INTRODUCTION

- Rucaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, is approved in the United States as monotherapy for patients with BRCA1/2-mutated mCRPC who have been treated with androgen receptor (AR)-directed therapy and a taxane.
- Enzalutamide is an AR-signaling inhibitor approved in the United States for the treatment of patients with CRPC or metastatic castration-sensitive prostate cancer.
- Synthetic lethality has been observed, independent of DNA damage repair (DDR) gene defects, when combining AR-directed therapy (eg, enzalutamide) and a PARP inhibitor for prostate cancer.
- Preliminary results from the phase 1b RAMP study (NCT01793963) investigating the combination of rucaparib and enzalutamide in unselected patients with mCRPC have shown promising signs of antitumor activity, and its safety profile was consistent with that of each drug when used as monotherapy.
- Concomitant treatment with rucaparib and enzalutamide did not lead to significant changes in the pharmacokinetic (PK) profile for either agent or their metabolites.

METHODS

- Enrolled patients had a histologically or cytologically confirmed adenocarcinoma or poorly differentiated carcinoma that was refractory to prior docetaxel treatment and were naive to an AR-directed therapy (eg, enzalutamide, abiraterone) and ≤2 lines of chemotherapy.
- Patients received rucaparib monotherapy (600 mg twice daily) during a 1-week run-in period, followed by rucaparib (600 mg once daily) + enzalutamide (160 mg once daily) in continuous 28-day cycles.
- Doselimiting toxicities were assessed during the first 2 cycles of combination treatment, and trough PK was evaluated for rucaparib and enzalutamide and their respective metabolites.
- Primary endpoints were PK and safety for the combination.
- Secondary endpoints were the change from baseline in prostate-specific antigen (PSA) levels and the objective response rate per modified Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST) and Prostate Cancer Clinical Trials Working Group 3.

RESULTS

- As of December 2, 2020, 8 patients had received treatment (Table 1).

Table 1. Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>73 (65-75)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>White</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>0</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>1</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Baseline PSA, median (ng/mL)</td>
<td>20 (16-26)</td>
</tr>
<tr>
<td>Gleason score, n (%)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>1</td>
<td>2 (25)</td>
</tr>
<tr>
<td>2</td>
<td>2 (25)</td>
</tr>
<tr>
<td>3</td>
<td>4 (50)</td>
</tr>
<tr>
<td>4</td>
<td>1 (12.5)</td>
</tr>
</tbody>
</table>

- Overall, 6 (75%) of 8 patients reported a decline in PSA from baseline, including 4 (50%) with a confirmed PSA response (Figure 2).
- Genomic Characteristics: Genomic data were available for 6 (75%) of 8 treated patients, all of whom had received prior AR-directed therapy (Figure 1).
- AR alterations, including rearrangements, amplifications, and single nucleotide variants, were observed in 4 (67%) patients (Table 2).
- Mutations in TP53 were detected in 4 (67%) patients and PTEN in 2 (33%) patients.
- No BRCA1, BRCA2, or PALB2 alterations were detected.
- The only DDR gene alteration found was a truncating (<1% allele frequency) alteration of CHK2 in 1 (17%) patient (Figure 2).

Efficacy

- Overall, 6 (75%) of 8 patients reported a decline in PSA from baseline, including 4 (50%) with a confirmed PSA response (Figure 2).
- Patients previously treated with AR-directed therapies demonstrated reductions in PSA following the combination treatment even in the presence of multiple AR alterations and in the absence of DDR gene alterations (Table 2).
- Patient 4 had 3 AR alterations including AR H875Y (variant allele frequency [VAF] 3.1%), AR L702H (3.6%), and rearrangement and reported a best PSA change from baseline of −22.5%.
- Patient 8, with a low allele frequency point mutation in AR TR78A (VAF <1%), had the greatest reduction in PSA from baseline (best PSA change of −99.3%) and achieved a confirmed complete radiographic response.
- The patient also had a PSA53 (TP53 R34Q) and TM6P2S2.ERG gene fusion.

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REFERENCES