**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)\(^{11}\)

• Rucaparib has clinical activity in patients with tumours that have homogenous recombination deficiency (HRD), a phenomenon that is characterised by mutations in BRCA1 or BRCA2, mutations in other homologous recombination repair genes (e.g., RAD51C, RAD51D), and/or genomic loss of heterozygosity (LOH).\(^{2,3}\)

• 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.

• 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.

• 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:\(^{21}\)

- In patients who received rucaparib twice daily (BID: dose range, 240–440 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.

- Across dosing schedules (240–440 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.\(^{21}\)

- 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 phase and a dose expansion phase 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).

**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.
  - Explore pharmacodynamic objectives.
  - Assess concordance of genomic alterations observed in baseline matched tumour samples and plasma.
  - Assess genomic alterations over time and disease progression in plasma samples.
  - Assess PK of rucaparib metabolites.

**REFERENCES**


12. This is the first study to investigate the safety, tolerability, antitumour activity, and PK of rucaparib in a cohort composed entirely of Japanese patients.

13. This study will help establish a recommended dose for rucaparib monotherapy in Japanese patients with an advanced solid tumour.

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**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.