Unresolved Issues in the Use of Adjuvant Trastuzumab

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. Another important research issue 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 — presented in San Antonio in December — reveal a benefit for both AC → docetaxel/trastuzumab and docetaxel/carboplatin/trastuzumab. Another important research issue is the optimal duration of adjuvant trastuzumab, which is being addressed in the HERA trial comparing one- to two-year treatment.

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
FinHer	Node-positive or high-risk node-negative	Docetaxel → FEC* Vinorelbine → FEC* *HER2-positive further randomized to H qwk x 9 weeks vs no H	Brief duration of H Effect of combination with potentially synergistic chemotherapy

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

SOURCES: Baselga J et al. *Semin Oncol* 2004;31(5 Suppl 10):51-7; Joensuu H et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 2; NCI Physician Data Query, September 2005.

SEQUENTIAL VERSUS 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

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

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

PROTOCOL-DEFINED CARDIAC EVENTS

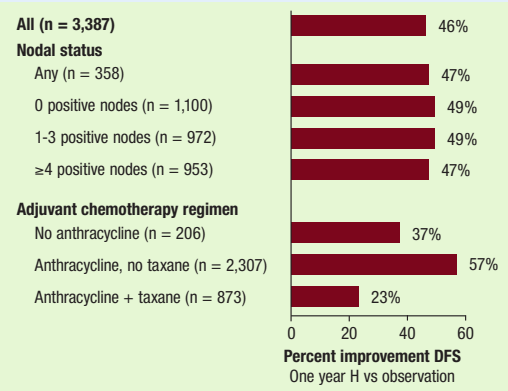
Trial	Arm of study	Protocol-defined cardiac event rate*
BCIRG 006[1]	AC → D AC → DH CDH	1% 2% 1%
NSABP-B-31[2]	AC → TH AC → T	4% 1%
NCCTG-N9831[3]	AC → T AC → T → H AC → TH → H	0% 2% 3%
BIG 1-01, HERA[4]	Observation One year H	2% 8%

AC = doxorubicin/cyclophosphamide; D = docetaxel; H = trastuzumab
C = carboplatin; T = paclitaxel

* Note that the definition of cardiac events varied between protocols

SOURCES: [1] Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 1. [2] Romond EH et al. *N Engl J Med* 2005;353:1673-84. [3] Perez EA et al. Presentation. ASCO 2005;Abstract 556. [4] Gelber RD. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 11.

HERA TRIAL: RELATIVE REDUCTION IN RECURRENCE RATE



DFS = disease-free survival; H = trastuzumab

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

SELECT PUBLICATIONS

Gelber RD on behalf of the HERA Study Team. **Trastuzumab (Herceptin) following adjuvant chemotherapy significantly improves disease-free survival in HER2-positive early breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 11.

Joensuu H et al. **Trastuzumab in combination with docetaxel or vinorelbine as adjuvant treatment of breast cancer: The FinHer trial.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 2.

Perez EA et al. **NCCTG N9831 May 2005 Update.** Presentation. ASCO 2005;Abstract 556.

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.

Slamon D et al. **Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer patients: First interim efficacy analysis.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 1.

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

What was particularly exciting about Dr Slamon's presentation was that it appears that he has identified a predictive marker for who requires anthracyclines in this population. Mike Press from UCLA looked at the little strip of DNA that's amplified in HER2-driven breast cancer, and noted that some of the amplicons were short and only included the HER2 gene, but some were substantially longer and also included the topoisomerase2 alpha gene (TOPO2A). TOPO2A is the target for anthracyclines. And to everyone's pleasant surprise, in the one third of patients who had coamplification of the HER2 and TOPO2 genes, the anthracycline was very effective.

What they found for the two thirds of patients who did not have the coamplification — where only HER2 was amplified — TCH seemed to be superimposable over the top of the anthracycline-containing arm.

— John Mackey, MD (Interview, December 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, peerwise, 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

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 cross over 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)

OPTIMAL DURATION OF ADJUVANT TRASTUZUMAB

The FinHer trial was a provocative study. It was a small study, but it looked at a short duration of trastuzumab exposure, on the order of nine weeks, and it suggested that women who got even a short exposure of trastuzumab did better than women who did not receive trastuzumab. That underscores the fact that the one-year duration of trastuzumab chosen for the major adjuvant trials was an arbitrary time point.
I think now that we've established a principle of therapy, it is going to be important to nail down the optimal duration and sequencing.

— Harold J Burstein, MD, PhD. Meet The Professors Session San Antonio Breast Cancer Symposium 2005