Evaluation of Rucaparib in Japanese Patients With a Previously Treated Advanced Solid Tumor

Abstract CT124

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SUMMARY

- **Rucaparib 600 mg twice daily had a manageable safety profile for Japanese patients with advanced solid tumors, similar to that observed in prior studies of rucaparib[1-3]**
- **The pharmacokinetic profile for rucaparib in Japanese patients overlapped with that of Western patients[4]**
- **Among patients with measurable disease, 18.5% (5/27) achieved an objective response and 51.9% (14/27) had stable disease per Response Evaluation Criteria In Solid Tumors version 1.1**
- **These results support further exploration of rucaparib 600 mg twice daily in Japanese patients**

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INTRODUCTION

- Rucaparib is an oral, poly(ADP-ribose) polymerase inhibitor approved in patients with recurrent ovarian cancer or metastatic castration-resistant prostate cancer[5,6]
  - In the United States, rucaparib is approved for the maintenance treatment of patients with recurrent ovarian cancer who have responded to platinum-based chemotherapy and as monotherapy treatment for patients with *BRCA1* or *BRCA2* (BRCA)–mutated, relapsed ovarian cancer who have received ≥2 prior lines of platinum-based chemotherapy
  - Rucaparib is also approved in the United States as monotherapy treatment of patients with BRCA mutation-associated metastatic castration-resistant prostate cancer after androgen receptor-directed therapy and a taxane-based chemotherapy
- The safety and pharmacokinetics (PK) of rucaparib have previously been evaluated in patients with solid tumors[4]; however, <10% of patients studied were Asian
- Given the limited number of Asian patients in prior studies of rucaparib, this phase 1 study (NCT03499444) investigated the safety, PK, and antitumor activity of rucaparib in Japanese patients

METHODS

- The study was conducted in 2 parts: a 3+3 dose escalation phase to establish the recommended dose in Japanese patients, and a dose expansion phase to further assess safety, PK, and efficacy of the recommended dose
- For the dose escalation phase, we enrolled patients with a locally recurrent or metastatic solid tumor that had progressed on standard treatment
  - Dose-limiting toxicities (DLTs) were assessed in the first 21 days
- For the dose expansion phase, we enrolled patients with a locally recurrent or metastatic solid tumor that had progressed on standard treatment; the tumor was one of the following:
  - High-grade serous ovarian cancer
  - Breast cancer with a *BRCA1* or *BRCA2* mutation per local or central test
  - Other solid tumor with a homologous recombination repair gene mutation per local or central test
- Patients in the dose escalation phase were required to have evaluable disease (defined as ≥1 target or nontarget lesion) per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST); patients in the dose expansion phase were required to have measurable disease per RECIST at baseline
- For all patients, plasma samples for PK assessments were collected predose and from 15 minutes to 10 hours postdose on days 1 and 15
  - On day 1, patients were required to fast overnight until 4 hours postdose; all other doses could be taken with or without food
- The primary objective was to assess safety and tolerability of escalating doses of rucaparib in Japanese patients with an advanced solid tumor
- Secondary objectives included establishment of the recommended dose of rucaparib monotherapy in Japanese patients, characterization of steady-state PK profile of rucaparib in Japanese patients, and evaluation of antitumor activity (per RECIST) of rucaparib

RESULTS

- As of February 9, 2021, 29 patients had received rucaparib (**Table 1**)
  - Three dose escalation cohorts (400 mg twice a day [BID], n=3; 500 mg BID, n=6; and 600 mg BID, n=6) were evaluated
  - An additional 14 patients were enrolled in the dose expansion phase at the recommended dose of 600 mg BID
- Median (range) time on treatment was 5.1 (1.3–20.1) months overall and 5.3 (1.4–20.1) months for patients who received 600 mg BID (n=20); 1 patient was ongoing at the time of data cutoff

Table 1. Summary of Baseline Characteristics

Characteristic	Rucaparib 400 mg BID (n=3)	Rucaparib 500 mg BID (n=6)	Rucaparib 600 mg BID (n=20)	Overall (N=29)
Age, median (range), years	67.0 (45.0–68.0)	61.5 (44.0–73.0)	59.5 (43.0–74.0)	61.0 (43.0–74.0)
Female, n (%)	3 (100)	6 (100)	16 (80.0)	25 (86.2)
ECOG PS, n (%)				
0	3 (100)	4 (66.7)	15 (75.0)	22 (75.9)
1	0	2 (33.3)	5 (25.0)	7 (24.1)
Tumor type, n (%)				
Ovarian	2 (66.7)	1 (16.7)	9 (45.0)	12 (41.4)
Primary peritoneal	1 (33.3)	2 (33.3)	2 (10.0)	5 (17.2)
Pancreatic	0	0	4 (20.0)	4 (13.8)
Breast	0	2 (33.3)	1 (5.0)	3 (10.3)
Other	0	1 (16.7)	4 (20.0)	5 (17.2)
Number of prior anticancer therapies, median (range)	3.0 (1.0–9.0)	2.5 (1.0–7.0)	2.5 (1.0–6.0)	3.0 (1.0–9.0)
BRCA gene mutation, n (%)[a]				
BRCA1	0	0	3 (15.0)	3 (10.3)
BRCA2	0	0	2 (10.0)	2 (6.9)
None	1 (33.3)	0	12 (60.0)	13 (44.8)
Not available	2 (66.7)	6 (100)	3 (15.0)	11 (37.9)

Visit cutoff date: February 9, 2021.
[a]Based on local genomics results from all patients and additional central Foundation Medicine, Inc., results available from 14 patients in the 600 mg BID dose expansion cohort.
BID, twice a day; BRCA, *BRCA1* or *BRCA2*; ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety

- One DLT was reported in the 500 mg BID cohort (treatment interruption >7 days due to grade 1/2 nausea, vomiting, diarrhea, fatigue)
  - No other DLTs were reported; therefore, the recommended dose in Japanese patients was determined to be 600 mg BID
- Across all doses, the most frequent any-grade treatment-emergent adverse events (TEAEs) were alanine aminotransferase/aspartate aminotransferase increased, anemia, and nausea (**Table 2**)
  - The most frequent grade ≥3 TEAE was anemia
- Among patients who received 600 mg BID, 85.0% (17/20) had a TEAE leading to treatment interruption or dose reduction, most commonly due to anemia (55.0%; 11/20)

Table 2. TEAEs Occurring in ≥15% of Patients Overall

	Rucaparib 400 mg BID (n=3)		Rucaparib 500 mg BID (n=6)		Rucaparib 600 mg BID (n=20)		Overall (N=29)	
n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	3 (100)	2 (66.7)	6 (100)	4 (66.7)	20 (100)	14 (70.0)	29 (100)	20 (69.0)
ALT/AST increased	2 (66.7)	0	6 (100)	2 (33.3)	16 (80.0)	5 (25.0)	24 (82.8)	7 (24.1)
Anemia	2 (66.7)	1 (33.3)	5 (83.3)	3 (50.0)	17 (85.0)	11 (55.0)	24 (82.8)	15 (51.7)
Nausea	2 (66.7)	0	6 (100)	0	12 (60.0)	0	20 (69.0)	0
Decreased appetite	1 (33.3)	0	2 (33.3)	0	12 (60.0)	0	15 (51.7)	0
Neutrophil count decreased	2 (66.7)	2 (66.7)	3 (50.0)	2 (33.3)	10 (50.0)	6 (30.0)	15 (51.7)	10 (34.5)
Platelet count decreased	2 (66.7)	1 (33.3)	3 (50.0)	2 (33.3)	10 (50.0)	6 (30.0)	15 (51.7)	9 (31.0)
Fatigue	1 (33.3)	0	2 (33.3)	0	10 (50.0)	0	13 (44.8)	0
White blood cell count decreased	2 (66.7)	2 (66.7)	3 (50.0)	1 (16.7)	8 (40.0)	2 (10.0)	13 (44.8)	5 (17.2)
Vomiting	1 (33.3)	0	2 (33.3)	0	10 (50.0)	0	13 (44.8)	0
Dysgeusia	0	0	2 (33.3)	0	10 (50.0)	0	12 (41.4)	0
Diarrhea	1 (33.3)	0	2 (33.3)	0	7 (35.0)	0	10 (34.5)	0
Blood alkaline phosphatase increased	1 (33.3)	0	2 (33.3)	0	6 (30.0)	0	9 (31.0)	0
Upper respiratory tract infection	0	0	2 (33.3)	0	5 (25.0)	0	7 (24.1)	0
Stomatitis	1 (33.3)	0	0	0	5 (25.0)	0	6 (20.7)	0
Blood creatinine increased	0	0	0	0	5 (25.0)	0	5 (17.2)	0
Constipation	1 (33.3)	0	1 (16.7)	0	3 (15.0)	0	5 (17.2)	0
Malaise	0	0	1 (16.7)	0	4 (20.0)	0	5 (17.2)	0
Rash	1 (33.3)	0	0	0	4 (20.0)	0	5 (17.2)	0

Visit cutoff date: February 9, 2021.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice a day; TEAE, treatment-emergent adverse event.

Pharmacokinetics

- Steady-state PK was evaluated for the 400, 500, and 600 mg BID cohorts (**Table 3**)
  - Although the steady-state AUC_{0-12} (CV%) in the 600 mg BID cohort was higher than that in Western patients who received rucaparib 600 mg BID (16,900 h × ng/mL [54]),[4] this difference was not considered clinically significant because the safety profile was similar between Japanese and Western patients

Table 3. Steady-State PK in the Dose Escalation Cohorts

Characteristic	Rucaparib 400 mg BID (n=3)	Rucaparib 500 mg BID (n=6)	Rucaparib 600 mg BID (n=20)
C_{max}, mean (CV%), ng/mL	1690 (38.7)	3650 (61.9)[a]	2800 (37.0)[b]
t_{max}, median (range), h	1.48 (1.47–2.45)	3.95 (2.47–9.95)[a]	2.50 (0.93–9.83)[b]
C_{min}, mean (CV%), ng/mL	1590 (38.7)	2380 (78.5)	2130 (44.4)
AUC_{last}, mean (CV%), h × ng/mL	14,400 (36.6)	30,200 (64.7)[a]	23,800 (39.9)[b]
CL/F, mean (CV%), L/h	26.1 (45.2)	22.1 (68.5)[c]	24.3 (34.6)[d]
AUC_{0-12}, mean (CV%), h × ng/mL	17,200 (35.8)	33,900 (78.9)[c]	28,100 (40.8)[d]

[a]n=5. [b]n=18. [c]n=3. [d]n=13. AUC_{0-12}, area under the concentration-time curve up to 12 h; AUC_{last}, area under the concentration-time curve up to last time point (10 h) with a quantifiable concentration; BID, twice a day; CL/F, apparent total clearance of drug after oral administration; C_{max}, maximum concentration; C_{min}, minimum concentration; CV, coefficient of variation; PK, pharmacokinetics; t_{max}, time to maximum concentration.

Efficacy

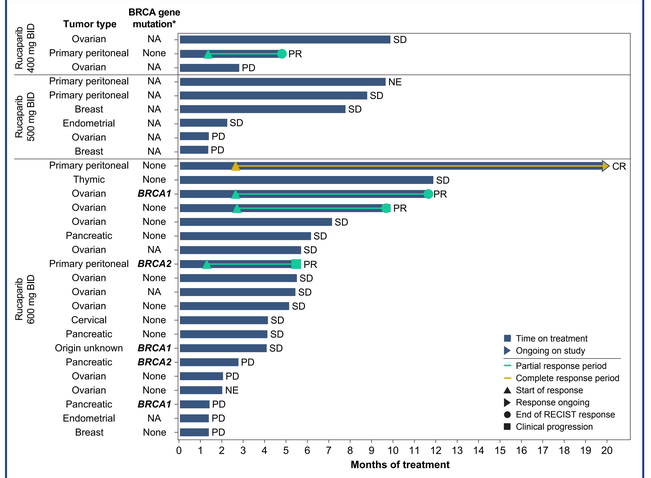
- Among patients with measurable disease, the confirmed objective response rate was 18.5% (5/27) overall and 21.1% (4/19) for patients who received 600 mg BID (**Table 4**; **Figure**); the majority of patients had a best response of stable disease (51.9%; 14/27)

Table 4. Confirmed ORR per RECIST for Patients With Measurable Disease at Baseline

	Rucaparib 400 mg BID (n=3)	Rucaparib 500 mg BID (n=5)	Rucaparib 600 mg BID (n=19)	Overall (n=27)
ORR, n (%) [95% CI]	1 (33.3) [0.8–90.6]	0 (0) [0.0–52.2]	4 (21.1) [6.1–45.6]	5 (18.5) [6.3–38.1]
Complete response	0	0	1 (5.3)	1 (3.7)
Partial response	1 (33.3)	0	3 (15.8)	4 (14.8)
Stable disease	1 (33.3)	3 (60.0)	10 (52.6)	14 (51.9)
Progressive disease	1 (33.3)	2 (40.0)	5 (26.3)	8 (29.6)

Visit cutoff date: February 9, 2021.
BID, twice a day; ORR, objective response rate; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Figure. Time on Rucaparib Treatment and Best Confirmed RECIST Response to Date



Visit cutoff date: February 9, 2021.
Text at the end of each line represents the best confirmed RECIST response reported.
*Based on local genomics results from all patients and additional central Foundation Medicine, Inc., results available from 14 patients in the 600 mg BID dose expansion cohort.
BID, twice a day; BRCA, *BRCA1* or *BRCA2*; CR, complete response; NA, not available; NE, not evaluable (no measurable disease per RECIST at baseline); PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease.