

Trastuzumab Trials Steal Show at ASCO Meeting

Early analyses of three phase III randomized controlled trials provide solid evidence that trastuzumab (Herceptin) increases progression-free survival, time to first distant recurrence, and overall survival in women with localized invasive breast cancer. The monoclonal antibody was approved by the U.S. Food and Drug Administration in 1998 for the treatment of metastatic breast cancer in women whose tumors overexpress the HER-2 protein.

Two studies run by U.S. cooperative groups, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and the North Central Cancer Treatment Group (NCCTG) N9831, were stopped early after a combined interim analysis showed that they had met their primary endpoint of increased disease-free survival. A third study, the Herceptin Adjuvant Trial (HERA), run by the Breast International Group, is still ongoing, but data from the first scheduled interim analysis were also positive.

The trial data were presented during a special symposium at the annual meeting of the American Society of Clinical Oncology (ASCO) last month in Orlando. At the close of the session, George W. Sledge Jr., M.D., of the Walther Cancer Center at Indiana University in Indianapolis, and the discussant for the three trials, said in an interview, "I have never seen anything like this in 25 years of breast cancer research."

Melding Trials

The designs of the two U.S. studies were similar; both included women with HER-2–positive locally invasive breast cancer that had been treated by lumpectomy or mastectomy and axillary dissection. Both trials compared the efficacy of doxorubicin and cyclophosphamide followed by paclitaxel either with or without concurrent trastuzumab. (See graphic, p. 871.) The NCCTG trial included a third arm that tested sequential

administration of trastuzumab—patients started on the drug after the completion of 12 weeks of paclitaxel.

With the agreement of the National Cancer Institute's Cancer Therapy Evaluation Program (CTEP), the investigators from both trials performed a combined analysis of the two studies. (The sequential trastuzumab arm was not included in the combined analysis.)



George W. Sledge Jr.

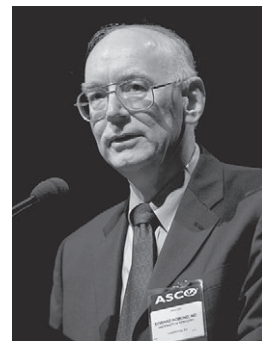
CTEP had stipulated that if the first interim analysis showed a specific statistically significant improvement in disease-free survival in the trastuzumab arms, the trials would be halted. Indeed, the trials were closed on the basis of the early analysis, although both trials had completed enrollment.

After a median follow-up of 2.0 years (2.4 years in the NSABP trial and 1.5 years in the NCCTG trial), 8.0% of women in the trastuzumab arm had had a recurrence, compared with 15.5% of women in the control arm. Disease-free survival was 75% and 87% at 3 years in the control and trastuzumab arms, respectively, and 67% and 85% at 4 years. (Sledge cautioned, however, that the confidence intervals on the survival estimates are quite wide given the short median follow-up time.)

The result was highly statistically significant for all women regardless of age, hormone receptor status, tumor size, number of positive nodes, and the study in which they participated (B-31 or N9831). In addition, the data from the individual trials mirror each other, said Edward H. Romond, M.D., of the University of Kentucky in Lexington, who led the NSABP trial and presented the data.

The time to first distant recurrence was significantly improved in the combined analysis, with 11.5% of women in the control arm developing distant disease versus 5.7% in the trastuzumab arm, a highly statistically significant reduction in risk of recurrence. "Surprisingly, even though the median follow-up is only 2 years, the *P* value is significant for overall survival," Romond said of the fact that there were 92 deaths (5.5%) in the control arm compared with 62 (3.7%) in the treatment arm.

At the time of the combined analysis, the NCCTG trial had not yet reached its predetermined parameters for a comparison between the control arm and the concurrent therapy arm or between the concurrent and sequential arms. Despite that, the data safety monitoring board for the trial requested an unplanned interim analysis of the sequential and concurrent



Edward H. Romond

arms of the trial to assist in patient management decisions.

Looking at the data from the NCCTG trial alone, the researchers found no significant difference in

disease-free survival between chemotherapy alone and the sequential therapy arm. However, there was a statistically significant improvement in disease-free survival in the concurrent trastuzumab arm when it was compared with the sequential therapy arm.

The HERA Trial

Martine J. Piccart-Gebhart, M.D., Ph.D., head of the Medicine Department of the Jules Bordet Institute in Brussels and lead investigator of the HERA trial, presented the trial's first interim results.

The European-based trial is comparing 1 and 2 years of trastuzumab with a control group in women who had already completed adjuvant chemotherapy.

The current data are from the first planned interim analysis, but only data from the 1-year trial arm and the control arm were released by the data monitoring committee. The 2-year disease-free survival was 77.4% in the control arm and 85.8% in the treatment arm.

There was also an improvement in relapse-free survival in the treatment arm and a similar improvement in distant disease-free survival in the trastuzumab group compared with the control group. Overall survival showed a trend toward improvement but is not at this time statistically different.

Cardiac Toxicity

A major concern in designing all three trials is the cardiac toxicity associated with trastuzumab. For that reason, all of the trials required strict cardiac assessment prior to enrollment and monitoring at regular intervals during therapy. Despite these precautions, there were increased cardiac incidents in all of the treatment arms compared with the control arms.

In the HERA trial, 2.2% of women in the control arm showed a greater than 10-point drop in left ventricle ejection fraction (LVEF) to below an overall LVEF of 50%, compared with 7.1% in the treatment arm. In addition, none of the women in the control arm had symptomatic evidence of cardiac heart failure without evidence of LVEF changes, whereas 0.5% of the women in the treatment arm did. There was one cardiac death in the control arm.

In the B-31 trial, the rate of congestive heart failure was 0.6% in the control arm and 4.0% in the trastuzumab arm, and in N9831 it was 0.0% in the control arm, 2.2% in the sequential trastuzumab arm, and 3.3% in the concurrent trastuzumab arm.

“The fly in the ointment is that Herceptin plus chemotherapy produces cardiac toxicity,” said Gabriel N. Hortobagyi, M.D., chairman of the Department of Breast Medical Oncology at the University of Texas M. D. Anderson

Trials of Trastuzumab as Adjuvant Therapy for Breast Cancer

NSABP B-31:

Arm 1: doxorubicin/cyclophosphamide (AC) q 3 weeks x 4, paclitaxel q 3 weeks x 4
Arm 2: AC q 3 weeks x 4, paclitaxel q 3 weeks x 4 + weekly trastuzumab for 1 year

NCCTG N9831:

Arm A: AC q 3 weeks x 4, weekly paclitaxel x 12
Arm B: AC q 3 weeks x 4, weekly paclitaxel x 12, weekly trastuzumab for 1 year
Arm C: AC q 3 weeks x 4, weekly paclitaxel + trastuzumab x 12, weekly trastuzumab x 40

HERA Trial:

Arm 1: Standard therapy, trastuzumab q 3 weeks for 1 year
Arm 2: Standard therapy, trastuzumab q 3 weeks for 2 years
Arm 3: Standard therapy

Cancer Center in Houston, though the problem may be less obvious in sequential therapies. However, women with cardiac issues were excluded from all of these trials, so the latest data are a low estimate of the problem, he said.

Importantly, after 6 months of terminating or completing trastuzumab



Edith A. Perez

therapy, a substantial proportion of these women were safely taken off their cardiac medicine, indicating that the toxicity may be reversible.

Experts cautioned that

long-term follow-up data will need to be collected to really know what this risk is.

Impact of Early Stoppage

The overwhelmingly positive data led to an early closing of the U.S. trials. Patients in the control arm are now allowed to cross over to trastuzumab therapy if they are within 6 months of completing their adjuvant chemotherapy.

“There is always concern when you close a trial early whether or not it is going to damage the overall survival and follow-up data,” said Sledge. “I don’t think that is going to be the case. Some of the secondary endpoints, especially with N9831, have very short follow-up—far shorter than its planned interim analysis. If there is a lot of crossover,

there is a possibility that it will pollute the results of the study.” That said, he noted that only 700 of the 3,300 women in the N9831 trial remain on chemotherapy, so the number who are eligible to cross over is not large.

Given the fact that CTEP approved the combined analysis, the expectation among breast cancer experts is that trastuzumab will be approved rapidly by the FDA for use in women with invasive local disease. “The FDA’s standard for adjuvant therapy has always been disease-free survival, and with two trials showing such striking improvements in disease-free survival, I would be highly surprised if this wasn’t rapidly approved,” said Sledge.

One of the striking results from the trials, said Sledge, is how quickly the women relapse and suffer distant recurrences without trastuzumab therapy. He said that was an indication of how aggressive these cancers are. “Biology has spoken, and we should listen,” Sledge said.

The optimal duration of trastuzumab therapy is still unknown, but for Edith A. Perez, M.D., of the Mayo Clinic in Jacksonville, Fla., who led the N9831 trial and presented the data at ASCO, the question is not immediately pressing. “We have enough information right now to improve the lives of so many women, we don’t have to wait for the answer to that one small question,” she said. “We can get that figured out in the next few years. But we have an answer today. We are really improving survival.”

—Rabiya S. Tuma