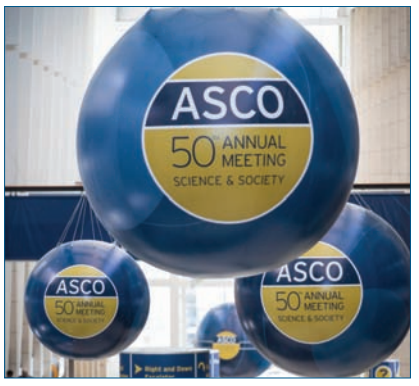
Recurrent Ovarian Cancer: PFS Doubles with Oral Non-Chemotherapy Combo

BY ROBERT H. CARLSON

CHICAGO—Exciting things are happening in ovarian cancer treatment. New drugs are changing survival for patients, and treatments are increasingly refined as clinicians gain understanding of how to place novel drugs into current chemotherapy options.

As discussed here in various sessions at the American Society of Clinical Oncology Annual Meeting, tyrosine kinase inhibitors (TKIs) and PARP (poly [ADP-ribose] polymerase) inhibitors are among the most promising of the new classes of drug, showing benefit in patients in both early and advanced stages of the disease.



A trial of the two drugs combined was discussed in an oral abstract session on gynecologic cancer (***Abstract LBA5500***). The trial, comparing the combination of the oral anti-angiogenic TKI cediranib and the oral PARP inhibitor olaparib in treatment of women with recurrent platinum-sensitive high-grade serous or BRCA-related ovarian cancer, showed that progression-free survival was doubled compared with use of the PARP inhibitor alone.

In the Phase II trial, median progression-free survival was nine months for olaparib alone, versus 17.7 months for the combination, and, while both drugs are still investigational, experts speaking in the session said the results signal a revolution in ovarian cancer treatment.

"Many patients in my experience benefit from PARP inhibitors for a long time, some for a number of years, and that is very different from chemotherapy," said the co-chair of the session, Rebecca Sophie Kristeleit, MD, PhD, Senior Lecturer in Experimental Therapeutics and Consultant Medical Oncologist, University College London Cancer Institute. "If you are integrating chemotherapy with novel agents, the whole landscape of how a patient survives changes if the patient is on a drug for two years and is benefiting from it."

She noted that the TKI bevacizumab is effective in ovarian cancer and is licensed in Europe, so having another TKI option is potentially very important to patients who have been exposed to bevacizumab before, because they may have new sensitivities to a TKI-type approach for an antiangiogenic.

More options complicate management of the disease, she said, "but more options are always better than fewer."

The biggest challenge at the moment is defining subgroups effectively to focus the patients into the most appropriate therapy, she said. "What's very exciting is that this is a combination of two molecularly targeted agents with two different mechanisms, and this is in the absence of chemotherapy. This is a real step change in what we are doing."

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Study Details

Joyce F. Liu, MD, MPH, Instructor in Medical Oncology at Dana-Farber Cancer Institute, who presented the trial combining a PARP inhibitor and an anti-angiogenic agent, explained that preclinical studies had shown that the two classes of drugs may work synergistically in ovarian cancer. In the randomized, open-label Phase II trial, which was supported by the National Cancer Institute, 90 women were randomly assigned to receive olaparib in 400 mg capsules twice daily (46 patients), or olaparib at 200 mg twice daily plus cediranib at 30 mg daily (44 patients). Treatment continued until disease progression.

The women had no prior treatment with anti-angiogenic drugs in the setting of recurrent ovarian cancer or with PARP inhibitors.

The objective response rate was significantly improved in the combination arm: 47.8 percent in the olaparib arm (two complete responses and 21 partial responses) versus 79.6 percent for the combination (three complete responses and 33 partial responses).

Progression-free survival was the primary study endpoint, and median follow-up was 16.6 months.

Liu said the improvement in progression-free survival with the combination—nine months for olaparib alone versus 17.7 months for the combination—compares favorably with the eight to 13 months progression-free survival seen in previous trials of standard chemotherapy in platinum-sensitive patients.

Active When BRCA Status Unknown

The number of patients who were BRCA carriers in the study was equally distributed between the two treatment groups: 25 in the olaparib arm and 23 in the combination arm.

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Liu said that in prior trials, PARP inhibitors appear to have the most activity in women with either platinum-sensitive ovarian cancer or in patients with BRCA mutations in their tumors, but this trial showed only a trend in that direction.

Median progression-free survival was 16.5 months for olaparib alone versus 19.4 months for the combination in patients with platinum-sensitive or BRCA-mutated tumors. But in patients without a mutation or whose status was unknown, the difference was much more marked, with an increase in progression-free survival from 5.7 months on olaparib alone to 16.5 months for the PARP-inhibitor/antiangiogenic combination.

Liu said it might also be reasonable to explore whether the combination treatment is effective in women with platinum-resistant disease.

Weigh Toxicities against Survival Gains

Adverse events occurred more frequently in the combination arm, including hypertension, fatigue, and diarrhea, the last of which was managed with Imodium or Lomotil. The overall rate of grade 3/4 toxicity was seven percent for olaparib alone versus 70 percent for the patients receiving the combination.

And dose reductions were called for more often in the combination arm: in 24 percent (11 of 46) of patients in the olaparib-only arm versus 77 percent (34 of 44) of the combination arm. That in-

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FDA Approves MRI Contrast Agent for Improved Evaluation of Breast Cancer

The U.S. Food and Drug Administration has approved Gadavist (gadobutrol) injection for intravenous use with magnetic resonance imaging of the breast to assess the presence and extent of malignant breast disease.

"The Phase 3 GEMMA studies demonstrate that Gadavist-enhanced breast MRI provided a statistically significant improvement in the identification of the extent of breast cancer versus unenhanced MRI," principal investigator Gillian Newstead, MD, FACR, Clinical Director for the Section of Breast Imaging at the University of Chicago Medical Center, said in a news release.

The approval is based on priority review of two, identically designed, multicenter, Phase III studies (GEMMA-1 and GEMMA-2) conducted in 13 countries, which enrolled 787 patients with recently diagnosed breast cancer.

MRI images were analyzed by three independent radiologists who confirmed that Gadavist enhanced breast MRI-improved ability to assess the presence and extent of breast cancer when compared with images from unenhanced breast MRI. Gadavist-enhanced breast MRI demonstrated superior sensitivity (80% to 89%) to detect the presence and extent of malignant disease compared with unenhanced breast MRI (37% to 73%).

Gadavist, made by Bayer HealthCare, was first approved in the U.S. in 2011 for intravenous use in diagnostic MRI in adults and children (age two and older) to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system.

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cluded fatigue in 27 percent of patients receiving the combination versus 11 percent for olaparib alone; diarrhea at 23 percent versus none, respectively; and hypertension at 41 percent versus none.

At an ASCO news briefing highlighting promising new findings in targeted therapies, Don S. Dizon, MD, Director of the Oncology Sexual Health Clinic at Massachusetts General Hospital, speaking as an ASCO expert, noted that while the combination of cediranib plus olaparib resulted in a significantly higher response rate, it was at the expense of higher toxicity.

"Whether this response translates into gains in survival needs further follow up," he said.

In addition, he said, women with recurrent platinum-sensitive ovarian cancer are the patients most likely to benefit from surgical debulking, and surgery is still an option after treatment with these two non-chemotherapy agents. "If we are able to resect recurrent disease that is considered platinum sensitive, that will provide a survival advantage," he said, adding, though, that this has not been proven in a randomized trial.

Discussant Remarks

The Discussant for the study, Jonathan A. Ledermann, MD, Professor of Medical Oncology at University College London Cancer Institute, who was chief investigator for both the ICON 6 trial of cediranib and Study 19 of olaparib, said in his remarks that the combination of olaparib and cediranib "may herald the beginning of treatments that avoid chemotherapy in certain patients with recurrent ovarian cancer."

There is good rationale for combining the two drugs, he said, and the progression-free survival of 17.7 months is a significant improvement over what has been seen in major trials to date—11.1 months in ICON 6 with cediranib, 12.4 in the OCEANS trial with bevacizumab, and 11.3 in the CALYPSO trial.

Ledermann said he was particularly intrigued by the large difference in this new trial in progression-free survival in patients with wild-type BRCA or in whom BRCA was unknown.

Progression-free survival for patients with wild-type or unknown BRCA status was 5.7 months for olaparib alone versus 16.5 months for the combination, compared with women with either platinum-sensitive ovarian cancer or known BRCA mutations for whom the difference was 16.5 versus 19.4 months, respectively.

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Quality of life must be considered in these patients, Lederman said, pointing to the 77 percent rate of dose reduction, although it was difficult to assign this to one or the other study regimen. And "quite remarkably," these outcomes were achieved without chemotherapy, he said.

"Can olaparib-cediranib actually replace chemotherapy? That should certainly be considered."

But another question to be addressed is whether the addition of olaparib maintenance therapy to platinum-based chemotherapy plus cediranib could improve patient outcome—"that is a trial worth doing," he said.

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ASCO/Phil McCarten

JONATHAN LEDERMANN, MD: "For anti-angiogenesis treatments to be truly useful, a suitable biomarker has to be developed—as a predictive biomarker, VEGF levels are very disappointing."

Redefine 'Platinum Sensitive'

While giving her perspective on the PARP inhibitor trial, which included only patients with platinum-sensitive disease, Kristeleit said it may be time to replace the terms "platinum sensitive," "platinum resistant," and "platinum refractory."

"These are fairly old terms that were rightly used when they were first identified years ago, but today we are understanding that this is a biological continuum," she said. In practice, platinum-based combinations are still used in some ovarian cancers that are deemed platinum-resistant. "I believe these new drugs will be used in all settings of ovarian cancer [platinum sensitive, platinum resistant, etc.], and in other gynecological cancers as well, but in different settings and different combinations."

Strategies for placing novel drugs into current platinum-based chemotherapy options are evolving, Kristeleit continued. "It may be possible to use them sequentially, intermittently exposing patients to platinum-based chemotherapy followed by maintenance with one targeted agent and then another, and using chemotherapy again further down the line—"that may mean you'll maintain platinum sensitivity longer."

> "What's very exciting is that this is a combination of two molecularly targeted agents with two different mechanisms, and this is in the absence of chemotherapy—a real step change in what we are doing."