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Recurrent Ovarian Cancer: More Than One Way to Inhibit Angiogenesis

BY ROBERT H. CARLSON

NEW YORK CITY—Phase III trials have shown that the anti-VEGF agent bevacizumab has an important role in treating advanced ovarian cancer. But VEGF is not the only driver of angiogenesis, and targeting VEGF is not the only way to inhibit angiogenesis in this disease.

Antiangiogenic agents with different mechanisms of action include the multi-targeted tyrosine kinase inhibitors that target VEGFR, angiopoietin antagonists, PARP inhibitors, and molecules that target the folate receptor.

"We've been hypnotized a bit that [angiogenesis] is about VEGF, because there are other drivers," said Bradley Monk, MD, Professor in the Division of Gynecologic Oncology at Creighton University School of Medicine at St. Joseph's Hospital and Medical Center in Phoenix. Dr. Monk discussed new agents in ovarian cancer in a presentation here at the Chemotherapy Foundation Symposium.

Dr. Monk said he has a degree of optimism about treating ovarian cancer, but that is countered by the large number of pathways involved in ovarian cancer and the limited number of drugs approved for it by the Food and Drug Administration.

"Ovarian cancer is one of the deadliest solid tumors, yet there is no FDA-approved targeted agent, and no new drugs at all have been approved by the FDA for ovarian cancer in more than five years," he said.

Folate an Important Target

Folate is a promising target in ovarian cancer, but not through the mechanism by which folate is taken into the cell. The target is the folate receptor, which Dr. Monk said is an emergency pathway that is overexpressed in ovarian cancer. This molecule can be targeted with a humanized antibody that induces antibody-dependent cytotoxicity and complement cytotoxicity.

The antifolate farletuzumab (MORab-003) has shown antitumor activity and favorable toxicity in Phase I and II trials in first relapse of platinum-sensitive ovarian cancer, Dr. Monk said.

"This is an exciting approach, because [in a Phase II trial) there was a 90% normalization in CA-125 and a 70% response rate."

Folate-linked drugs can be attached to a wide variety of compounds, Dr. Monk said, including chemotherapy, immunotherapy, gene therapy imaging agents, liposomes, nano-particles, and proteins.

And because folate is small compared with antibody, folate-linked drugs can achieve superior tumor penetration, he said.

EC-145, a conjugate that selectively binds to cells that overexpress the folate receptor, is in an ongoing Phase II

BRADLEY MONK, MD, noted that two large randomized Phase III trials with AMG-386 plus paclitaxel (TRINOVA-1) and with pegylated liposomal doxorubicin (TRINOVA-2) are ongoing, and a front-line trial (TRINOVA-3) is planned.

randomized trial combined with pegylated liposomal doxorubicin. Dr. Monk said this combination yielded better disease control in second- or third-line treatment than does pegylated liposomal doxorubicin alone.

Because there are no predominant driving mutations of any importance in ovarian cancer, Dr. Monk said researchers

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→MAMMOGRAMS

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Phil Hunnicky/Georgetown

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Not the Case, Though, with Non-Radiologists

Breast cancer specialists who are not radiologists, though, were a bit more tempered.

Screening recommendations are aimed at the general population, not the individual patient, noted Claudine Isaacs, MD, Director of the Clinical Breast Cancer Program at Georgetown's Lombardi Comprehensive Cancer Center.

Still, "while there is general agreement on the benefits of mammography in women between the ages of 40 and 50 with a family history of this disease, this study suggests that mammography is equally beneficial in those without a positive family history," she said.

Edith A. Perez, MD, Director of the Breast Cancer Program and Professor of Medicine in the Division of Hematology/Oncology at the Mayo Clinic in Jacksonville, FL, said, "An overall goal of screening in this decade is to determine whether there are tools to improve selection of patient's who should undergo screening mammography.

"One of the factors that has been considered is whether ascertainment of family history would be useful," she said.

EDITH A. PEREZ, MD: "This new and relevant data set appears to negate the impact of assessing family history as a method to optimize selection of patients for mammography."

"However, this new and relevant data set appears to negate the impact of assessing family history—[especially] first-generation history—as a method to optimize selection of patients for mammography."