Genomic Characteristics Associated With Clinical Activity of Rucaparib in Patients With BRCA1- or BRCA2-Mutated Metastatic Castration-Resistant Prostate Cancer (mCRPC)

INTRODUCTION

• There are limited treatment options available for patients with mCRPC following docetaxel treatment and irredescent therapy.1
• Up to 12% of patients with mCRPC harbor a deleterious germline and/or somatic alteration in the DNA damage repair (DDR) genes BRCA1 and BRCA2.2,3
• Preliminary results of 98 patients with a deleterious BRCA2 or BRCA2 alteration from the phase 2 TRITON2 study (NCT02935034) in patients with mCRPC who progressed on an AR-directed therapy and chemotherapy demonstrated investigator-assessed confirmed radiographic and prostate-specific antigen (PSA) responses in 44% (25/57) and 52% (51/98) of patients, respectively.2,4
• Here, we present associations of genomic and clinical characteristics of clinical activity of rucaparib in these 98 mCRPC patients with BRCA1/2 deficiency.

METHODS

Enrolled patients had a deleterious germline or somatic alteration in BRCA1 and/or BRCA2 determined by local, central, or plasma tissue/tumor test. All patients had ≥16 weeks of follow-up from the first dose of rucaparib. Response was determined per modified RECIST/PCWG3 criteria in patients with measurable disease at baseline (per investigator). Response was defined as complete or partial response to treatment with rucaparib confirmed by a consecutive assessment conducted at least 3 weeks later.

DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Age, median (yrs)</th>
<th>ECOG PS, n (0-2)</th>
<th>Tumor type, n/N (%)</th>
<th>Measurable disease, n/N (%)</th>
<th>Overall response, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2</td>
<td>72 (53-80)</td>
<td>0.1 (0.1-0.2)</td>
<td>44/98 (45.9%)</td>
<td>4/21 (19%)</td>
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</tr>
<tr>
<td>BRCA1</td>
<td>60 (46-79)</td>
<td>0.1 (0.1-0.2)</td>
<td>23/44 (52.3%)</td>
<td>3/13 (23.1%)</td>
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</tr>
<tr>
<td>BRCA2</td>
<td>75 (53-88)</td>
<td>0.1 (0.1-0.2)</td>
<td>12/19 (63.2%)</td>
<td>2/12 (16.7%)</td>
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<tr>
<td>Germline</td>
<td>70 (52-80)</td>
<td>0.1 (0.1-0.2)</td>
<td>37/83 (44.6%)</td>
<td>4/27 (14.8%)</td>
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</tr>
<tr>
<td>Somatic</td>
<td>65 (40-88)</td>
<td>0.1 (0.1-0.2)</td>
<td>40/99 (40.4%)</td>
<td>4/21 (19%)</td>
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</tr>
</tbody>
</table>

BRCAL/2 ALTERATION TYPES AND ZYGOSITY

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<tr>
<th>BRCA1/2</th>
<th>Alteration, n/N (%)</th>
<th>Genotype, n/N (%)</th>
</tr>
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<tr>
<td>BRCA1</td>
<td>8/21 (38%)</td>
<td>Heterozygous</td>
</tr>
<tr>
<td>BRCA2</td>
<td>14/77 (18%)</td>
<td>Homozygous</td>
</tr>
</tbody>
</table>

RESPONSE BY ALTERATION TYPE

From the tissue NSG assay response rates were 46% (13/28) and 57% (24/42) of the other allele at the locus of the BRCA1/2 alteration. Long-term survival after other mechanisms could not be ruled out.

RESPONSE BY ALTERATION ZYGOSITY

In patients with a deleterious BRCA1/2 alteration the objective response rate (ORR) was determined per modified RECIST/PCWG3 criteria. The majority of patients had frameshift alterations (45%, 44/98) or homozgyous loss (20%, 20/98) by a consecutive assessment conducted at least 3 weeks later.

RESPONSE BY GERMINE/SOMATIC STATUS

• Patients with deleterious BRCA1/2 alterations were identified from the plasma test (35%, 34/98), central tumor test (27/80) or local test (38%, 37/98). 10% (6/63) of patients had a somatic alteration and 36% (35/98) had a germline BRCA2 alteration.

HOMOZYGOUS LOSS OF BRCA1 OR BRCA2

• Twenty percent (20%) of patients with BRCA1/2 alterations had homozygous loss of BRCA1 or BRCA2 (Fig. 1). 10% (95%) had BRCA2 loss, 1 patient (5%) had BRCA1 loss and 75% (15/19) of BRCA2 losses were loss of the whole gene.

CONCLUSIONS

- The TRITON2 study enrolled mCRPC patients with a deleterious DDR gene alteration to evaluate the potential benefit of treatment with the PARP inhibitor rucaparib.
- Rucaparib has encouraging antitumor activity in patients with a BRCA1/2 alteration.
- Confirmed radiographic responses have been observed in patients with a germline or somatic BRCA1 or BRCA2 alteration.
- Patients with mono- and biallelic BRCA2 alterations show similar ORR.
- An ORR of 67% (19/27) was observed in patients with BRCA1 alteration.

REFERENCES

Parker et al. 77. 2018;70(2):686-90.

ACKNOWLEDGMENTS

- The majority (67%, 18/27) did not have a tissue sample available.
- The plasma assay identified 7 patients (26%) with a germline and 20 patients (74%) with a somatic PARP1421 alteration (Fig. 3).
- The majority (55%, 16/27) of patients had a frameshift alteration.


Figs. 1–5. Response by Alteration Type

 RESPONSE IN PATIENTS IDENTIFIED BY PLASMA ASSAY

- 28% (27/98) of patients with a BRCA1/2 alteration were identified for rucaparib treatment through central plasma testing.
- The majority (87%, 182/207) did not have a tissue sample available.
- The plasma assay identified 7 patients (26%) with a germline and 20 patients (74%) with a somatic PARP1421 alteration (Fig. 3).
- The majority (55%, 16/27) of patients had a frameshift alteration.

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