Unresolved Issues in the Use of Adjuvant Trastuzumab

28TH ANNUAL San Antonio Breast Cancer Symposium 14

Recent results of large randomized adjuvant trials of trastuzumab — NSABP-B-31, NCCTG-N9831, HERA and BCIRG 006 — have changed the management of HER2-positive early breast cancer, but a number of unresolved issues remain. Should adjuvant trastuzumab and chemotherapy be administered concurrently or sequentially? N9831 suggests that adjuvant trastuzumab concurrent with the taxane portion of chemotherapy improves disease-free survival more than sequential trastuzumab, but the HERA trial demonstrates benefit with adjuvant trastuzumab used after the completion of a variety of chemotherapy regimens. What is the optimal chemotherapy regimen in this setting? BCIRG 006 reported a low incidence of cardiac events for adjuvant trastuzumab in combination with a nonanthracycline-containing regimen, and initial efficacy results — announced in a press release and to be presented at this meeting — reveal a benefit for both AC → docetaxel/trastuzumab and docetaxel/carboplatin/trastuzumab, although the relative magnitude of benefit of these two arms is not clearly defined.

BCIRG 006 AND RANDOMIZED TRIALS OF ADJUVANT TRASTUZUMAB

Protocol ID	Eligibility	Randomization	Key issues evaluated
BCIRG 006	Node-positive or high risk node-negative HER2+ (FISH+)	AC → docetaxel AC → docetaxel + H → H (total one year H) Carboplatin + docetaxel + H → H (total one year H)	Nonanthracycline/H combination H concurrent with chemotherapy
NSABP-B-31	Node-positive HER2+ (IHC 3+ or FISH+)	AC → paclitaxel AC → paclitaxel + H (total one year H)	Combined analysis with N9831 Weekly or every three-week taxane with concurrent H
NCCTG-N9831	Node-positive or high risk node-negative HER2+ (IHC 3+ or FISH+)	AC → paclitaxel AC → paclitaxel → H (total one year H) AC → paclitaxel + H (total one year H)	Combined analysis with NSABP-B-31 Weekly taxane with concurrent or sequential H Effect of three-month delay between doxorubicin and H on cardiotoxicity
BIG 1-01, HERA	Node-positive or node-negative HER2+ (IHC 3+ or FISH+) Any chemotherapy ± XRT	Any chemotherapy → H (one year) Any chemotherapy → H (two years) Any chemotherapy	Duration of H Value of H versus no H following adjuvant chemotherapy

H = trastuzumab; AC = doxorubicin/cyclophosphamide; XRT = radiation therapy

SOURCES: NCI Physician Data Query, September 2005; Baselga J et al. *Semin Oncol* 2004;31(5 Suppl 10):51-7.

COMPARISON OF SEQUENTIAL AND CONCURRENT TRASTUZUMAB WITH CONTROL AC → T: NSABP-B-31/NCCTG-N9831

Parameter	Number of patients	Number of events	Percent improvement	*p*-value*
AC → T vs AC → T + H → H*				
Disease-free survival	2,379	395	52	3×10^{-12}
Overall survival	NR	154	33	0.015
AC → T vs AC → T → H†				
Disease-free survival	1,964	220	13	0.2936
Overall survival	NR	79	15	0.4752

* Joint analysis of NSABP-B-31/NCCTG-N9831; † NCCTG-N9831
AC = doxorubicin/cyclophosphamide; T = paclitaxel; H = trastuzumab; NR = not reported

SOURCE: Perez EA et al. Presentation. ASCO 2005;Abstract 556.

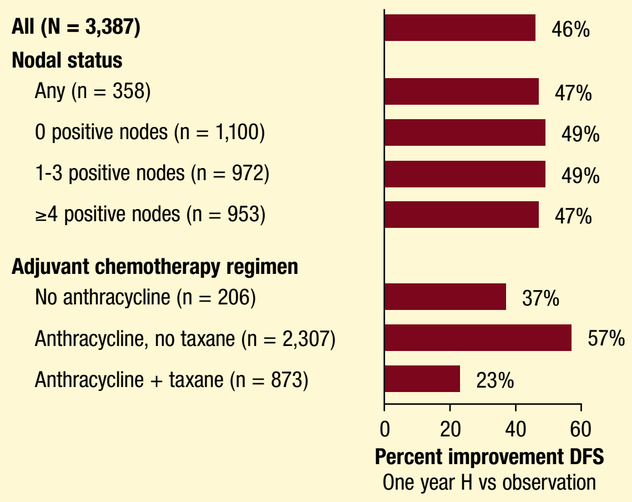
PROTOCOL-DEFINED CARDIAC EVENTS IN ADJUVANT TRASTUZUMAB TRIALS

Trial	Arm of study	Protocol-defined cardiac event rate*
BCIRG 006[1]	AC → D AC → DH CDH	1.2% 2.3% 1.2%
NSABP-B-31[2]	AC → TH AC → T	4.1% 0.8%
NCCTG-N9831[3]	AC → T AC → T → H AC → TH → H	0% 2.2% 3.3%
BIG 1-01, HERA[4]	Observation One year H	2.33% 8.81%

* Note that the definition of cardiac events varied between protocols.
AC = doxorubicin/cyclophosphamide; D = docetaxel; C = carboplatin
T = paclitaxel; H = trastuzumab

SOURCES: [1] Slamon DJ. NSABP Annual Meeting Satellite Symposium 2005. [2] Romond EH et al. *N Engl J Med* 2005;353:1673-84. [3] Perez EA et al. NCCTG N9831 May 2005 Update. Presentation. ASCO 2005;Abstract 556; [4] Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353:1659-72.

HERA TRIAL: RELATIVE REDUCTION IN RECURRENCE RATE



H = trastuzumab; DFS = disease-free survival

SOURCE: Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353:1659-72.

SELECT PUBLICATIONS

De Laurentiis M et al. **Targeting HER2 as a therapeutic strategy for breast cancer: A paradigmatic shift of drug development in oncology.** *Ann Oncol* 2005;16(Suppl 4):iv7-iv13.

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. **NCCTG N9831 May 2005 Update.** Presentation. ASCO 2005;Abstract 556.

Perez EA, Rodeheffer R. **Clinical cardiac tolerability of trastuzumab.** *J Clin Oncol* 2004;22(2):322-9.

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.

SELECTION OF CHEMOTHERAPY TO COMBINE WITH TRASTUZUMAB

In terms of nonprotocol chemotherapy/trastuzumab combinations, at this point, we try, whenever possible, to avoid anthracycline-containing regimens because of the known interaction in terms of cardiac safety of trastuzumab with anthracyclines, and we're not restricted to TCH when using a nonanthracycline regimen. There are a number of different drugs that interact very well with trastuzumab. However, we usually do use TCH in the adjuvant setting and will continue to do so until we see that it is inferior and the safety profile doesn't make up for that inferiority.

— Dennis J Slamon, MD, PhD.* Breast Cancer Update: *Special NSABP Edition 2005

CONCURRENT VERSUS SEQUENTIAL CHEMOTHERAPY/TRASTUZUMAB

The only test of concomitant versus sequential treatment was from N9831, and when you look at the curves presented and the comparisons, one can't remain neutral. The concomitant arm (with paclitaxel) has a hazard rate that falls in line with what we're seeing in the other trials, whereas the sequential arm is, peer wise, not statistically significant. It is not inappropriate for a medical oncologist to look at that data and be more impressed with concomitant therapy.

— Norman Wolmark, MD.* Breast Cancer Update: *Special NSABP Edition 2005

...Trials of adjuvant treatment have not determined whether the potentiation of the effect of chemotherapy by trastuzumab warrants concurrent chemotherapy and trastuzumab administration, or whether sequential treatments would be adequate. Similarly, the optimal duration of therapy may depend on how, precisely, trastuzumab works. As yet, there is no defined threshold of HER 2 gene amplification that predicts which HER2-positive tumors will respond to treatment. It seems probable that the greater the degree of gene amplification, the greater the potential benefit, but this possibility has not been tested clinically.

— Harold J Burstein MD, PhD.* N Engl J Med *2005;353(16):1652-4.

DURATION OF ADJUVANT TRASTUZUMAB: DELAYED IMPLEMENTATION OF ADJUVANT TRASTUZUMAB

The HERA trial is evaluating the duration question. In their trial, one arm has no trastuzumab, the second arm has one year and the third arm has two years of trastuzumab after chemotherapy. Because the data at this point address one year of trastuzumab, I believe that's the appropriate length of time.

As for the delayed implementation of trastuzumab in the Intergroup trial, they're supplying trastuzumab to the control group of patients who want to crossover out to one year of follow-up. There are theoretical arguments that a year is somewhat of an arbitrary length. The peak in relapses occurs at about two to three years, so I could see a rationale for treating beyond a year, particularly for patients at high risk with multiple nodes. However, that rationale is going beyond the data we have and is somewhat speculative.

— Peter M Ravdin, MD, PhD.* Breast Cancer Update *2005 (8)

TRASTUZUMAB SAFETY AND EFFICACY

We acknowledge that we have only an incomplete picture of the risks associated with trastuzumab. The risk of cardiotoxicity is currently low in our trial, but this could change with longer follow-up.

Another concern is that longer follow-up may show that trastuzumab is not effective in reducing the incidence of disease recurrence in the central nervous system. Brain metastases developed in approximately one third of the women receiving trastuzumab as treatment for advanced breast cancer, despite control of systemic disease. It is not clear whether such central nervous system metastases reflect aggressive disease or poor penetration of trastuzumab into the brain.

— Martine J Piccart-Gebhart, MD, PhD et al.* N Engl J Med *2005;353(16):1659-72.