo	32.5 (19.5–254.6)	48.0 (15.4–187.5)	46.5 (15.4–254.6)
ECOG PS, n (%)			
0	2 (40.0)	14 (35.0)	16 (35.6)
1	3 (60.0)	25 (62.5)	28 (62.2)
≥2	0	1 (2.5)	1 (2.2)
Baseline PSA, median (range), ng/mL	82.8 (59.8–4669.0)	44.7 (3.5–4782.0)	52.0 (3.5–4782.0)
Gleason score ≥8, n (%)	3 (60.0)	30 (75.0)	33 (73.3)
≥3 prior CRPC therapies, n (%)	2 (40.0)	15 (37.5)	17 (37.8)
Measurable disease status and type (per investigator), n (%)			
Measurable disease	4 (80.0)	23 (57.5)	27 (60.0)
Only measurable nodal disease	3 (60.0)	11 (27.5)	14 (31.1)
Measurable visceral ± nodal disease	1 (20.0)	12 (30.0)	13 (28.9)
No measurable disease	1 (20.0)	17 (42.5)	18 (40.0)
Bone-only disease	1 (20.0)	12 (30.0)	13 (28.9)
Other	0	5 (12.5)	5 (11.1)
Gene alteration status, n (%)			
Germline	2 (40.0)	13 (32.5)	15 (33.3)
Somatic	3 (60.0)	27 (67.5)	30 (66.7)

Enrollment cutoff date: April 16, 2018; visit cutoff date: June 29, 2018. Median duration of follow-up at visit cutoff was 5.7 months (range, 2.6–16.4 months).
CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PSA, prostate-specific antigen.

BRCA1/2 ALTERATION TYPES AND ZYGOSITY

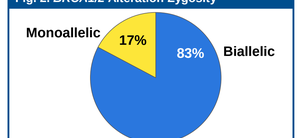
- The majority of patients had frameshift alterations (49%, 22/45) or homozygous loss (27%, 12/45) of *BRCA1/2* (Fig. 1)
- Two-thirds of patients (30/45) had a somatic and 1/3 had a germline *BRCA1/2* alteration

Fig. 1. *BRCA1/2* Alteration Types



- *BRCA1/2* mutation zygosity was determined based on tissue profiling
- 36 patients submitted a tissue sample, 32 (89%) from prostate tumors and 4 (11%) from metastases
- 30 of 36 samples (83%) were sequenced successfully
- *BRCA1/2* alteration zygosity could be determined for 29 patients
- The majority (83%, 24/29) of patients with known zygosity had a biallelic alteration (Fig. 2)

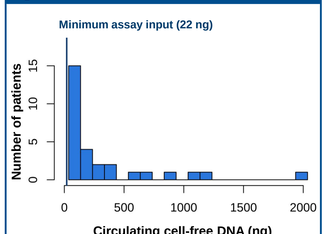
Fig. 2. *BRCA1/2* Alteration Zygosity



PLASMA cfDNA TESTING

- Patients were screened for deleterious DDR gene alterations using tissue or plasma samples
- Archival and recently obtained tissues were allowed
  - However, archival samples may not be representative of metastatic disease
- Plasma samples were taken at the time of progression on prior therapy
  - Plasma samples may reflect the current disease state more accurately than tissue samples
- Circulating cell-free DNA (cfDNA) was purified from plasma samples
  - Includes circulating tumor DNA (ctDNA) and DNA from nonmalignant cells

Fig. 3. Distribution of cfDNA in Plasma



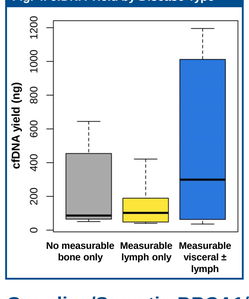
- Plasma samples were available for 89% (40/45) of patients
- The majority of samples (98%, 39/40) had sufficient cfDNA for successful sequencing (Fig. 3)
- 95% (37/39) of patients had sufficient ctDNA to detect at least 1 nongermline variant in 1 of 70 cancer-related genes
- The plasma assay detected *BRCA1/2* alterations in 94% (29/31) of patients*

*Excluding 8 patients with homozygous loss, which the plasma assay is not validated to detect.

CORRELATION OF GENOMIC AND CLINICAL FACTORS

- Plasma samples were collected at approximately the same time (within 6 weeks) as the assessment of baseline clinical factors
  - Associations between baseline cfDNA yield, cell-free tumor fraction, variant allele frequency, somatic/germline status, and baseline clinical factors were assessed

Fig. 4. cfDNA Yield by Disease Type

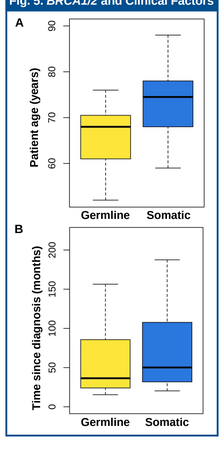


- Patients with visceral disease had the highest plasma cfDNA yield at baseline (Fig. 4)
- All patients with bone-only disease had sufficient cfDNA to detect a *BRCA1/2* alteration
- There was no correlation between baseline sum of target lesions (STL) and cfDNA yield (r=0.13, P=0.61)
  - There was a trend toward patients with larger STL having higher tumor fraction (r=0.46, P=0.07)
- There was no correlation between baseline PSA levels and cfDNA yield

Germline/Somatic *BRCA1/2* Status and Clinical Factors

- Several findings support the hypothesis that germline *BRCA1/2* alterations are a prognostic factor in prostate cancer associated with more rapid progression to advanced disease
- Of patients with known stage at diagnosis, more than half (57%) with a germline *BRCA1/2* alteration were diagnosed at stage T3 or higher, compared to 42% with a somatic *BRCA1/2* alteration
- Patients with a germline alteration were younger at the time of entering TRITON2 (median age, 68 years) than patients with a somatic alteration (median age, 75 years) (Fig. 5A)
- Variant allele frequency was higher for germline than somatic alterations
  - Gleason score at diagnosis was higher in patients with higher allele frequency alterations
  - Variant allele frequency was higher in younger patients (r=-0.66, P<0.01)
- The median time between prostate cancer diagnosis and enrollment into TRITON2 was shorter in patients with a germline (36.4 months) than somatic alteration (50.2 months) (Fig. 5B)

Fig. 5. *BRCA1/2* and Clinical Factors



RESPONSE BY GERMLINE/SOMATIC *BRCA1/2* ALTERATION

- Responses were observed in patients with germline or somatic *BRCA1/2* alterations, despite germline *BRCA1/2* alterations being a potential prognostic factor

Characteristic	Germline *BRCA1/2*	Somatic *BRCA1/2*	Overall *BRCA1/2*
Confirmed investigator-assessed objective response, n/N (%) [95% CI][a]	5/10 (50.0) [18.7–81.3]	6/15 (40.0) [16.3–67.7]	11/25 (44.0) [24.4–65.1]
Confirmed PSA response, n/N (%) [95% CI][b]	10/15 (66.7) [38.4–88.2]	13/30 (43.3) [25.5–62.6]	23/45 (51.1) [35.8–66.3]

[a]Per modified RECIST/PCWG3 criteria; includes patients who had measurable disease at baseline per the investigator and ≥16 weeks of follow-up or who discontinued treatment.
[b]Defined as ≥50% reduction in PSA from baseline; includes patients who had ≥8 weeks of follow-up or who discontinued treatment.
CI, confidence interval; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

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
  - The plasma assay is minimally invasive and reliably detects alterations in patients with disease that is difficult to biopsy
- Rucaparib has encouraging antitumor activity in patients with a deleterious alteration in *BRCA1* or *BRCA2*
  - Among evaluable patients with a deleterious *BRCA1/2* alteration, 44.0% (11/25) had a confirmed radiographic response and 51.1% (23/45) had a confirmed PSA response
- Compared to patients with a somatic *BRCA1/2* alteration, patients with a germline *BRCA1/2* alteration:
  - Were diagnosed at a more advanced stage
  - Were younger at time of enrollment into TRITON2
- Responses to rucaparib were observed in patients with germline or somatic *BRCA1/2* alterations

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