Rucaparib was granted accelerated approval by the US Food and Drug Administration for the treatment of patients with BRCA1/2 mutant advanced ovarian cancer in January this year, making it the second drug in its class for this indication. It is a poly(ADP-ribose) polymerase inhibitor that works by blocking the repair of damaged DNA in cancer cells and triggering cell death.

The approval was based on findings from 2 single-arm clinical trials in which rucaparib led to complete or partial tumor shrinkage in more than half of the patients enrolled. A pooled analysis included 106 patients from the phase 2 trials, Study 10 (NCT01482715; N = 42) and ARIEL2 (NCT01891344; N = 64), in which patients with BRCA1/2 mutation-positive ovarian cancer who had progressed on 2 or more previous chemotherapy regimens, received 600 mg rucaparib twice daily.

Study 10 included only patients with platinum-sensitive disease and eligible patients were aged 18 years or older, with a known deleterious BRCA mutation, evidence of measurable disease as defined by Response Evaluation Criteria in Solid Tumors (version 1.1), sufficient archival tumor tissue, histologically confirmed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer and relapsed disease confirmed by radiologic assessment. Meanwhile, ARIEL2 had similar eligibility criteria, except that patients with platinum-sensitive, resistant, and refractory disease were included.

Both studies excluded patients with active second malignancies, and for those with a history of prior cancer that had been curatively treated, no evidence of current disease was required and chemotherapy should have been completed more than 6 months or bone marrow transplant more than 2 years before the first dose of rucaparib. Patients who had previously been treated with a PARP inhibitor, with symptomatic and/or untreated central nervous system metastases, or who had been hospitalized for bowel obstruction within the previous 3 months, were also ineligible.

Across the 2 trials, the median age of trial participants was 59 years, 78% were white, and all had an Eastern Cooperative Oncology Group performance status of 0 (fully active, able to carry on all pre-disease performance without restriction) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature). Both trials used a surrogate endpoint for approval, measuring the percentage of patients who experienced complete or partial tumor shrinkage, the overall response rate (ORR), while taking rucaparib.

In Study 10, the ORR was 60%, including a complete response (CR) rate of 10% and a partial response (PR) rate of 50%, over a median duration of response (DoR) of 7.9 months; in ARIEL2, the ORR was 50%, and CR and PR were 8% and 42%, over a median DoR of 11.6 months (pooled analysis, median DoR of 9.2 months: ORR, 54%; CR, 9%; PR, 45%).

Across studies, the most common adverse events included nausea, fatigue, vomiting, and anemia, and the most common grade 3/4 AEs were anemia, fatigue/asthenia, and increased alanine aminotransferase or aspartate aminotransferase levels, with 8% of patients discontinuing therapy because of AEs. The recommended dose is 600 mg PO twice daily. Prescribing physicians should be aware of the risk for MDS or acute myeloid leukemia, and for embryofetal toxicity. Complete blood count should be monitored at baseline then monthly. If hematologic toxicities occur, treatment should be interrupted and blood counts monitored. Pregnant women and those of reproductive age should be advised about the risk to the fetus or the need for effective contraception during treatment and 6 months after the last dose.

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PARP inhibitors push DNA repair-defective cancer cells over the edge

Rucaparib is the second drug in its class to be approved for the treatment of patients with ovarian cancer. It works by blocking the activity of the poly(ADP-ribose) polymerase (PARP) 1 and 2 proteins. The PARP family are enzymes that detect a particular kind of DNA damage – breaks in a single strand of the double helix, known as single-strand breaks. They bind to sites of damaged DNA through their DNA binding domain and help to recruit proteins that repair this damage to the site.

PARP inhibitors not only block this enzymatic activity, they also, with varying degrees of potency, prevent PARP from letting go of the DNA once repair proteins arrive – a phenomenon known as PARP “trapping.” Both mechanisms of action prevent the repair of DNA and block subsequent transcription and DNA replication and drive the accumulation of a more lethal type of DNA damage, the double-strand break.

Cells with dsDNA damage can still be rescued through several repair pathways, the most effective of which is the homologous recombination (HR) pathway. The BRCA1 and BRCA2 genes encode enzymes that, among their many cellular roles, are central players in the HR pathway. Mutations in these genes can lead to defective HR repair in cells, driving the genomic instability that is a hallmark of cancer. Indeed, BRCA1/2 mutations are associated with hereditary breast and ovarian cancer and also increase the risk for uterine, cervical, colon, and pancreatic cancers, as well as melanoma.

PARP inhibitors are particularly effective in killing cells in which the HR pathway does not work properly, because the dsDNA breaks that form cannot be repaired, triggering cell death. Though patients with BRCA1/2 mutations are the most widely studied population, it is suspected that patients who have cancers with other HR pathway defects (or “BRCAness”) would also be susceptible to PARP inhibition.

Mechanism of action: rucaparib

PARP enzymes repair single-strand breaks in DNA, but their activity is blocked by PARP inhibition, leading to the formation of double-strand breaks. This damage can still be repaired by the homologous recombination repair pathway, except in cells in which the HR pathway is defective, such as those with mutations in the BRCA1/2 genes, where damage goes unrepaired leading to cell death.


The recommended dose according to the prescribing information is 600 mg, in the form of two 300-mg tablets taken orally twice daily with or without food. Physicians prescribing rucaparib should be aware of the potential for myelodysplastic syndrome or acute myeloid leukemia and for embryofetal toxicity. Complete blood count should be monitored at baseline and monthly thereafter and treatment should not be initiated until after patients have made a complete recovery from any hematologic toxicities caused by prior chemotherapy.

If hematologic toxicities occur while taking rucaparib, treatment should be interrupted and blood counts monitored until recovery and failure to recover to grade 1 or higher after 4 weeks should prompt referral to a hematologist for further investigation, while confirmed diagnosis of myelodysplastic syndromes or acute myeloid leukemia should lead to discontinuation of rucaparib. Pregnant women and those of reproductive potential should be
advised of the potential risk to a fetus or the need for effective contraception during treatment and for 6 months after the last dose of rucaparib.

Rucaparib is indicated only for the treatment of patients with confirmed \textit{BRCA1/2} mutations, so the drug was approved in conjunction with a companion diagnostic. FoundationFocus CDxBRCA is the first next-generation sequencing-based test to receive FDA approval and detects the presence of deleterious \textit{BRCA} gene mutations in tumor tissue samples. Rucaparib is marketed as Rubraca by Clovis Oncology Inc, and the companion diagnostic by Foundation Medicine Inc.

\textbf{References}

