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Olaparib–Carboplatin Combination Showed Early Signs of Clinical Activity Against Ovarian and Triple-negative Breast Cancers

The sequence of treatment had no effect on toxicity

PHILADELPHIA — The order in which olaparib (Lynparza) and carboplatin chemotherapy were administered to patients with recurrent women’s cancers did not significantly alter the side effects experienced by the patients, and the combination therapy showed preliminary signs of clinical activity in these patients, according to data from a [phase I clinical trial](#) presented at the [AACR Annual Meeting 2015](#), held here April 18-22.

“The PARP [poly ADP-ribose polymerase] inhibitor olaparib was recently approved by the FDA for treating women with ovarian cancer who have a germline BRCA mutation,” said Victoria L. Chiou, MD, a medical oncology fellow in the [Women’s Malignancies Branch](#) at the National Cancer Institute in Bethesda, Maryland. “Studies to identify treatment combinations that might increase the number of patients benefiting from olaparib are important. We asked the question: What is the best way to deliver combination therapy using olaparib and carboplatin to maximize DNA damage, which likely correlates with antitumor effects, and minimize clinical toxicities.

“We found that the overall sequence of treatments did not significantly impact the side effects that patients felt,” continued Chiou. “Moreover, we identified a safe drug treatment schedule that also had preliminary activity, known as tumor shrinkage, in women with breast cancer and ovarian cancer. In fact, among women with ovarian cancer on the trial with germline BRCA mutations we saw a 60 percent overall response rate with the combination, which is higher than the approximately 30 percent reported response rate for olaparib treatment of heavily pretreated ovarian cancer patients who have a germline BRCA mutation.”

Chiou explained that the research team was concerned about their preclinical discovery that olaparib pretreatment before carboplatin led to decreased carboplatin-induced DNA damage in tumor cells carrying BRCA1 mutations and launched the phase I clinical trial to explore whether there was an optimal way to deliver the olaparib/carboplatin drug combination.

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The researchers enrolled 59 patients with recurrent women's cancers in the clinical trial. Among the patients, 47 had ovarian cancer, 10 had triple-negative breast cancer, one had a uterine carcinosarcoma, and one had endometrial cancer. Twenty-six of the ovarian cancer patients and four of the triple-negative breast cancer patients had a germline BRCA mutation.

The patients were randomized to one of two treatment arms: in arm A, patients received olaparib before carboplatin in cycle one and carboplatin before olaparib in cycle two; in arm B, patients received carboplatin before olaparib in cycle one and olaparib before carboplatin in cycle two. From cycle three, patients received the same treatment regimen. Toxicity was analyzed at the end of every treatment cycle and response at the end of every two cycles.

Intra-patient and inter-cohort comparisons showed no significant differences in the frequency of grade 3/4 adverse events. The most common grade 3/4 adverse events were neutropenia and anemia.

According to Chiou, the most updated results show that olaparib given for seven days, in combination with carboplatin given once every 21 days, demonstrated preliminary clinical activity in heavily pretreated patients with breast and ovarian cancer. Among 54 patients the researchers observed one complete response, which lasted for 23 months in a woman with triple-negative breast cancer, and 24 partial responses, 20 in women with ovarian cancer and four in women with triple-negative breast cancer.

“We currently have two patients still on study,” Chiou added. “One woman has had a partial response that has persisted more than 19 months and another woman who had stable disease documented at the initial time of abstract submission has since achieved a partial response and has been on the study for more than 12 months.

“I am excited to share these findings. This clinical trial is part of a larger body of clinical trials being done by the Women's Malignancies Branch at the National Cancer Institute,” Chiou continued. “Every day, my team is working hard to bring new ideas from the bench to the bedside for treatment of women with breast and ovarian cancer. There is more work to be done. This is just the beginning.”

This study was supported by funds from the intramural program of the National Cancer Institute, with funding to the Center for Cancer Research under an umbrella Cooperative Research and Development Agreement with AstraZeneca. Chiou was previously a recipient of the AACR-GlaxoSmithKline Outstanding Clinical Scholar award for research on PARP inhibitors in triple-negative breast cancer presented at the AACR Annual Meeting 2014. Chiou declares no conflicts of interest.

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Founded in 1907, the American Association for Cancer Research (AACR) is the world's oldest and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 35,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and cancer advocates residing in 101 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis, and treatment of cancer by annually convening more than 25 conferences and educational workshops, the largest of which is the AACR Annual Meeting with over 18,500 attendees. In addition, the AACR publishes eight prestigious, peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit www.AACR.org.

Abstract Number: 1458

Title: Pharmacokinetic/pharmacodynamic study of sequence specificity of the PARP inhibitor, olaparib (O) and carboplatin (C) in recurrent women's cancers (NCT01237067)

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Abstract Body:

Background: O/C are active in gBRCA1/2m+ or BRCA-like breast and ovarian cancer (Br/OvCa). Our in vitro data suggest that pretreatment with O before C attenuates C-induced DNA double stranded breaks (DSBs) and cytotoxicity. We hypothesize O/C sequence may affect DNA DSBs and toxicity in pts.

Methods: Eligible pts had recurrent women's cancers, normal end-organ function, and evaluable disease. Pts were randomized to arm A or B for intra-pt and inter-cohort analysis of PK/PD endpoints.

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Treatment schedule arms				
	Cycle (cyc) 1	Cyc 2	Cyc 3-8	Cyc 9+
Arm A	O tablet 200mg bid d1-7⇒C AUC4 d8	C AUC4 d1⇒O tablet 200mg bid d2-8	O tablet 200mg bid d1-7, C AUC4 d1or2	maintenance O tablet 300mg bid
Arm B	C AUC4 d1⇒O tablet 200mg bid d2-8	O tablet 200mg bid d1-7 ⇒C AUC4 d8		

21pts were required per arm for 80% power to determine one SD difference between arms. PBMCs were collected prior to and 24hrs after O or C on cyc 1&2 for comet DNA damage assay and PAR incorporation ELISA. Toxicity was evaluated q3 wks, and response q2 cyc by RECISTv1.1

Results: 59 women (age 59 [25-74]; 47 OvCa (26 gBRCAm+)/10 triple negative BrCa [TNBC; 4 gBRCAm+]/1 uterine carcinosarcoma/1 endometrial Ca) were treated. All had prior therapy (median 5[2-14]). Intra-pt comparisons of PD endpoints indicated O/C yields greater DNA DSBs than O or C alone (median fold change compared to baseline; 1.21+/- 0.30 SD v. 1.13 or 0.97 [arm A], 1.33 +/- 0.67 SD v. 1.02 or 1.04 [arm B], both p<0.05). Intra-pt and inter-cohort comparisons show no significant differences in DNA DSBs, PAR incorporation and frequencies of Gr3/4 AEs as a function of the order of the schedule. Gr3/4 AEs included neutropenia (22%), anemia (12%), thrombocytopenia (10%), and C hypersensitivity (3%). Responses (54pts) included 1 CR (2%, 23mo; TNBC) and 23 PR (43%, 9[5-15]mo; 20 OvCa/3 TNBC). gBRCAm+ pts had a higher response rate (RR; 1CR/19 PR) compared to BRCAwt/unknown (4 PR; 65% v. 17%, p<0.001).

Conclusions: Combination O/C induced greater DNA damage than single agents, consistent with the higher than expected RR. However, the O/C sequence did not impact DNA damage, PAR incorporation or toxicity. O tablets 200mg bid x 7d with C AUC 4 q 21d is active and tolerable in recurrent women's cancers, especially for gBRCAm+ pts.