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


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

Data from the international, multicenter, open-label, phase 2 trial TRITON2 (CO-338-052; NCT02025254) have shown that the poly(ADP-ribose) polymerase (PARP) inhibitor talazoparib has antitumor activity in mCRPC.4 Here we present associations of genomic characteristics and baseline clinical factors in 45 mCRPC patients with BRCA1/2 alterations 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 alteration4
- Central screening of tumor tissue or plasma was performed using next-generation sequencing assays by Foundation Medicine, Inc.
  - 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 Colortier Genomic assay5

DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>n/N (%)</td>
<td>45/45 (100)</td>
</tr>
<tr>
<td>Age range, years (median [interquartile range])</td>
<td>68 (73-96)</td>
</tr>
<tr>
<td>Time since cancer diagnosis, median (range), mo.</td>
<td>18 (0-297)</td>
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<td>Gleason score ≥8, n (%)</td>
<td>37 (82.8)</td>
</tr>
<tr>
<td>Baseline PSA, median (range), ng/mL</td>
<td>254.6 (78-4782.0)</td>
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<tr>
<td>≥3 prior CRPC therapies, n (%)</td>
<td>13 (28.9)</td>
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<tr>
<td>Bone only, n (%)</td>
<td>13 (28.9)</td>
</tr>
<tr>
<td>Visceral only, n (%)</td>
<td>14 (31.1)</td>
</tr>
<tr>
<td>Only measurable nodal disease, n (%)</td>
<td>6 (13.3)</td>
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<tr>
<td>No measurable disease, n (%)</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>Only measurable skeletal disease, n (%)</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>Time to progression (months), median (range)</td>
<td>4 (1.0-51.0)</td>
</tr>
<tr>
<td>Response to rucaparib, n (%)</td>
<td>17 (37.8)</td>
</tr>
<tr>
<td>Overall alteration zygosity was determined for 29 patients</td>
<td>48.0</td>
</tr>
</tbody>
</table>
| Table 1: Baseline characteristics of 45 mCRPC patients with deleterious BRCA1/2 alterations.

PLASMA ctDNA 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.
- Circulating tumor cfDNA was purified from plasma samples.
- ctDNA was analyzed using the Foundation Medicine multigene test (Myriad Genetics, Inc).

BRC/2 ALTERATION TYPES AND TYSOGENITY
- The majority of patients (94%, 29/31) had a somatic and 1/3 had a germline alteration (Fig. 2).
- The plasma assay detected 1 (20.0%)
- Of patients with known stage at diagnosis, more patients with visceral disease had the highest plasma BRCA1/2 cfDNA yield at baseline (Table 2).

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.

RESPONSE BY GERMLINE/SOMATIC BRCA1/2 ALTERATION
- Responses were observed in patients with germline or somatic BRCA1/2 alterations.
- The BARCA1/2 alteration identified as the potential prognostic factor was time to progression (TTP).

REFERENCE
- Presented at AACR; March 31, 2019; poster 727.

ACKNOWLEDGMENTS
- The TRITON2 study is enrolling mCRPC patients with a deleterious DDR gene alteration to evaluate the potential benefit of treatment with the PARP inhibitor talazoparib.
- The trial is supported by Clovis Oncology, Inc and the Prostate Cancer Foundation.