Abstract 0327

Open-Label, Phase 1 Safety and Pharmacokinetic Study to Evaluate Rucaparib in Japanese Patients with a Previously Treated Advanced Solid Tumour

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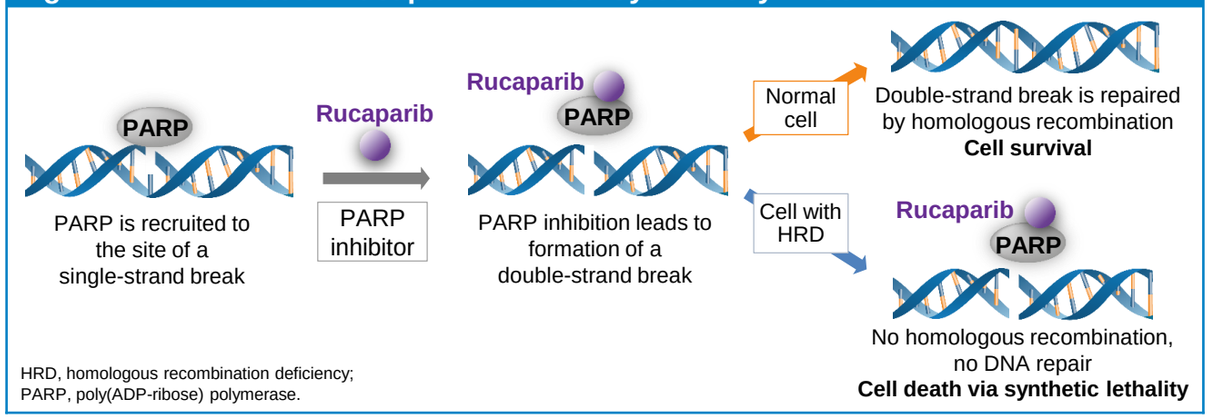
INTRODUCTION

- Rucaparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3, all of which play a role in DNA repair
- In vitro studies have shown that rucaparib-induced cytotoxicity involves inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes that result in DNA damage, apoptosis, and death in cancer cells (**Figure 1**)[1-5]

Figure 1. Schematic of Rucaparib-Induced Cytotoxicity in Cells with HRD



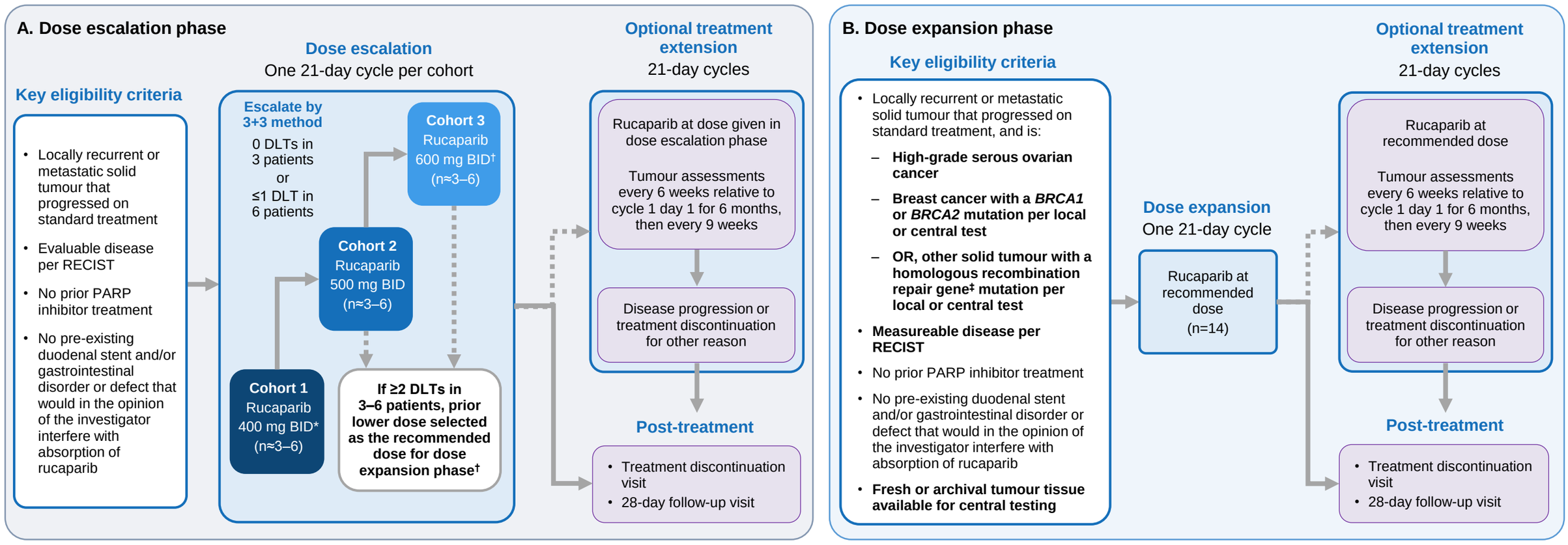
HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase.

- Rucaparib has clinical activity in patients with tumours that have homologous recombination deficiency (HRD), a phenomenon that is characterised by mutations in *BRCA1* or *BRCA2*, mutations in other homologous recombination repair genes (eg, *RAD51C*, *RAD51D*), and/or genomic loss of heterozygosity[6-8]
- Rucaparib is approved in the United States for the treatment of adult patients with deleterious *BRCA* mutation (germline and/or somatic)–associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 2 or more chemotherapies and for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy[9]
- In Europe, rucaparib is indicated as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, *BRCA*-mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with 2 or more prior lines of platinum-based chemotherapy and who are unable to tolerate further platinum-based chemotherapy[10]
- Rucaparib is currently not licensed anywhere else in the world
- A phase 1–2 study (CO-338-010 [Study 10; NCT01482715]) conducted in Canada, England, Israel, and the United States investigated single-dose and steady-state pharmacokinetic (PK) profiles of rucaparib administered across a range of doses[11]
  - In patients who received rucaparib twice daily (BID; dose range, 240–840 mg) in the phase 1 portion of the study, steady state was reached by cycle 1 day 8; mean maximum concentration ranged from 971–3170 ng/mL[11]
  - Across dosing schedules (240–840 mg BID), median time to maximum concentration ranged from 3.2–6.0 hours after a single dose and 1.5–4.0 hours after repeated dosing of rucaparib[11]
  - Notably, most patients were white (86.7%); only 10.0% were Asian
- Given that the PK profile of rucaparib was not investigated in a large number of Asian patients in Study 10 or other studies, the current study (CO-338-081; NCT03499444) is evaluating the safety and PK of rucaparib in a cohort composed entirely of Japanese patients

TRIAL OVERVIEW

- This 2-part study includes a dose escalation portion and a dose expansion portion that will establish and confirm the recommended dose of rucaparib in Japanese patients with an advanced solid tumour that has progressed on standard treatment
- In the first part of the study, the dose of rucaparib will be escalated using a standard 3+3 methodology (**Figure 2A**)
- In the dose expansion portion of the study, 14 additional patients will be enrolled to further assess the safety, tolerability, and PK profile of the recommended dose of rucaparib (**Figure 2B**)

Figure 2. Study Design



*If there are ≥2 DLTs in 3–6 patients at 400 mg BID, then 300 mg BID may be evaluated.
†Select as recommended dose provided that ≥6 patients were evaluated at that dose and there was ≤1 DLT in 6 patients.
‡*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*.
BID, twice daily; DLT, dose-limiting toxicity; PARP, poly(ADP-ribose) polymerase; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

TRIAL OBJECTIVES

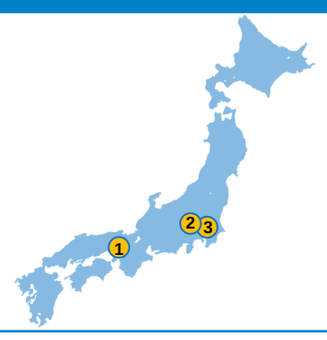
- Primary objective
  - Assess safety and tolerability of escalating doses of rucaparib in Japanese patients with an advanced solid tumour
- Secondary objectives
  - Establish recommended dose of rucaparib monotherapy
  - Characterise single-dose and steady-state PK profile of rucaparib
  - Evaluate antitumour activity (per RECIST version 1.1) of rucaparib
- Exploratory objectives
  - Assess concordance of genomic alterations observed in baseline matched tumour samples and plasma
  - Assess genomic alterations over time and at disease progression in plasma samples
  - Assess PK of rucaparib metabolites

TRIAL ENROLMENT

Figure 3. Sites Participating in the Trial

Patients are being enrolled at 3 sites in Japan

1. Hyogo Cancer Center, Hyogo
2. Saitama Medical University International Medical Center, Saitama
3. National Cancer Center Hospital, Tokyo



SUMMARY

- This is the first study to investigate the safety, tolerability, antitumour activity, and PK of rucaparib in a cohort composed entirely of Japanese patients
- This study will help establish a recommended dose for rucaparib monotherapy in Japanese patients with an advanced solid tumour

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