Research To Practice: Adjuvant Trastuzumab

How have the recent dramatic findings of the adjuvant trastuzumab trials — NSABP-B-31, NCCTG-N9831, HERA and BCIRG 006 — altered the clinical practice of medical oncologists in the United States? In a post-ASCO survey of breast cancer investigators and medical oncologists, the overwhelming majority would now recommend adjuvant trastuzumab plus chemotherapy for patients with HER2-positive, node-positive and higher-risk, node-negative breast cancers. When asked about the sequential versus concurrent use of trastuzumab and chemotherapy, most oncologists stated they would utilize adjuvant trastuzumab following the completion of the anthracycline portion of the chemotherapy and concurrent with the taxane. Additionally, oncologists are commonly offering patients delayed adjuvant trastuzumab, particularly in patients with node-positive tumors, within a year of completing adjuvant chemotherapy. MUGA scans are the most common approach to monitoring cardiac effects of therapy, and trastuzumab is much less frequently recommended for patients in their seventies and eighties, perhaps because of cardiac concerns. This survey was done prior to the press release of BCIRG data on trial 006, and it will be interesting to evaluate how this data set — presented at the San Antonio meeting in December — will impact selection of chemotherapy regimens, including the choice of paclitaxel versus docetaxel and the use of TCH (docetaxel/carboplatin/trastuzumab).

CLINICAL USE OF ADJUVANT TRASTUZUMAB

What adjuvant therapy would you recommend for a 55-year-old woman in average health with an ER/PR-negative, HER2-positive (confirmed by FISH), Grade II tumor (tumor size and nodal status as indicated)?

	1.2-cm, negative nodes		2.4-cm, negative nodes		1.2-cm, 3 positive nodes	
Chemotherapy alone	20%	30%	2%	14%	—	6%
Trastuzumab + chemotherapy	78%	70%	98%	86%	100%	94%
AC	9%	12%	6%	14%	—	—
AC → paclitaxel	56%	40%	79%	48%	82%	68%
TAC	2%	—	—	4%	—	10%
FAC/ FEC x 6	—	6%	—	4%	—	—
AC → docetaxel	7%	12%	9%	16%	14%	16%
Other	4%	—	4%	—	4%	—

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

DELAYED ADJUVANT TRASTUZUMAB

The patient is a 55-year-old woman who receives adjuvant AC → paclitaxel for a 2.4-cm, ER/PR-negative, HER2-positive, Grade II tumor (node status specified below). Would you recommend adjuvant trastuzumab at each of the following time points?

	Node-negative		3 positive nodes		10 positive nodes	
Six months after completion of chemotherapy	76%	58%	96%	82%	96%	84%
One year after completion of chemotherapy	50%	32%	70%	54%	82%	58%
Two years after completion of chemotherapy	2%	8%	14%	14%	36%	38%
Four years after completion of chemotherapy	—	4%	5%	8%	9%	22%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

CLINICAL USE OF ADJUVANT TRASTUZUMAB

In which type of patients with HER2-positive disease have you utilized or do you plan to utilize adjuvant trastuzumab?

In most or all node-positive patients	7%	22%
In most or all node-positive and high-risk, node-negative patients	91%	58%
In some node-positive patients	—	4%
In some node-positive and high-risk, node-negative patients	2%	16%

Would you recommend adjuvant trastuzumab for a patient who is in average health with a 1.2-cm, ER/PR-positive, HER2-positive, Grade II tumor with three positive nodes?

	Age 35		Age 55		Age 75		Age 85	
Yes	100%	90%	100%	90%	84%	66%	31%	38%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

SEQUENCING OF ADJUVANT TRASTUZUMAB

In general, which of the following best describes how you utilize adjuvant trastuzumab?

Sequentially, after the completion of all adjuvant chemotherapy	4%	20%
Concurrently, with all chemotherapy	—	20%
Sequentially, after the completion of anthracycline portion of chemotherapy but concurrent with taxane	96%	60%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

DEFINING HER2 POSITIVITY

What documentation of HER2 positivity do you require to use adjuvant trastuzumab?

FISH+	36%	34%
IHC 3+	—	4%
Both FISH+ and IHC 3+	9%	12%
Either FISH+ or IHC 3+	55%	50%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

OVERVIEW OF NSABP-B-31, NCCTG-N9831 AND HERA

As a result of the data presented at ASCO in 2005, trastuzumab has now become a standard of care in the adjuvant setting for HER2-positive breast cancer. We saw a stunning validation of the biology of HER2 and the concept that we could diminish the likelihood of recurrence and improve overall survival through the use of targeted therapy. We saw that by two years after randomization, one quarter of the patients in the control arm had relapsed.

In the joint analysis of NCCTG-N9831 and NSABP-B-31, around 25 percent had relapsed by approximately three years. This is a bad disease, and partly because of that, we see a high event rate early in these trials.

A striking benefit was seen with trastuzumab, including a survival benefit with a median follow-up of just two years. That is unprecedented in any adjuvant trial. In the HERA trial, all the patients received trastuzumab after rather than concurrent with chemotherapy, and those data were positive with an impressive 45 percent reduction in hazard rate.

— *George W Sledge Jr, MD.* Breast Cancer Update *2005 (6)*

NCCTG-N9831: CARDIAC SAFETY OF ADJUVANT TRASTUZUMAB

Although our trial demonstrated that clinical cardiac events are observed in patients receiving adjuvant trastuzumab, the difference is less than four percent compared to the control arm. The numbers are actually a bit lower than the numbers in NSABP-B-31 but statistically quite similar. At this point, we have not seen any difference in cardiac events between the two trastuzumab-containing arms. Not every patient has a reversal of their cardiac events, but most patients definitely improve not only in terms of the clinical symptomatology but also measurable left ventricular ejection fraction.

— *Edith A Perez, MD.* Breast Cancer Update *2005 (4)*

ADJUVANT TRASTUZUMAB IN NODE-NEGATIVE TUMORS

The HERA study included patients with node-negative disease as long as their tumors were greater than one centimeter. The NSABP trial had no patients with node-negative disease, and in the NCCTG study, patients with node-negative disease accounted for 14 percent of the total population but only six percent of the events. It's unlikely that the relative benefits of trastuzumab will differ in patients with node-negative versus node-positive disease. On the other hand, the absolute benefit will differ, because patients with node-negative disease, particularly with small tumors, have a lower risk of recurrence. In my mind, it's reasonable to consider trastuzumab for patients who were eligible for the studies. The group of women that I'm a little more cautious about are those with relatively small, ER-positive, node-negative breast cancer.

— *Eric P Winer, MD.* Breast Cancer Update *2005 (7)*

ROLE OF DELAYED ADJUVANT TRASTUZUMAB

The HERA trial suggests that administering trastuzumab after chemotherapy may be beneficial, so the question becomes: How long after chemotherapy will it be beneficial? In the case of estrogen receptors, we have two European randomized trials that evaluated the late use of tamoxifen in patients with estrogen receptor-positive breast cancer, and both were positive. Will we see a similar benefit with delayed adjuvant trastuzumab? It's a reasonable and important question, particularly for those patients in the control arms of N9831 and B-31 who are more than 18 months out from treatment. I'm not going to be dogmatic about this, but I do believe it's reasonable to discuss the option of trastuzumab with such patients.

— *George W Sledge Jr, MD.* Breast Cancer Update *2005 (6)*

SELECT PUBLICATIONS

Geyer CE Jr et al. **Cardiac safety analysis of the first stage of NSABP B-31, a randomized trial comparing the safety and efficacy of Adriamycin and cyclophosphamide (AC) followed by Taxol to that of AC followed by Taxol plus Herceptin in patients (Pts) with operable, node-positive (N+), HER-2 overexpressing breast cancer (HER2+BC).** San Antonio Breast Cancer Symposium 2003;Abstract 23.

Perez EA et al. **Interim cardiac safety analysis of NCCTG N9831 Intergroup adjuvant trastuzumab trial.** *Proc ASCO* 2005;Abstract 556.

Perez EA et al. **NCCTG N9831 May 2005 Update.** Presentation. ASCO 2005.

Perez EA et al. **HER2 testing by local, central, and reference laboratories in the NCCTG N9831 Intergroup Adjuvant Trial.** *Proc ASCO* 2004;Abstract 567.

Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353:1659-72.

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353:1673-84.