Rucaparib boosts progression-free survival in BRCA mutant recurrent ovarian cancer

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Rucaparib maintenance therapy increases progression-free survival in BRCA mutant recurrent ovarian cancer by 77%, according to late-breaking results from the ARIEL3 trial reported today at the ESMO 2017 Congress in Madrid.

Most ovarian cancer presents as advanced disease and 80% of those patients will recur after first line treatment. Patients often respond again to chemotherapy, particularly platinum-based, but they almost inevitably relapse again and eventually die of their disease. Maintenance treatments are needed to reduce recurrence in patients who have already relapsed.

The PARP enzyme helps to initiate the repair of DNA damage so that cells can continue to divide. DNA repair processes are inherently impaired in tumour cells with BRCA mutations. PARP inhibitors, such as rucaparib, block DNA repair and cells with BRCA mutations die.

Just over 20% of patients with ovarian cancer have BRCA mutations and are susceptible to PARP inhibitors. Some others with the disease are also susceptible, such as patients who respond to platinum-based chemotherapy and those with a high degree of genomic loss of heterozygosity (LOH) - meaning the tumour DNA is scarred and DNA repair mechanisms are faulty.

ARIEL3 included 564 patients with high grade ovarian cancer who had responded to platinum-based chemotherapy in the second or third line of treatment. Patients were randomised 2:1 to rucaparib maintenance therapy or placebo. The primary endpoint was progression-free survival, which was measured sequentially in three groups if benefit was found in the previous group: 1) BRCA mutant; 2) BRCA mutant or BRCA wild type with high LOH (together called homologous recombination deficient or HRD); 3) intention to treat (entire study population).

Rucaparib led to a statistically significant improvement in progression-free survival in all three groups. Progression-free survival increased from 5.4 months to 16.6, 13.6, and 10.8 months in groups 1, 2, and 3, respectively, with hazard ratios of 0.23, 0.32, and 0.36, respectively.

"The improvement in progression-free survival was greatest in the BRCA mutated group, who had a 77% increase, but it was seen across three subgroups that were evaluated," said first author Prof Jonathan Ledermann, Professor of Medical Oncology, UCL Cancer Institute, London, UK.

In exploratory analyses, patients without BRCA mutations (wild type) were divided into those with high and low LOH. As expected, patients with high LOH had more improvement in progression-free survival than those with low LOH. But in both high and low LOH subgroups, rucaparib was statistically significantly better than placebo.

Ledermann said: "We had hoped that the LOH test would distinguish responders from non-responders but both high and low LOH groups benefitted. However, the magnitude of progression-free survival benefit was greater in the BRCA wild type/LOH high patients."

Rucaparib was well tolerated and just 13% of patients had to discontinue the medication due to side effects. The safety profile of rucaparib in ARIEL3 was consistent with previous phase II studies.

Ledermann concluded: "PARP inhibitors are the biggest development in ovarian cancer therapy since the introduction of platinum drugs in the late 1970s and early 1980s. Rucaparib is clearly an exemplary member of this exciting class of drugs that can be used to treat women with recurrent ovarian cancer in the maintenance setting."

Commenting on the results, Dr Andrés Poveda,

Head of the Gynaecological Cancer Clinic, Oncology Foundation Institute Valencia, Spain, Chair of the Gynaecologic Cancer Intergroup (GCIG), Member of the ESMO Faculty on Gynecological cancer, said: "ARIEL3 achieved a huge decrease in the risk of relapse with rucaparib. All of the patient subgroups benefitted, especially those with BRCA mutations but also homologous recombination deficient (HRD) patients."

"In Europe the PARP inhibitor olaparib is licensed as maintenance therapy but only for patients with germline BRCA mutations," he added. "We are awaiting a decision on niraparib, another PARP inhibitor. The addition of rucaparib would expand the population of patients receiving benefit from this type of drugs."

Poveda concluded: "Personalised medicine has arrived in high grade serious ovarian cancer. Further studies are needed to identify predictive biomarkers of response to PARP inhibitors. Specifically, we need to know whether there are non-HRD factors that predict response."

More information: Abstract LBA40_PR 'ARIEL3: A Phase 3, Randomised, Double-Blind Study of Rucaparib vs Placebo Following Response to Platinum-Based Chemotherapy for Recurrent Ovarian Carcinoma (OC)' will be presented by Prof Jonathan Ledermann during Proffered Paper session 'Gynaecological cancers' on Friday, 8 September 2017, 16:00 to 17:30 (CEST) in the Cordoba Auditorium.

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