Rucaparib + Enzalutamide in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC): Pharmacokinetics (PK) and Safety Data From the Phase 1b RAMP Study

Abstract 79

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SUMMARY

- **Combination treatment with rucaparib 600 mg twice daily (BID) and enzalutamide 160 mg once daily (QD) in patients with mCRPC (n=7) had no clinically significant effect on PK profiles of either drug**
- **The overall safety profile of rucaparib and enzalutamide was consistent with that associated with each drug as monotherapy**
  - **No dose-limiting toxicities were observed with the combination**
- **Rucaparib combined with enzalutamide demonstrated promising signs of antitumor activity, with a confirmed prostate-specific antigen response (PSA50) in 50% (4/8) of patients and a confirmed complete radiographic response in the 1 patient with measurable disease**
- **These results support further study of rucaparib 600 mg BID and enzalutamide 160 mg QD combination in mCRPC; a randomized phase 3 trial is planned (NCT04455750)**

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Supplementary Material
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REFERENCES

1. Rubraca (rucaparib) tablets [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2020.
2. Xtandi (enzalutamide) tablets [prescribing information]. Northbrook, IL: Astellas Pharma US, Inc.; 2020.
3. Asim et al. *Nature Comm.* 2017;8:374.
4. Clarke et al. *Lancet Oncol.* 2018;19:975-86.
5. Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209115Orig1s000MultiDisciplineR.pdf. Accessed January 19, 2021.
6. Chowdhury et al. *Ann Oncol.* 2020;31(4 suppl):S533-4.
7. Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203415Orig1s000ClinPharmR.pdf. Accessed January 19, 2021.

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INTRODUCTION

- Rucaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, is approved in the United States as monotherapy for *BRCA1/2*-mutated metastatic castration-resistant prostate cancer (mCRPC) that has been treated with androgen receptor (AR)-directed therapy and a taxane[1]
- Enzalutamide, an AR inhibitor, is approved in the United States for the treatment of patients with CRPC or metastatic castration-sensitive prostate cancer[2]
- Synthetic lethality has been observed, independent of DNA-damage repair gene defects, when combining AR-directed therapy (eg, enzalutamide) and a PARP inhibitor for prostate cancer[3,4]
- Enzalutamide is a strong inducer of cytochrome P450 (CYP) 3A4, and nonclinical studies suggest that CYP3A4 may contribute to the formation of oxidative metabolite of rucaparib M324[5]
  - A consistent decrease in rucaparib concentration and increase in M324 concentration would suggest effects of enzalutamide on rucaparib pharmacokinetics (PK) by CYP3A4 induction
- The phase 1 RAMP study (NCT04179396) is investigating the combination of rucaparib and enzalutamide in unselected patients with mCRPC to assess potential drug-drug interactions, PK, and safety

METHODS

- Patients were enrolled with histologically or cytologically confirmed adenocarcinoma or poorly differentiated carcinoma of the prostate after 0–2 lines of AR-directed therapy (eg, enzalutamide, abiraterone) and ≤2 lines of chemotherapy for mCRPC; prior PARP inhibitor treatment was not allowed
- Patients received rucaparib monotherapy (600 mg twice daily [BID]) during a 1-week run-in period, followed by rucaparib (600 mg BID) + enzalutamide (160 mg once daily [QD]) in continuous 28-day cycles
- Dose-limiting toxicities (DLTs) were assessed during the first 2 cycles (see **Supplementary Material**)
- Trough PK was evaluated for rucaparib and enzalutamide and their respective metabolites, M324 and *N*-desmethyl enzalutamide
  - Plasma PK samples were collected on days 6 and 7 during the run-in period, on days 1, 8, 15, and 22 of cycles 1 and 2, and on day 1 of cycles 3, 4, 6, and 8; all samples were collected prior to the morning doses
- Next-generation sequencing was performed to detect DNA-damage repair gene alterations (eg, *BRCA1/2*) or genomic signatures associated with resistance to treatment
- 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 (ORR) 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

Characteristic	Patients (N=8)
Age, median (range), yr	68.5 (56.0–79.0)
Race, n (%)	
Asian	1 (12.5)
White	7 (87.5)
ECOG PS, n (%)	
0	5 (62.5)
1	3 (37.5)
Baseline PSA, median (range), ng/mL	20.0 (2.5–155.0)
Gleason score ≥8, n (%)[a]	7 (87.5)
Number of prior mCRPC therapies, n (%)[b]	
0	1 (12.5)
1	1 (12.5)
2	4 (50.0)
≥3	2 (25.0)
Number of prior AR-directed therapies, n (%)	
0	1 (12.5)
1	6 (75.0)
2	1 (12.5)

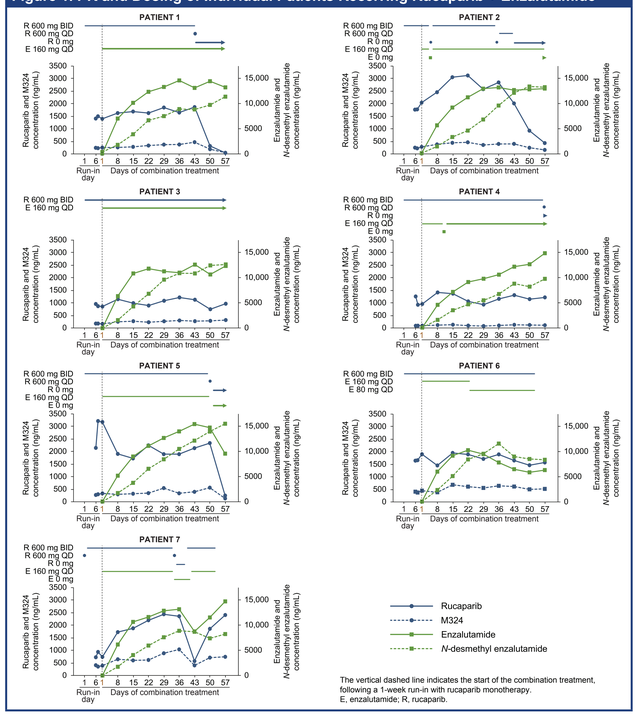
Visit cutoff date: December 2, 2020.
AR, androgen receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.
[a]One patient had an unknown Gleason score. [b]Defined based on class of agent and not disease status at time of treatment; does not include luteinizing hormone–releasing hormone analogs, first-generation antiandrogens, or hormones.

- No deleterious *BRCA1* or *BRCA2* alterations were identified among the 7 patients who provided tissue and/or plasma samples

Pharmacokinetics

- In the 7 PK-evaluable patients, rucaparib and its metabolite M324 reached apparent steady-state PK at the end of the run-in period
  - Moderate intra- and inter-patient PK variability was observed (**Figure 1**)
- Six out of 7 patients had dose reductions for rucaparib and/or enzalutamide during the first 2 cycles
- Concomitant treatment with enzalutamide did not lead to significant decreases in rucaparib concentration or increases in M324 concentration (**Figure 1; Supplementary Figure 1**)
- PK concentrations of rucaparib in this study were consistent with those observed in the TRITON2 study of rucaparib monotherapy (NCT02952534)[6] (**Supplementary Figure 2**)
- Enzalutamide and *N*-desmethyl enzalutamide trough PK values overlapped with those observed from prior studies[7]

Figure 1. PK and Dosing of Individual Patients Receiving Rucaparib + Enzalutamide



The vertical dashed line indicates the start of the combination treatment, following a 1-week run-in with rucaparib monotherapy.
E, enzalutamide; R, rucaparib.

Safety

- Median treatment duration was 119.5 days (range 44.0–260.0 days)
- No DLTs were reported among 6 evaluable patients
  - Two patients were not evaluable for DLTs due to enzalutamide dose reductions during the DLT period
- Among the 8 patients overall, the most common any-grade treatment-emergent adverse events (TEAEs) were nausea, decreased appetite, and fatigue (**Table 2**)
  - The most common grade ≥3 TEAEs were anemia and fatigue
- Of 8 patients, 7 (87.5%) required treatment interruption or dose reduction of rucaparib (n=2), enzalutamide (n=2), or both (n=3) due to TEAEs

Table 2. TEAEs Occurring in ≥2 Patients Treated With Rucaparib and Enzalutamide (N=8)

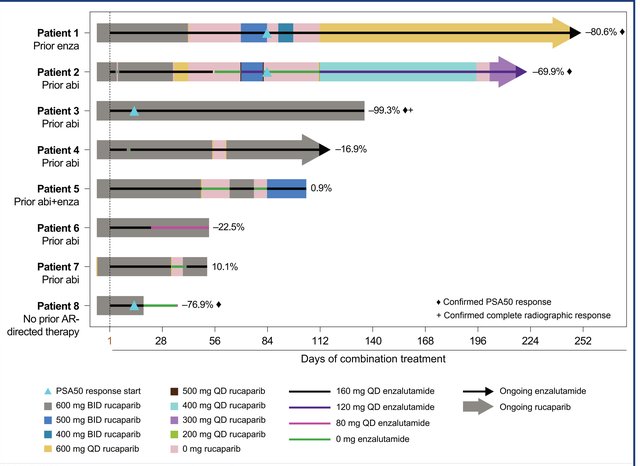
	Any grade n (%)	Grade ≥3 n (%)
Any TEAE	8 (100.0)	7 (87.5)
Nausea	7 (87.5)	1 (12.5)
Decreased appetite	6 (75.0)	0
Fatigue[a]	6 (75.0)	4 (50.0)
Anemia[b]	5 (62.5)	5 (62.5)
Dysgeusia	5 (62.5)	0
Thrombocytopenia[c]	4 (50.0)	0
Increased ALT/AST	3 (37.5)	1 (12.5)
Decreased white blood cell count	3 (37.5)	1 (12.5)
Diarrhea	3 (37.5)	0
Dyspnea	3 (37.5)	0
Abdominal distension	2 (25.0)	0
Cognitive disorder	2 (25.0)	0
Decreased creatinine renal clearance	2 (25.0)	1 (12.5)
Dyspnea exertional	2 (25.0)	0
Hypophosphatemia	2 (25.0)	0
Neutropenia[d]	2 (25.0)	1 (12.5)

Visit cutoff date: December 2, 2020. TEAEs were classified using MedDRA terminology.
[a]Asthenia and fatigue. [b]Anemia and decreased hemoglobin. [c]Thrombocytopenia and decreased platelets. [d]Neutropenia and decreased absolute neutrophil count.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Efficacy

- Among the 8 patients, 6 (75%) had a decline in PSA, and 4 (50%) had a confirmed PSA50 response (reduction ≥50% from baseline confirmed by a consecutive measurement ≥3 weeks later; **Figure 2** and **Supplementary Figure 3**)
- One patient had measurable disease at baseline (a solitary 21 mm bladder lesion) and achieved a confirmed complete radiographic response by investigator assessment
- At the time of data cutoff, 3 patients remained on study, including 2 (25%) patients who were on study for >6 cycles

Figure 2. Duration of Rucaparib and Enzalutamide Treatment in Patients



All PSA/RECIST responses were ongoing at the time of visit cutoff/study discontinuation.
Values shown represent the best percent change from baseline in PSA levels.
abi, abiraterone; AR, androgen receptor; BID, twice daily; enza, enzalutamide; PSA, prostate-specific antigen; PSA50, reduction of ≥50% from baseline in PSA level; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.