

Clinical trial shows drug combination may be effective in recurrent ovarian cancer

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Significant improvement with the use of a combination drug therapy for recurrent ovarian cancer was reported at the annual meeting of the American Society of Clinical Oncology (ASCO) meeting in Chicago today. This is the first ovarian cancer study to use a combination of drugs that could be taken orally. The drugs were tested in a phase I combination study followed by a randomized phase 2 trial sponsored by the National Cancer Institute (NCI), part of the National Institutes of Health. The trial compared the activity of the combination of the drug olaparib, which blocks DNA repair, and the blood vessel inhibitor drug cediranib, vs. olaparib alone. Trial results showed a near doubling of progression-free survival benefit for the combination therapy over use of the single drug alone.

"The findings of this study are exciting because they support the idea that combining these two targeted oral therapies results in significant activity in [ovarian cancer](#), more so than olaparib alone," said Joyce Liu, M.D., MPH, the lead investigator and medical oncologist at the Susan F. Smith Center for Women's Cancers at Dana-Farber Cancer Institute, Boston. "We are looking forward to further exploring this combination in ovarian cancer and potentially increasing effective treatment options for our patients with this cancer."

There are over 22,000 cases of ovarian cancer diagnosed annually in the United States alone. Seventy-five percent of these cases are classified as high grade serous type, and they show more advanced disease at diagnosis and are more aggressive. Of this high-grade type, about three-

quarters will regress after initial treatment but nearly all will recur and need follow-up treatment. That treatment will be based on how the cancers have responded to previous therapies and are broken down into two categories:

- Platinum-Sensitive – these are patients most likely to benefit from PARP inhibition. PARP (Poly ADP-Ribose Polymerase) inhibitors, such as olaparib, are targeted drugs that block an enzyme involved in many functions in the cell, including the repair of DNA damage.
- Platinum-Resistant – these are patients whose disease recurred within six months of conventional chemotherapy (using the drugs cisplatin or carboplatin) and are generally less responsive to subsequent treatments and have not responded as well to PARP inhibitors. They are currently treated with non-platinum chemotherapy, single-agents, with or without addition of the blood vessel inhibitor drug called bevacizumab.

An anti-angiogenic agent, or blood vessel inhibitor, called cediranib (which inhibits a protein known as VEGFR) and olaparib, a PARP inhibitor, are each clinically active in recurrent ovarian cancer. Pre-clinical studies suggest these agents add to and enhance the activity of each other, and a phase 1 study showed that the combination of cediranib and olaparib was well-tolerated with minimal side-effects. Hence, a total of 90 patients from nine centers were randomly assigned to one of two study arms for the phase II clinical trial: the first taking capsules of olaparib (400 mg twice daily) and the other taking a combination of the two drugs (200 mg olaparib in capsule-form twice daily and 30 mg tablets of cediranib once daily). The study arms were stratified by BRCA gene mutation status and receipt of prior anti-angiogenic therapy.

Patients, whose median age was 58, were enrolled from October 2011 to

June 2013. As of March 2014, median progression-free survival was 9.2 months for olaparib and 16.7 months for the combination therapy, which is a significant advantage. The overall rate of toxicity was higher for patients on the [combination therapy](#). Fatigue, diarrhea, and hypertension were the most common toxic effects, all of which were manageable.

"Of particular note is the fact that both drugs used in this trial are in pill form," said Percy Ivy, M.D., associate chief of NCI's Investigational Drug Branch. "Therefore, this therapy could be used anywhere in the world where patients can be monitored for dehydration due to diarrhea side-effects and blood pressure due to hypertension side-effects."

Based on these results, two phase 3 trials are being planned for platinum-sensitive and platinum-resistant ovarian cancer patients by one of NCI's new National Cancer Trial Network Groups, the NRG Oncology Group (formerly 3 cooperative groups: the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG).

More information: Liu, JF, et al. A randomized phase 2 trial comparing efficacy of the combination of the PARP inhibitor olaparib and the anti-angiogenic cediranib against olaparib alone in recurrent platinum-sensitive ovarian cancer. NCT 01116648.

[www.cancer.gov/clinicaltrials/ ... n=HealthProfessional](http://www.cancer.gov/clinicaltrials/...n=HealthProfessional)

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