[News * Analysis * Commentary * Controversy]

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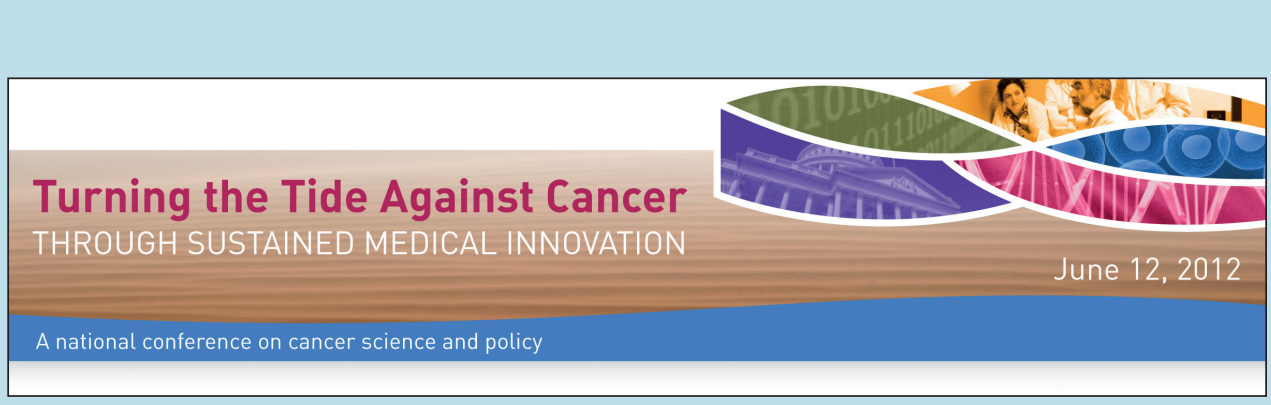
Lippincott Williams & Wilkins Wolters Kluwer Health

White Paper Predicts: With Continued, Specific Efforts, Cancer Can Become Chronic & Manageable by 2022

BY PEGGY EASTMAN

That was the conclusion of the document by representatives from AACR, the Personalized Medicine Coalition, and Feinstein Kean Healthcare, distributed at this conference. Read what John Mendelsohn, Siddartha Mukherjee, Laura Esserman, and others had to say.

Page 22

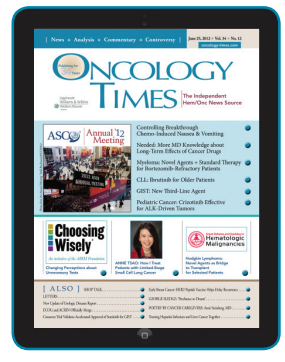


Key Takeaways!

ASCO Annual '12 Meeting

- Personal Picks—ASCO President SANDRA SWAIN
- Hematologic (ALL, CML, CLL, Plasma Cell Dyscrasias)—RAVI VIJ
- GU–WALTER STADLER
- Lung Cancer – RENALDO MARTINS
- Plus: JOE SIMONE on ASCO Past, Present, & Future

Starting on p. 7



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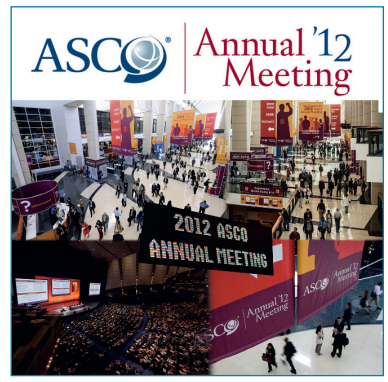
[ALSO]

PERIODICALS

Platinum-Resistant Ovarian Cancer: Bevacizumab Extends PFS

But, Says Discussant: Stop Phase III Trials of Molecularly Targeted Agents in Ovarian Cancer!

BY ROBERT H. CARLSON



CHICAGO—For patients with platinum-resistant recurrent ovarian cancer, a combination of bevacizumab and standard-of-care chemotherapy cuts the risk of disease progression almost in half compared with chemotherapy alone. This and other outcomes from the randomized Phase III AURELIA trial from France were described here at the American Society of Clinical Oncology Annual Meeting (***Abstract LBA5002***).

But in a provocative turn, the Discussant for the study recommended stopping Phase III trials of molecularly targeted agents in ovarian cancer because there are no large groups of homogeneously genomically defined patients with serous cancer, and because there is no strong predictive biomarker in epithelial ovarian cancer.

New Standard Option

"Bevacizumab combined with chemotherapy should be considered a new standard option in platinum-resistant ovarian cancer," said Eric Pujade-Lauraine, MD, PhD, who presented the data on behalf of the AURELIA investigators and the Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO).

He said the results are very significant because the addition of bevacizumab offers a new treatment option for the 20 percent of women who have primary platinum-resistant disease, as well as those whose disease later becomes platinum resistant.

Pujade-Lauraine, Professor of Medicine at Université Paris Descartes, said AURELIA is the first randomized Phase III trial in platinum-resistant ovarian cancer to demonstrate benefit with biologic therapy and benefit with a combination regimen vs. monotherapy.

He noted that bevacizumab efficacy with platinum in front-line therapy has already been demonstrated in the Gynecologic Oncology Group 0218 and

continued on page 29

→EMILIA

continued from page 26

since effective palliative treatment of metastatic breast cancer has rarely been associated with substantially improved survival in the refractory setting. The results of this trial suggest that median survival will be significantly prolonged in women treated with T-DM1."

He said more work will be needed to determine if the benefits of T-DM1-based therapy are restricted to patients with HER-2 gene amplification, or if patients with lesser degrees of HER-2 overexpression can be effectively treated as well.

"The utility of T-DM1 in trastuzumab-resistant disease raises obvious questions about the ultimate role of trastuzumab that justify thoughtful clinical investigations that are underway," he concluded.

Trastuzumab has again proved its versatility in breast cancer, this time in combination with the powerful cytotoxic emtansine to treat women with HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

'New Type of Precision Medicine'

Asked for a comment about the study, Andrew Seidman, MD, a breast cancer researcher and attending physician at Memorial Sloan-Kettering Cancer Center, called the results "welcome news."

Seidman, also Professor of Medicine at Weill-Cornell Medical College, said Blackwell's overview of the EMILIA trial highlights one of the most important studies in breast cancer at this meeting—"a new type of precision medicine for breast cancer that is using an old friend, trastuzumab, as a delivery vehicle for a potent cytotoxic agent."

"The immunoconjugate, T-DM1, is in a sense a smart bomb," he said. "It's a way to deliver cytotoxic chemotherapy where you want it to be, and largely, but not completely, avoid post-toxicity."

Speaking of his own experience with T-DM1 at Memorial Sloan-Kettering Cancer Center, ANDREW SEIDMAN, MD, said, "It is kind and gentle. This is not your grandmother's chemotherapy."

He said it is very gratifying to see that this drug outperformed two oral agents given in combination, capecitabine and lapatinib, a standard treatment. "When I say outperformed, it controlled breast cancer for a longer period of time. At first glance, this will likely translate to an overall survival advantage with longer follow-up."

Seidman said he has personal experience with T-DM1 in clinical trials at Memorial Sloan-Kettering: "It is kind and gentle. This is not your grandmother's chemotherapy."

He said he has heard that T-DM1 may be approved by the FDA sometime in 2012.

Also Important: Pertuzumab

Seidman added that it is important to look at a study about pertuzumab, another HER2-targeted agent also developed by Genentech and Roche—the MARIANNE trial of T-DMI and pertuzumab (***clinicaltrials.gov/ct2/show/NCT01120184***).

"The MARIANNE Phase III trial results are awaited to define a possible role for the combination of T-DM1 and pertuzumab as first-line combination therapy of HER2 metastatic breast cancer, " he said.

"Pertuzumab may actually enter our clinics and be used commercially even before TDM-1. So in a sense we have an 'embarrassment of riches' right now for HER-2-positive breast cancers."

He noted that researchers are refining targeted therapy by finding new targets and developing new molecules to hit those targets, by better profiling patients with gene signatures, and finding combination therapies for dual inhibition—"We're also finding that cancer cells, as they have been for many years, are often smarter than the doctors who treat them."

'Old Friend'

Both Dr. Blackwell in her presentation and Dr. Seidman in his interview called trastuzumab "an old friend." In an e-mail exchange, Seidman explained:

"Trastuzumab is indeed an old friend. Since approximately 1999 it has been prolonging survival for women with HER-driven metastatic breast cancer, and doing the same for women with earlier stage disease as adjuvant therapy since 2005. Friends treat us with kindness, and other than uncommon cardiac events, most would agree that it is a kind and gentle agent."

→AURELIA

continued from page 28

ICON7 studies, and efficacy in relapsed, platinum-sensitive disease was demonstrated in the OCEANS study.

Standard therapy for recurrent platinum-resistant disease is single-agent chemotherapy. "Bevacizumab is an anti-VEGF antibody and it is effective in ovarian cancer because that is a highly VEGF-driven disease," he said.

Women eligible for inclusion in the study had to have ovarian cancer that progressed within six months of completing at least four cycles of platinum-based therapy and to have had no history of bowel complications.

Chemotherapies in the combination were paclitaxel, pegylated liposomal doxorubicin, or topotecan. A total of 361 women were randomly assigned to receive standard chemotherapy alone (182 patients) or in combination with bevacizumab (179) until disease progression or unacceptable toxicity. Those in the control arm could cross over to bevacizumab monotherapy at disease progression.

Robert H. Carlson

ERIC PUJADE-LAURAINE, MD, PHD: "Bevacizumab is an anti-VEGF antibody and it is effective in ovarian cancer because that is a highly VEGF-driven disease."

Median follow-up was 13.5 months for women receiving standard chemotherapy and 13 months for the bevacizumab group.

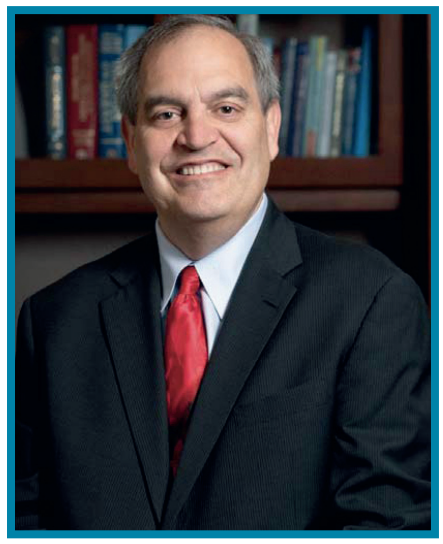
The principal finding was that median progression-free survival was 3.4 months for patients receiving standard chemotherapy alone vs. 6.7 months for those receiving bevacizumab, with a hazard ratio of 0.48.

The combination improved PFS regardless of age, the relapse-free interval, the extent of disease, the presence of ascites, or the type of chemotherapy administered, Pujade-Lauraine reported.

The 12.6 percent response rate in the standard-chemotherapy group was about what was expected in this patient population, compared with the significant improvement response rate in the bevacizumab-treated group, he said.

Toxicity Profiles

He said the toxicity profile of bevacizumab was similar to that seen in previous trials:



MICHAEL SEIDEN, MD, PHD: "The genomics of serous cancer argue against Phase III trials….In addition, there is no strong predictive biomarker—not even a good mediocre predictive biomarker—in epithelial ovarian cancer."

hypertension grade 2 and above was more frequent in the bevacizumab arm, 20.1 percent vs. 6.6 percent; proteinuria grade 2 and above was also more frequent in the bevacizumab-treated group—10.6 vs. 0.6 percent.

The rates of fatigue, abdominal pain, vomiting, and dyspnea were lower in the bevacizumab group. As expected, peripheral sensory neuropathy and hand-foot syndrome of at least Grade 3 was higher in the bevacizumab arm. Pujade-Lauraine speculated that this was perhaps because more patients were responding and received more chemotherapy.

From past experience with bevacizumab the investigators were concerned about intestinal perforation, he said. In this study the Grade 2 and above perforation rates were 1.7 percent for bevacizumab and none with chemotherapy alone. Grade 2 and above fistula/abscess occurred in 2.2 percent of the bevacizumab patients vs. none in the chemotherapy-alone arm.

But, he added, patients at high risk of GI perforation were excluded from the study based on a history of bowel obstruction or abdominal fistula or clinical or radiological evidence of rectosigmoid involvement.

He noted in an interview that he warns colleagues not to use the new bevacizumab-chemotherapy regimen in such patients.

Bevacizumab is made by Genentech-Roche. The majority of AURELIA investigators, including Dr. Pujade-Lauraine, disclosed consultant or advisory roles or research funding from Roche Diagnostics.

Discussant: Radical Suggestion

The Discussant for the study, Michael Seiden, MD, PhD, President and Chief Executive Officer of Fox Chase Cancer Center, made a radical suggestion: In this time of rigorous cost constraints, he said, researchers should stop all randomized Phase III trials of molecularly targeted agents in ovarian cancer.

Successful Phase III trials of targeted agents require enrolling large groups of patients with similar molecular characteristics. But "the genomic data in ovarian cancer are overwhelming that there are not large groups, not even medium-size groups, of homogeneously genomically defined patients within the most common category, serous cancer," he said. "The genomics of serous cancer argues against Phase III trials."

In addition, he said, essentially every successful Phase III or randomized Phase II study that has led to FDA approval of a molecularly targeted drug has had an undeniably powerful biomarker, such as HER-2 amplification, BCR-ABL translocation, or PFL-RAR translocation. "But there is no strong predictive biomarker—not even a good mediocre predictive biomarker—in epithelial ovarian cancer," he said.

Seiden speculated that it would take "deep sequencing" of DNA from 10,000 patients with a single histologic subtype of ovarian cancer to find even a small group of genomically homogeneous patients. "Would it be reasonable to require that all trials of molecular targeted agents, regardless of what the agent is, first be required to submit the full genomics of patients entering clinical trial?" he asked. "With the plummeting costs of genomic sequencing, this wouldn't add a dramatic amount of dollars to the cost of clinical trials in the not too distant future."

He went even further, suggesting that insurers or the Centers for Medicare & Medicaid Services shouldn't pay for clinical care of patients with epithelial ovarian cancer until the genome of the patient has been submitted.

"We should consider redistributing some of our research investment more broadly towards prevention, immunotherapy and the biology that underpins tumor initiation," he said.

"Strict inclusion criteria minimized the incidence of bevacizumab adverse events. This is the first Phase III trial in platinum-resistant ovarian cancer to show benefit with a targeted therapy and improved outcome with a combination versus monotherapy."