Proceedings and Interviews from a
CME Symposium at the NSABP 2005 Group Meeting

Targeted Adjuvant Systemic Therapy of Breast Cancer:
Current and Future Role of Trastuzumab

Breast Cancer® UPDATE

NSABP®

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Breast Cancer Update
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. To bridge the gap between research and patient care, *Breast Cancer Update* uses one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists medical oncologists in the formulation of up-to-date clinical management strategies. The purpose of this special issue of *Breast Cancer Update* is to present the most current research developments in the targeted therapy of breast cancer, including results of recent trials of adjuvant trastuzumab.

GLOBAL LEARNING OBJECTIVES

After completing this activity, the participant should be better able to:

- Describe a clinical algorithm to optimally assess targets for adjuvant systemic therapy (HER2, ER/PR) at initial diagnosis of early breast cancer and the rationale for targeting these pathways.
- Describe results of recent clinical trials of adjuvant trastuzumab and counsel appropriate patients with HER2-positive early breast cancer about the absolute risks and benefits of adjuvant trastuzumab.
- Discuss a management strategy for use of adjuvant trastuzumab in combination with chemotherapy and/or endocrine therapy.
- Describe and implement a clinical algorithm for assessment of cardiac function in patients who are candidates for or are receiving adjuvant trastuzumab.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of this special edition of *Breast Cancer Update* is to support these objectives by offering the perspectives of Drs Geyer, Kaufman, Leyland-Jones, Romond, Slamon and Wolmark and information presented at the recent NSABP meeting on the integration of the most recent emerging clinical research data in targeted therapy and adjuvant trastuzumab into the management of breast cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 6.25 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **www.BreastCancerUpdate.com** includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **blue underlined text**. This monograph also contains clinical investigator PowerPoint presentations.

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UPCOMING EDUCATIONAL EVENTS

28th Annual San Antonio Breast Cancer Symposium
December 8-11, 2005
San Antonio, Texas
Event website: **www.sabcs.org/Index.asp**

Radiation Therapy Oncology Group Meeting
January 19-22, 2006
Miami Beach, Florida
Event website: **www.rtog.org**

Miami Breast Cancer Conference
February 22-25, 2006
Miami Beach, Florida
Event website: **www.cancerconf.com**

National Comprehensive Cancer Network 11th Annual Conference
March 8-12, 2006
Hollywood, Florida
Event website: **www.nccn.org**

Fifth European Breast Cancer Conference
March 21-25, 2006
Nice, France
Event website: **www.fecs.be**

American Association for Cancer Research 97th Annual Meeting
April 1-5, 2006
Washington, DC
Event website: **www.aacr.org**

NSABP Group Meeting
April 28-May 1, 2006
Denver, Colorado
Event website: **www.nsabp.pitt.edu**

American Society of Clinical Oncology 42nd Annual Meeting
June 2-6, 2006
Atlanta, Georgia
Event website: **www.asco.org**

EDITOR'S NOTE

Neil Love, MD

Homecoming surprises

On September 19, 2005, after several decades of attending NSABP membership meetings and listening in rapt attention as Bernie Fisher and his team forced the field forward, I finally had the opportunity to sit at the dais with clinical research leaders at the front of the room.

By way of background, in June, during a lunch break at our CME group's annual colorectal cancer Think Tank, I approached NSABP chairman Dr Norman Wolmark with the idea of partnering on a special education symposium covering the landmark adjuvant trastuzumab data that had just been presented at the ASCO meeting in Orlando.

The idea was to invite key clinical investigators from the major cooperative groups — BIG, NCCTG-Intergroup and BCIRG — that conducted the adjuvant trastuzumab trials to join NSABP researchers in discussing where we've been, where we are and where we're heading in adjuvant therapy for patients with HER2-positive tumors.

We proposed a special two-hour symposium during the NSABP group meeting with the edited proceedings of that event published along with individual interviews of the faculty members as an audio/print/web enduring education piece for physicians. What made this idea even more enticing was that the 2005 NSABP meeting was scheduled to take place in my hometown of Baltimore (pronounced "Balamer" by natives).

I tossed this idea out to Norm without any idea how he would react, but after munching thoughtfully a bit more on his salad, he said, "It seems like a short turnaround time, but send me a proposal, and if you think this can be pulled off, we'll consider it."

A couple weeks later, we were up and running with Charles Geyer as the NSABP point person on the project. We were also fortunate enough to recruit the "father" of trastuzumab, Dennis Slamon, along with Brian Leyland-Jones and Peter Kaufman to join Norm, Chuck and Edward Romond from the NSABP to serve as the faculty for this unique event. Two months later, as we were wrapping up our planning for this meeting, my first homecoming surprise occurred.

I was exchanging emails with John Mackey — a key figure in the BCIRG — about an upcoming CME meeting, when I happened to ask him about the current status of BCIRG trial 006, the fourth and perhaps most intriguing of the international adjuvant trastuzumab trials.

Investigators had been telling me for months that this critical study was very close to its first analysis and that the definitive presentation of the initial data set was likely to occur at the San Antonio Breast Cancer Symposium in December. Of course, the principal investigator for 006 is Dennis Slamon.

One of the reasons for the intense interest in 006 is that this BCIRG trial was the only one of the four major studies that included a treatment arm without an anthracycline — TCH (docetaxel, carboplatin, trastuzumab). Many researchers, including Dr Slamon, were expecting this regimen to provide equal or greater efficacy compared to AC → docetaxel/trastuzumab (AC → TH) but with little or no cardiac toxicity.

To my surprise, Dr Mackey told me that, in fact, the requisite number of events (recurrences) in 006 had just occurred, and the Independent Data Monitoring Committee (IDMC) was to meet and review these data just a few days prior to our NSABP event.

I digested this information and concluded that like the other adjuvant trastuzumab studies, 006 was likely to show an important advantage to adding the anti-HER2 antibody and that, as with other important trial results in oncology over the last few years, some type of press release was likely to be issued if the results were positive.

Sure enough, on September 15, just four days before the NSABP meeting, our scientific staff retrieved a press release from the BCIRG website announcing some intriguing findings — namely that patients on both the AC → TH and TCH arms of the study had experienced significantly fewer relapses than patients on the AC → T arm. Interestingly, although the press release indicated that there was not a statistically significant difference between the relapse rates of the two trastuzumab arms, to the naked eye, the relative reduction with TCH (39 percent) seemed less impressive than that of the AC → TH arm (51 percent).

Mama Mia! With Dr Slamon as part of our NSABP symposium, and hopefully willing to discuss his perspective on these fresh data nuggets, we were in the midst of a continuing medical education coup.

On this program, you will hear the results of that serendipitous timing as Dr Slamon comments on how he interprets the findings released by the IDMC, and this story will continue in December in San Antonio when the BCIRG 006 data will be presented by Dr Slamon as the initial plenary talk.

The second surprise came the day after the symposium, when I interviewed Dr Norman Wolmark. (Interviews with Dr Slamon and Dr Leyland-Jones are also on this program, and interviews with Drs Geyer and Kaufman will be

BCIRG press release, September 15, 2005

"This study has an Independent Data Monitoring Committee (IDMC) that reviewed findings from the trial, including cardiac safety data and the first interim efficacy analysis based on 322 events. The IDMC has agreed to release the data, as efficacy boundaries have been crossed for the two investigational arms. The relative reduction in the risk of relapse was 51% [95% CI: 35%-63%] and 39% [95% CI: 21%-53%] for the AC-TH and TCH arms, respectively, compared to the AC-T control arm. The IDMC had previously reviewed and released the cardiac safety (cut-off December 31, 2004) that showed the following proportion of protocol-defined cardiac events: 1.2%, 2.3% and 1.2% for the AC-T, AC-TH, and TCH arms respectively. Insufficient information is available at this time to evaluate the secondary endpoint of overall survival."
http://www.bcirg.org/Internet/Press+Releases/default.html

included on our next issue of *Breast Cancer Update*. Dr Romond was interviewed this summer for our series.)

Dr Wolmark has been a regular interviewee for our series since 1991, and working with this research giant over the years, I have found him — like Dr Fisher — not only to have encyclopedic oncologic knowledge but also to be a champion of patients and the clinical trials process.

In the process of setting up the NSABP education symposium, I had somewhat timidly sent Dr Wolmark an email commenting on our CME group's experience with education programs on lung cancer, a disease that takes 155,000 lives a year in this country alone. The few adjuvant trials in lung cancer that have been conducted are woefully underpowered, and it was only in the last three years that four "large" randomized studies had finally confirmed that adjuvant chemotherapy has a very significant impact on relapse rate and overall survival. The clinical benefit of this treatment strategy, in fact, is similar in magnitude to or greater than that has been observed in breast cancer trials since the ***1979*** NIH consensus conference.

My email to Dr Wolmark noted that these four critical lung cancer trials were conducted largely outside the United States and comprised an aggregate total of about 3,500 patients. With great humility, I asked Dr W if the NSABP would ever consider becoming involved in adjuvant lung cancer trials and perhaps developing working relationships with thoracic surgeons in the same manner that they have so successfully accomplished with breast and colorectal surgeons.

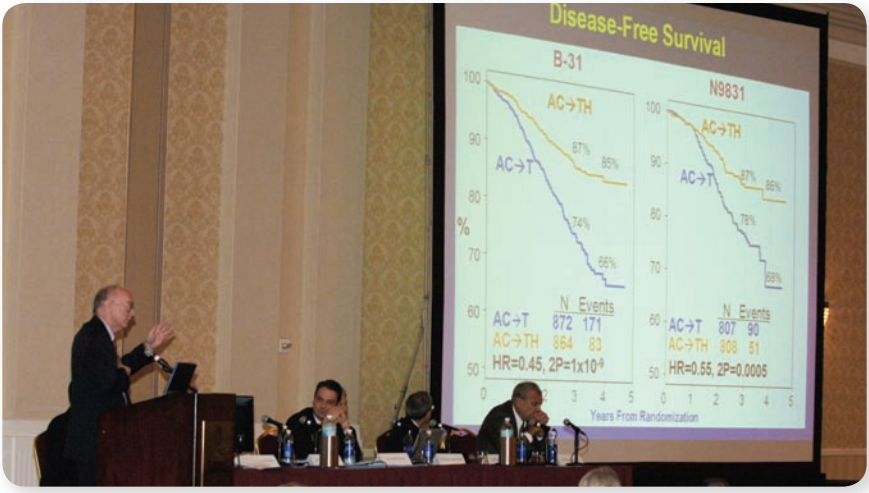
At the completion of his interview in Baltimore, I again raised my lung cancer question — initially off the record — and this led to a very interesting interlude of comments. Yes, the NSABP would potentially be willing to consider lung cancer trials if there was an imprimatur that this would be in the national interest. However, my query opened up a breached levee of criticism by Dr W directed at the NCI and its director Andrew von Eschenbach.

This brief thunderstorm of emotion left me wide eyed and slack jawed, and I suggested to Norm that if he really felt so strongly about this, maybe we should include his commentary on our audio program, editing out some of the colorful language, of course. Norm paused momentarily and, to my great satisfaction, agreed to allow this blistering commentary on the enclosed program.

That evening, dining with my family at Bo Brooks Crab House, happily cracking away at Balamer's finest bay-seasoned crustaceans, I reflected on my homecoming visit and felt a deep sense of satisfaction and gratitude to have had the honor to work so closely with the NSABP leadership and membership on this exciting project, but even more importantly, it was truly heartening to know that our CME group had the opportunity to assist clinicians in practice obtain the most up-to-date information on a fascinating, groundbreaking and definitely here-to-stay targeted biologic agent. ■

— Neil Love, MD
NLove@ResearchToPractice.net

The PowerPoint slides presented at the NSABP trastuzumab education symposium are included on the enclosed third audio CD and are posted at **www.BreastCancerUpdate.com/NSABP**.




Dr Charles Glover


Joint Analysis Flow Diagram

NSABP MEETING AGENDA

Targeted Adjuvant Systemic Therapy of Breast Cancer *Current and Future Role of Trastuzumab**

Dr Wolmark
Introduction

Dr Love
Education objectives, clinical cases for discussion and current patterns of care in the community

Dr Romond
Combined analysis of NSABP-B-31 and NCCTG-N9831 — Doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab as adjuvant therapy for patients with HER2-positive operable breast cancer.

Dr Slamon
BCIRG 006 — A randomized Phase III trial comparing AC → T versus AC → TH versus TCH in HER2-positive, node-positive or high-risk, node-negative breast cancer

Dr Leyland-Jones
HERA trial — A randomized comparison of one year versus two years versus no trastuzumab in women with HER2-positive breast cancer who have completed adjuvant chemotherapy

Dr Kaufman
NCCTG-N9831 — Sequential versus concurrent trastuzumab and chemotherapy

Dr Geyer
NSABP-B-31 cardiac toxicity data

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Dennis J Slamon, MD, PhD

Peter A Kaufman, MD

* PowerPoint slides from these presentations are on the enclosed third CD and at **BreastCancerUpdate.com**.

Tracks 1-6

Track 2

DR LOVE: What's your overall reaction to the clinical trial data on adjuvant trastuzumab that have become available in the last few months?

DR SLAMON: The data are quite stunning and are unlike a lot of adjuvant data we've seen in the past. The action part of this regimen is the biologic agent, trastuzumab, and it's giving us remarkable results. We all hoped for good results, but we were blown away by the degree of the results. I believe these data are going to hold up. We obviously need further follow-up, but these curves are pretty striking.

DR LOVE: Norm, what are your thoughts about the distant disease-free survival data from the combined NSABP-NCCTG analysis? Are we talking about cure?

DR WOLMARK: Everyone is hesitant to speak in terms of superlatives because we've been there and we've been disappointed. But certainly, we wait a lifetime to see curves separate in this way, with the treated line approaching the horizontal. So it is our sincere hope that we are talking about cure. There are sufficient data to suggest that is in fact what is happening.

As Ed Romond has pointed out, to see a survival difference with approximately two years of follow-up is extraordinary. There's every reason to believe that what we're seeing in disease-free survival and distant disease-free survival is going to be translated to overall cure. But, echoing Denny's admonitions, we ought to continue the follow-up as planned.

DR LOVE: One of the practical clinical questions is the issue of the patient with a node-negative tumor. We've discussed applying the relative risk reduction concept in adjuvant systemic therapy across the spectrum of risk, yet most of the patients who have been reported on so far have had node-positive disease. Dr Geyer, can we apply the relative risk reduction concept to smaller, node-negative tumors?

DR GEYER: That would have been a contentious point in the absence of the HERA data. However, the HERA data speak adequately to that issue. In that study, roughly a third of the patients had node-negative disease, and the Forest plot indicated that the lower boundary was to the left of one. Therefore, I believe that is a reasonable concept.

Track 3

DR LOVE: Do you think that docetaxel/carboplatin/trastuzumab (TCH) is a reasonable consideration for adjuvant therapy in the clinical setting?

DR GEYER: If you have a patient in whom the administration of anthracyclines is a concern, yes, without doubt, TCH makes a lot of sense. There are patients with whom you clearly would be concerned about utilizing doxorubicin due to pre-existing heart disease.

DR LOVE: Dr Slamon, what do we know about the side effects and toxicity of TCH versus AC/docetaxel or paclitaxel?

DR SLAMON: We have a lot of experience with taxanes and platinum salts based on studies in ovarian cancer and lung cancer. Therefore, we are pretty comfortable with the idea that they can be administered together. Myelotoxicity is the most significant adverse effect. I believe that TCH can be given safely, especially with growth factors. In treating a patient with a HER2-positive tumor, I'm less concerned with utilizing TCH than perhaps an anthracycline-based regimen, due to the potential cardiotoxicity.

DR LOVE: Ed, Chuck Vogel studied trastuzumab monotherapy in the metastatic setting. At present, we don't have data on trastuzumab without chemotherapy in the adjuvant setting. For an older patient for whom you're concerned about chemotherapy, do you think it's justifiable to consider trastuzumab monotherapy?

DR ROMOND: Trastuzumab would be a consideration if you were concerned about administering chemotherapy. However, sometimes we undertreat older patients with chemotherapy because of their age. I have not had difficulty giving chemotherapy to 75-year-old women who are in good health. However, if you had major concerns about toxicity in a patient with HER2-positive breast cancer, I certainly think trastuzumab monotherapy would be appropriate.

DR LOVE: Dr Slamon, what are your thoughts about trastuzumab monotherapy in the adjuvant setting?

DR SLAMON: Trastuzumab monotherapy is certainly an option if you have patients with coexisting medical issues that cause concern with administering chemotherapy. I absolutely agree that chronologic cutoffs are arbitrary. Our colleagues who practice oncology in a geriatric setting have taught us that there are performance analyses that can be done that will tell you whether or

not a patient can tolerate chemotherapy. In this older population, many more patients than we previously thought can tolerate chemotherapy, especially with some of the agents that we have to administer along with chemotherapy.

DR LOVE: Dr Kaufman, there is a lot of dose-dense AC/paclitaxel being given right now in this country. It is the most common regimen currently being utilized for patients with node-positive disease. What are your thoughts regarding dose-dense chemotherapy with trastuzumab?

DR KAUFMAN: That's an interesting question, and I've been asked that quite frequently since the data were presented. We have to be cautious with the use of trastuzumab in the setting of dose-dense therapy. In CALGB, we did not see an increased incidence of cardiotoxicity with dose-dense AC, but we did not carefully monitor cardiac safety in that trial. Cardiac monitoring was based on clinical symptomatology.

In theory, it's conceivable there may be an increased incidence of cardiotoxicity with dose-dense anthracyclines, even with sequential trastuzumab. Currently, it's probably safest and most appropriate to not use dose-dense anthracyclines with trastuzumab.

Track 4

DR LOVE: Dr Slamon, if you were evaluating a patient in her early fifties, perfectly healthy, no heart disease, with an ER-negative, PR-negative, node-negative tumor under one centimeter, would you discuss trastuzumab with her?

DR SLAMON: If it's a HER2-positive tumor, the critical thing is that the patient receives trastuzumab-based therapy. However, I am somewhat biased.

All of the other parameters that we evaluate and discuss — tumor size, node positivity or negativity, ER positivity or negativity — are not irrelevant but are less relevant than HER2 positivity. If I'm confronted with a patient with a HER2-positive tumor, I am going to recommend trastuzumab-based therapy. The choice of chemotherapy at this point is "dealer's choice."

DR LOVE: Dr Kaufman, a lot of people want to apply the criteria for clinical trial eligibility in treatment decision-making. The patient I've just described would not have been eligible for the HERA or NCCTG trials because the tumor was too small. Would you offer trastuzumab to that patient?

DR KAUFMAN: I agree with Dr Slamon that we really have to look at the HER2 positivity, but the cutoff for trial eligibility was a one-centimeter tumor. In this situation, we have to exercise some judgment. The issue is the size threshold. If the patient presents with a one- or two-millimeter tumor, I'm not sure I would recommend trastuzumab. But certainly, in a patient who is close to the eligibility criteria across the studies, it is very reasonable to consider recommending trastuzumab.

DR WOLMARK: I have more limited enthusiasm than my colleagues for recommending trastuzumab in that situation. The patient population in the NSABP-B-21 study did extremely well, regardless of HER2 status. Granted, that was a predominantly ER-positive population, but even the patients with small, ER-negative tumors had a good outcome. This underscores the fact that we need more objective parameters to determine risk in this subset of patients.

DR LOVE: Ed, what are your thoughts about the use of delayed trastuzumab, perhaps one or two years after the initial diagnosis?

DR ROMOND: A major consideration is the level of residual risk after that period of time. When you look at the curves of patients with a large number of positive lymph nodes, they continue to have events for a long period of time. If you have a patient with HER2-positive breast cancer whom you estimate still has significant residual risk, delayed trastuzumab is a consideration.

You also need to consider whether or not the patient has a potential risk for cardiac toxicity if you administer trastuzumab at this point, which shouldn't be any major consideration if you're using it by itself, and then what kind of incremental efficacy you could expect to see there.

But with the patients I see, if they have four or five positive nodes or something similar, and they're out even two or two and half years, I think they still have considerable residual risk.

The problem is that there are no absolute cutoffs. It has to come down to balancing these factors and discussing this with the patient.

Track 5

DR LOVE: It was interesting that in the NCCTG-N9831 trial, the sequential arm showed a 13 percent risk reduction, which is nonstatistically significant. Yet in the HERA study, utilizing a similar treatment strategy, there was 50 percent reduction. Norm, can you put this all together for us?

DR WOLMARK: No. I don't believe we can put it all together, because we do not have the power — divine or statistical — to do so. However, if we look at the data that Dr Kaufman presented on the N9831 trial, one can't remain neutral. Administering trastuzumab concomitantly with chemotherapy clearly resulted in a 36 percent reduction. Giving trastuzumab sequentially after chemotherapy resulted in a 13 percent reduction. Clinicians are going to be swayed by these data. If you delay trastuzumab beyond chemotherapy, you are going to pay a price in terms of efficacy.

Are these data inconsistent with the HERA data? Not necessarily. One explanation that Brian Leyland-Jones gave for the fact that the taxanes have a hazard rate of 0.77 — the lowest benefit from trastuzumab — is not because

we're dealing with a low-risk population but because the patients received more cycles of chemotherapy. Therefore, the trastuzumab was delayed.

The data from the HERA study and from N9831 are not inconsistent with one another, although, granted, we're not speaking from any standpoint of statistical power. There is a certain consistency. If you're going to yield the greatest benefit of trastuzumab, it should be administered as soon as possible and should be given concomitantly with chemotherapy.

DR LOVE: Dr Slamon, your preclinical work showing the synergy between trastuzumab and chemotherapy was part of the impetus to investigate sequential versus concomitant treatment. What are your thoughts about these data?

DR SLAMON: I'm obviously intrigued by this apparent dichotomy in the two data sets, but Norm addressed the issue quite well. The HERA investigators have always been open about the fact that the randomization occurred after chemotherapy, so keep this in mind as we evaluate the data. We are in the uncomfortable position of trying to make assumptions without having mature data.

We are not going to have to wait for years, but certainly, we're going to have to wait months for at least one updated analysis to be able to answer the question definitively. My preconceived notion based on the biologic data that we have is that administering trastuzumab with chemotherapy will make a difference.

SELECT PUBLICATIONS

BCIRG. **Interim analysis of phase III study shows Taxotere® (docetaxel)-based chemotherapy regimens combined with Herceptin® (trastuzumab) significantly improved disease free survival in early-stage HER2-positive breast cancer [press release].** September 15, 2005.

Burstein HJ. **The distinctive nature of HER2-positive breast cancer.** *N Engl J Med* 2005;353:1652-54. No abstract available

Hortobagyi GN. **Trastuzumab in the treatment of breast cancer.** *N Engl J Med* 2005;353:1734-6. No abstract available

Perez EA. **Further analysis of NCCTG-N9831.** Presentation. ASCO 2005. No abstract available

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

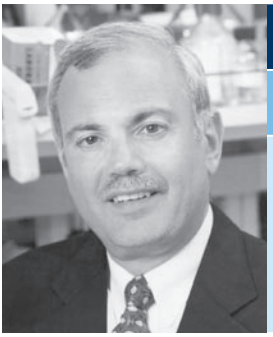
Piccart-Gebhart MJ. **First results of the HERA trial.** Presentation. ASCO 2005. **Abstract 556**

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

Romond EH et al. **Doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab as adjuvant therapy for patients with HER-2 positive operable breast cancer — Combined analysis of NSABP-B31/NCCTG-N9831.** Presentation. ASCO 2005. No abstract available

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

Slamon DJ. **Antibody-based therapeutics: More than a one-trick pony.** Presentation. ASCO 2005. No abstract available



INTERVIEW

Dennis J Slamon, MD, PhD

Dr Slamon is a Professor of Medicine, Chief of the Division of Hematology/Oncology and Director of Clinical/Translational Research at Jonsson Comprehensive Cancer Center at the David Geffen School of Medicine at UCLA in Los Angeles, California.

Tracks 1-18

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: Can you summarize the recently released efficacy data from the BCIRG 006 adjuvant trastuzumab trial?

DR SLAMON: The efficacy data are based on the first interim analysis of a three-arm trial with 300 events, and we recognize we're walking a fine line, but even so, both arms crossed their efficacy boundaries. We've known all along that trastuzumab was the critical molecule. The relevant question is: How does the TCH arm — the nonanthracycline arm — look relative to the anthracycline-containing arm? We have a lot of safety information now, and that's got to be weighed against the efficacy information.

What we can say now is that the risk reduction in the TCH arm is 0.39 (2.1). The risk reduction in the AC → TH arm is 0.51, which is almost identical to what was seen in the trials reported at ASCO for that kind of combination (Perez 2005; Piccart-Gebhart 2005a; Romond 2005a). There are very few event differences between the two trastuzumab arms. The two confidence intervals completely overlap, and the statisticians have said there is no statistical difference between the two arms.

DR LOVE: Oncologists have to make practical decisions with the information available. Based on these numbers, many may be thinking TCH will not be as effective as the anthracycline arm. What are your thoughts on that conclusion?

DR SLAMON: My thoughts are consistent with what the data show: There is a numerical difference and it's statistically insignificant. We need to wait until the data mature, and it's not going to take a long period of time. Physicians should do what they feel most comfortable with at this point. If they feel more comfortable with the AC → TH data, based on those relative differences despite the fact they are not different statistically, they should go with that arm, recognizing what everyone has said all along: Those patients are going to have to be watched very closely for cardiotoxicity.

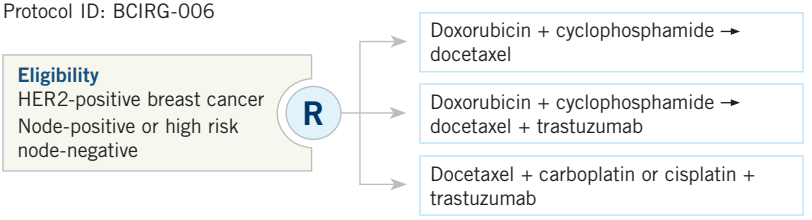
DR LOVE: What is the statistical likelihood that the TCH arm will be superior to the AC → TH arm?

DR SLAMON: I have no idea at this point. All I can tell you, without giving away information that will be presented at San Antonio, is that the results are based on very few event differences.

2.1

Phase III Study Comparing Doxorubicin/Cyclophosphamide/Docetaxel with or without Trastuzumab versus Docetaxel/Carboplatin or Cisplatin/Trastuzumab

Protocol ID: BCIRG-006



First interim efficacy analysis (N = 322 events)

Comparison	Relative reduction in risk of relapse	95% CI
AC → TH vs AC → T	51%	35%-63%
TCH vs AC → T	39%	21%-53%

AC = doxorubicin/cyclophosphamide; T = docetaxel; H = trastuzumab
C = cisplatin or carboplatin; CI = confidence interval

SOURCES: NCI Physician Data Query, October 2005; BCIRG Press Release, www.bcirg.org, October 2005.

DR LOVE: Do you think adjuvant TCH is a reasonable alternative in the clinical setting at this time?

DR SLAMON: Based on what we know, yes. TCH has been around a while in the metastatic setting, and a lot of data have been presented, even randomized data.

DR LOVE: Do you have an adjuvant protocol available to you right now?

DR SLAMON: We do not.

DR LOVE: When you see a younger patient with a node-positive breast cancer, which adjuvant therapies do you consider and what's your usual recommendation?

DR SLAMON: At this point we try, whenever possible, to avoid anthracycline-containing regimens because of the known interaction of trastuzumab with anthracyclines. However, we're not restricted to TCH. There are a number of different drugs that interact very well with trastuzumab, including vinorelbine, for which we have published data in the metastatic setting (Burstein 2003).

If the trastuzumab story has told us anything, it's that what we see in the metastatic setting gets even better in the adjuvant setting when we take it forward. I know oncologists in practice probably always go with what looks like the best number, and that makes sense, but I look at the composite picture.

We presented the data on cardiac safety from 006 (2.2), and the results are profoundly different from TCH, so it'll all depend on the weight of the efficacy data when we have sufficient numbers and how that stands up against the safety data.

If you look at left ventricular dysfunction progressively over time, both anthracycline-containing arms do worse. The information has been around a while that nontrastuzumab/anthracycline regimens do make an impact, and we have learned from the adjuvant trials with trastuzumab that we make an even bigger impact than we previously thought.

We thought we were out of the woods with the anthracycline doses we're using, and now we've found, as Chuck Geyer pointed out that the incidence is much higher than we thought, even for the standard arm, and this concerns me.

That has to be weighed against efficacy, and if the efficacy is strongly and statistically significantly different, then I think that has to be taken into consideration when you treat patients. We don't have data sufficient to speak to that at this point, but we will soon and when that data is available, it needs to be made public.

2.2

Incidence of Cardiac Events in BCIRG 006

Cardiac parameter	AC → T	AC → TH	TCH
Protocol-defined cardiac events[1]			
Events (patients)	12 (1,043)	25 (1,072)	13 (1,056)
Proportion	1.2%	2.3%	1.2%
	$p = 0.046$	$p = 0.07$	
	$p = 1.00$		
Absolute left ventricular ejection fraction (LVEF) declines >15%			
Events (patients)	6 (1,003)	25 (1,042)	4 (1,019)
Proportion	0.6%	2.4%	0.4%
	$p = 0.001$	$p < 0.001$	
	$p = 0.54$		

[1] Protocol definition of clinically significant cardiac events: Occurrence of one or more of the following:

- Cardiac death
- Grade III or IV LVEF (congestive heart failure)
- Grade III or IV arrhythmias (defined as event, unique to BCIRG 006 trial)
- Grade III or IV cardiac ischemia/infarction (defined as event, unique to BCIRG 006 trial)

SOURCE: Slamon D et al. Presentation. NSABP meeting. September 2005.

Track 5

DR LOVE: How would you treat a woman in her fifties with node-positive, HER2-positive disease?

DR SLAMON: We use TCH and will continue to do so until we see that it is inferior, and the safety profile doesn't make up for that inferiority.

DR LOVE: Can we anticipate that the relative risk reduction of trastuzumab-chemotherapy regimens will extend to patients who have node-negative disease, particularly with smaller tumors?

DR SLAMON: I would think so. Based on the biology of the disease, we know that when the HER2 alteration is present, it's a more aggressive disease. Now if you have a patient who has a smaller tumor, it has to be weighed against the likelihood of cure from the initial therapy — surgery and radiation therapy.

We also know there's a subpopulation of patients who are HER2-positive, who aren't cured, even if they have very small tumors. Treating with trastuzumab in the metastatic versus the adjuvant setting clearly isn't as advantageous.

My feeling is that we're dealing with a relatively benign agent in trastuzumab, when used correctly. It's an enormously expensive drug, and that has to be put

into context, but we have the two goalposts set. We know the drug is effective in the adjuvant setting and in metastatic disease. Between those two goalposts, I think it can be very effective.

Track 7

DR LOVE: What are your thoughts about the use of adjuvant trastuzumab monotherapy without chemotherapy in patients with comorbidities or of advanced age?

DR SLAMON: The orthodox answer is "no" — not outside the context of a clinical trial. My answer, and take it as my personal answer, is that the drug is effective, and if you're dealing with a patient not on a clinical trial, it's an individual sitting in front of you and the art of medicine still applies. If they've got significant comorbid disease, I would not withhold an effective therapy (Vogel 2002) because they don't meet some protocol. I would administer single-agent trastuzumab.

Track 8

DR LOVE: Most physicians seem to be using adjuvant trastuzumab for one year. Is that what you're doing?

DR SLAMON: Yes, but there are no clinical data to tell us how long to administer the drug. The one-year duration came from sort of an empiric extension of preclinical data, and my sense, based on those data, is that the optimal duration will be somewhere between six and 12 months.

Also, based on that same preclinical data, I don't think there'll be a big difference between one and two years. One good thing about the HERA trial is that it's asking that question so we'll get that information (2.3).

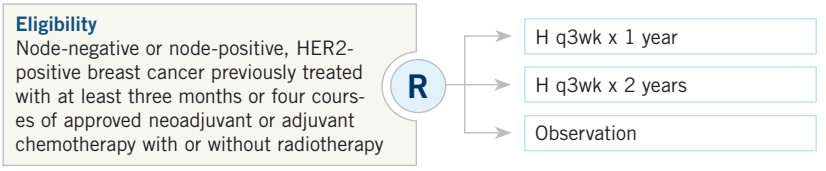
DR LOVE: It's a little difficult to interpret the data from the HERA trial as opposed to the NCCTG trial with regard to sequential versus concurrent therapy. The HERA study showed approximately a 50 percent risk reduction (Piccart-Gebhart 2005b; [2.4]), as was seen in the combined analysis (Romond 2005b). However, in the NCCTG trial there's a 13 percent nonstatistically significant reduction in the sequential arm (Perez 2005; [2.5]). How do you interpret those data?

DR SLAMON: I think it's far too early to make a call, and I think that's both the safe as well as the right answer. The HERA investigators have openly conceded the point that their data are more immature, vis-à-vis trastuzumab therapy, given the fact that they had an even longer period before the patients were randomized to trastuzumab, so their follow-up time is short.

2.3

Phase III Randomized Study of Trastuzumab (Herceptin®) in Women with HER2-Positive Primary Breast Cancer

Protocol IDs: BIG-01-01, EORTC-10011, "HERA"
Projected Accrual: 5,090 patients (Closed)



H = trastuzumab

SOURCE: Piccart-Gebhard M et al. *N Engl J Med* 2005b;353(16):1659-72. **Abstract**

Now they make up for that, in part, by large numbers, because they enrolled a lot of patients on the trial. But I think we need one more look at those data in terms of an update before we're really able to say that they're seeing the same kind of impact that we are seeing with the two cooperative group trials in the United States.

2.4

HERA Trial: Disease-Free Survival (DFS) for Patients Randomly Assigned to One Year of Trastuzumab or Observation After Completion of Adjuvant Chemotherapy

	Trastuzumab (n = 1,694)	Observation (n = 1,693)
Two-year DFS	85.8%	77.4%
Hazard ratio (95% CI)	0.54 (0.43-0.67)	
p-value	<0.0001	

CI = confidence interval

SOURCE: Piccart-Gebhart MJ et al. *N Engl J Med* 2005b;353(16):1659-72. **Abstract**

DR LOVE: The sequential versus concurrent arms in the NCCTG trial don't have very many events at this point, so could it be that that's the trial that's misleading?

DR SLAMON: It's true that the study doesn't have many events, but it has longer follow-up.

Track 9

DR LOVE: What about the issue of delayed trastuzumab? Should the patient with a HER2-positive tumor who's now six months, 12 months, or a couple of years after initial diagnosis be offered trastuzumab?

There's the orthodox answer, and there's what I think is the biologic answer. The orthodox answer is, there are no data that address whether giving it out further will be beneficial, and there's no trial with any data to speak to that.

The biologic answer is very similar to what I said earlier. You know trastuzumab works in the adjuvant and in the metastatic setting. The patient you're talking about sits between those two goalposts. If she has a disease that has escaped her primary site and it's a HER2-positive tumor, the likelihood of her receiving benefit from trastuzumab is there. So my sense is, biologically, it should be beneficial.

DR LOVE: In the clinical use of delayed aromatase inhibitor therapy, there's the mindset that the decision should be determined by the patient's risk at that point, and assuming therapy would significantly decrease that risk. Do you believe that approach makes sense in terms of initiating delayed adjuvant trastuzumab?

DR SLAMON: I think that's absolutely the way to go, but I don't think we have sufficient parameters or parametrics to measure that at this time.

2.5

NSABP-B-31/NCCTG-N9831 Disease-Free Survival Data

Joint analysis

Pairwise comparison	Number of events	Log rank *p*-value*	HR* (95% CI)
AC → T versus AC → T+H → H	395	3×10^{-12}	0.48 (0.39-0.60)

NCCTG-N9831 analysis

Pairwise comparison	Number of events	Log rank *p*-value*	HR* (95% CI)
AC → T versus AC → T → H (n = 1,964)†	220	0.2936	0.87 (0.67-1.13)
AC → T → H versus AC → T+H → H (n = 1,682)	137	0.0114	0.64 (0.46-0.91)

HR = hazard ratio
* Stratified — nodal status and receptor data
† For patients randomized before 1/1/2005

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

Track 11

DR LOVE: How should patients who received prior adjuvant trastuzumab be managed at relapse?

DR SLAMON: The thinking on treatment after progression following adjuvant trastuzumab falls into two camps: whether it makes sense to try something entirely different or to continue trastuzumab and add something new. The data we're seeing, based on preclinical information, would indicate that the latter makes sense. However, there are no clinical data to speak to that, and it's

going to be almost impossible to do a clinical trial to address it because of the half-life of the antibody.

We know that trastuzumab sticks around for a long period of time, so you'd be hard pressed to find a patient or an oncologist willing to wait until all the trastuzumab washes out before starting therapy in the face of progressive disease.

So by definition, if you switch to a different chemotherapy and you randomize to no continuation of trastuzumab versus continuation of trastuzumab, at week three when you add that chemotherapy, you're still doing a combination study. That's what makes it impossible to ask the question.

DR LOVE: Then what is your conclusion on this issue? How do you treat these patients?

DR SLAMON: The only conclusion I have is that if you've had a response to trastuzumab to begin with, I would continue trastuzumab therapy. The only place where I don't do that — based on no data, just sort of my gut feeling and what we know about the biology — is when the patient progresses within a few months of having stopped their chemotherapy, I'm less likely to continue trastuzumab. However, if the patient is slowly progressing through the trastuzumab therapy, there still may be an effect of the antibody, and we can add something different to it.

Track 15

DR LOVE: Can you comment on the work that your group has done evaluating bevacizumab plus trastuzumab and whether you see that moving into the adjuvant setting?

DR SLAMON: I certainly hope it moves into the adjuvant setting. I think there's more than enough very strong, compelling biologic and preclinical data indicating that this combination is rational.

There are now early clinical data, with very small numbers, both in the Phase I and II settings, which indicate that this is an active regimen, so I think it's ready to be moved into a larger trial. My sense is that in short order it should be ready to be moved into the adjuvant setting. We know how trastuzumab performs in the HER2-positive population, and the efficacy of bevacizumab was demonstrated in the ECOG-E2100 study (Miller 2005; [2.6]).

We now know — based not only on preclinical but clinical data — that the HER2 population has a higher VEGF level. All of the dots connect. Now it's a matter of showing that the combination is safe and showing some clear efficacy data that will allow us to think about launching a larger study.

DR LOVE: Can you talk more specifically about the Phase I and II data on the trastuzumab/bevacizumab combination?

2.6

ECOG-E2100 Efficacy Results

	Paclitaxel + bevacizumab (n = 330)	Paclitaxel (n = 316)	*p*-value
Response rate	28.2%	14.2%	<0.0001
Progression-free survival	10.97 months	6.11 months	<0.001
Overall survival	Hazard ratio = 0.674 (CI 0.495-0.917)		0.01

"In conclusion, this is a positive study. The addition of bevacizumab to paclitaxel significantly prolongs progression-free survival and increases the objective response rate with minimal increases in toxicity. Longer follow-up will be required to confirm the impact on overall survival. Future studies in this area should begin to explore the role of bevacizumab in the adjuvant setting and continue to investigate methods to identify those patients who are most likely to benefit from VEGF-targeted therapies."

SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

DR SLAMON: The Phase I data were with nine patients, three in one of three groups (Pegram 2004). The study evaluated three different doses of bevacizumab, because we didn't know the right dose when we launched it, along with standard-dose trastuzumab.

We saw responses in all three groups. Nine patients is a very small number, but the responses were pretty compelling in a first-line metastatic group. In addition, the third cohort was actually allowed beyond first-line treatment.

What we found was, in that total group of nine, there was one complete response, four partial responses, two stable diseases for greater than 11 months, and two patients who progressed. That was pretty exciting data for a small group, but you have to take that with a grain of salt because it's only with nine patients.

We've now expanded it into a Phase II study, looking at the two biologics together in first-line metastatic disease. What we're seeing up to this point is very similar to what we saw in the Phase I trial. We have 20 patients now in the Phase II, so a total experience with about 29 patients, and we're seeing the same kinds of response rates. We're very encouraged by the data. It needs to mature further, but I think it's a rational regimen, and I think it'll make its way to the clinic in terms of a big clinical study.

DR LOVE: Do you think this combination is ready to go into the adjuvant setting now?

DR SLAMON: I think it will go to the adjuvant setting. It's ready, but I tend to be a little more aggressive about looking at these things, maybe, than others. However, I would wait until we finish this Phase II study, which is supposed to accrue 50 patients and look at the response rate and duration in those patients. We'll know that relatively soon.

DR LOVE: Knowing the dangers of interpreting anecdotal cases or small series, other than the numbers in terms of response rates, is the magnitude of responses seen in the Phase I and II trials greater than you would have expected with trastuzumab alone?

DR SLAMON: Absolutely. I would not have expected it with trastuzumab alone or bevacizumab alone. If we were only basing it on thinking these might work well together versus the fact that the preclinical gene array data directed us, then I'd be a little more concerned, but given the fact that there are strong preclinical data, and now clinical data, I'm comfortable with it.

There's an enormous amount of preclinical data indicating that the pathways of the two agents are linked, which is compelling and reproducible. You can show that HER2-positive tumors have VEGF levels that are much higher than the general breast cancer population by gene array analysis.

DR LOVE: When you say the VEGF levels are high, is that a direct stimulant in terms of tumor growth?

DR SLAMON: Yes. We believe it's a direct stimulant. We can't test that in the clinic, but we can test it preclinically. In the clinic, we know the HER2-positive tumors — age-matched, stage-matched controlled — are more metastatic and grow more rapidly. Now there's direct growth stimulation of the HER2 pathway itself, and there's all the ancillary things you need to support faster and more aggressive tumor growth, not the least of which is neoangiogenesis, so it all makes sense.

DR LOVE: Do you believe bevacizumab potentiates chemotherapy by improving delivery and that's why it would work well with trastuzumab, or do you believe that, at least in HER2-positive breast cancer, there's something else going on with that combination?

DR SLAMON: I'm more in the camp of the latter, thinking there's something else going on. There are interesting data, including some data from clinical material, indicating that there may be this gradient phenomenon in terms of better penetration of chemotherapy. However, when you look at the doses achieved within the tissue, even when this is present, it's well above the IC50s.

The question is: Are higher doses achieved due to increased oncotic pressure, which is thought to be one of the mechanisms of VEGF? It's clear that the VEGF antibody will tie up circulating VEGF and that VEGF is one component needed for neoangiogenesis for a number of different kinds of tumors, so I think there is a lot of room for other mechanisms of how that would work.

DR LOVE: Do you believe that changing the oncotic pressure or profusion theoretically should be beneficial in terms of trastuzumab delivery?

DR SLAMON: Theoretically, but I would want to see supporting data that are reproducible. ■

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Hudis CA. **Clinical implications of antiangiogenic therapies.** *Oncology (Williston Park)* 2005;19(4 Suppl 3):26-31. **Abstract**

Ignoffo RJ. **Overview of bevacizumab: A new cancer therapeutic strategy targeting vascular endothelial growth factor.** *Am J Health Syst Pharm* 2004;61(21 Suppl 5):21-6. **Abstract**

Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.** Presentation. ASCO 2005. No abstract available

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Pegram MD et al. **Phase I combined biological therapy of breast cancer using two humanized monoclonal antibodies directed against HER2 proto-oncogene and vascular endothelial growth factor (VEGF).** San Antonio Breast Cancer Symposium 2004; **Abstract 3039**.

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Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER 2 positive breast cancer.** *N Engl J Med* 2005b;353(16):1673-84. **Abstract**

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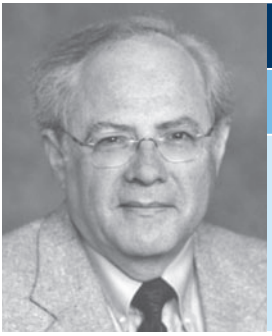


INTERVIEW

Norman Wolmark, MD

Dr Wolmark is Professor and Chairman of the Department of Human Oncology at Allegheny General Hospital, Professor at Drexel University College of Medicine and Chairman of the National Surgical Adjuvant Breast and Bowel Project in Pittsburgh, Pennsylvania.

Tracks 1-19

Select Excerpts from the Interview

Track 2

DR LOVE: Can you discuss the rationale for the combined analysis of the adjuvant trastuzumab trials?

DR WOLMARK: Originally, the NSABP-B-31 trial was going to be an indication trial. The NCCTG-N9831 trial was scheduled to begin later as it really didn't make sense to conduct the two trials concurrently in a population of patients with node-positive disease who account for only one quarter or perhaps

even less of the patient spectrum. As it turned out, by the time all of the regulatory prerequisites were met, the two trials started almost concomitantly.

So there were only a few months between the time the NSABP-B-31 trial started and the time N9831 started. No one had envisioned that would happen; it certainly wasn't planned. The rate of accrual for a quarter of the population with node-positive disease distributed between not only two competing studies but also a third, if you include the BCIRG 006 study (3.1), was less than ideal.

It became apparent that there was a need to really maintain focus on the goal of these trials, namely, to determine the efficacy of trastuzumab in women with breast cancer. If we were able to answer the question sooner, that was the right thing to do.

The combined analysis did not occur because someone decided, "We're going to have a look at the data." This was a very demanding and rigorous process for which a combined analysis plan was submitted to both the Cancer Therapy Evaluation Program and the FDA, as it required a number of changes, including our request to change the endpoint for analysis from overall survival to disease-free survival.

Once the combined analysis was approved, things moved very rapidly. The joint analysis plan was approved in January 2005, and the Data Monitoring Committee met during the third week of April. The first interim analysis indicated the number of requisite events had been surpassed. The requirement was for 355 events, and we actually had 395. The prerequisite for disclosure of the data was a p-value of 10^{-3}, and we had a p-value of 10^{-13}.

3.1 **Randomized Clinical Trials of Adjuvant Trastuzumab**

Trial (target accrual)	Eligibility	Randomization
NSABP-B-31 (closed) (2,043 patients)	Node-positive IHC 3+ or FISH+	AC x 4 → paclitaxel x 4 AC x 4 → paclitaxel x 4 + H qwk x 1 year
Intergroup NCCTG-N9831 (closed) (1,633 patients)	Node-positive or high risk node-negative IHC 3+ or FISH+	AC x 4 → paclitaxel qwk x 12 AC x 4 → paclitaxel qwk x 12 → H qwk x 1 year AC x 4 → (paclitaxel + H) qwk x 12 → H qwk x 40 wk
BIG-01-01 HERA (closed) (5,090 patients)	Node-positive and negative IHC 3+ or FISH+	H q3wk x 1 year H q3wk x 2 years No H
BCIRG 006 (closed) (3,222 patients)	Node-positive or high risk node-negative FISH+	AC x 4 → docetaxel x 4 AC x 4 → docetaxel x 4 + H (qwk x 12 wk) → H (qwk x 40 wk) (Docetaxel + C) x 6 + H (qwk x 18 wk) → H (qwk x 34 wk)

IHC = immunohistochemistry; FISH = fluorescent in situ hybridization; AC = doxorubicin + cyclophosphamide; H = trastuzumab; C = cisplatin or carboplatin

SOURCE: NCI Physician Data Query, November 2005.

DR LOVE: Do you have a sense of how much earlier we received the results because of this combined analysis?

DR WOLMARK: We saved a considerable amount of time — probably two years. The NSABP study alone also crossed the boundaries with the proviso that we use disease-free survival as an endpoint, which was not the primary endpoint of the single trial analysis.

DR LOVE: Just to clarify, the NSABP-B-31 trial contained two arms, and the NCCTG-N9831 trial consisted of three arms. The two common arms were used in the combined analysis, correct?

DR WOLMARK: Precisely. The arms were so similar that not to combine them, I believe, would have been a disservice to women with breast cancer.

DR LOVE: When people first heard this analysis was going to be conducted, there were a lot of questions about whether or not this type of evaluation was appropriate. However, after the results revealed such large differences, the analysis was no longer questioned (3.2). What is your interpretation of what occurred?

DR WOLMARK: The methodology used for the combined analysis was absolutely solid. It was the right thing to do because, in essence, the trials were the same trial with some minor variations in the common arms. If the result had been considerably less impressive or only marginal, I still believe the data would have been a reflection of what was actually happening.

3.2

Results from a Combined Analysis of Phase III Trials of Trastuzumab plus Adjuvant Chemotherapy in Women with Operable HER2-Positive Breast Cancer

	Chemotherapy with trastuzumab (n = 1,672)	Chemotherapy (n = 1,679)	Absolute difference	95% CI
DFS				
Three years	87.1%	75.4%	11.8%	8.1%-15.4%
Four years	85.3%	67.1%	18.2%	12.7%-23.7%
OS				
Three years	94.3%	91.7%	2.5%	0.1%-5.0%
Four years	91.4%	86.6%	4.8%	0.6%-9.0%
Distant DFS				
Three years	90.4%	81.5%	8.8%	5.5%-12.1%
Four years	89.7%	73.7%	15.9%	11.1%-20.8%

DFS = disease-free survival; OS = overall survival

SOURCE: Romond EH et al. *N Engl J Med* 2005;353:1653-84. **Abstract**

Track 5

DR LOVE: There is some confusion amongst community-based oncologists regarding the issue of concurrent versus sequential trastuzumab/chemotherapy because the HERA study data demonstrate positive results in patients who received trastuzumab after chemotherapy (Piccart-Gebhart 2005; [3.3]). Essentially, there was no benefit in the sequential treatment arm of the NCCTG-N9831 trial. How do you interpret those findings?

DR WOLMARK: The only test of concomitant versus sequential therapy was in the NCCTG-N9831 trial. When you look at the curves in the comparisons of both treatment arms to the control, I do not believe that one can remain neutral. The concomitant arm had a hazard rate that fell in line with what we're seeing in the other trials, including BCIRG 006 and the combined analysis. However, this is not true of the comparison between the control and sequential arm of N9831, which was associated with a hazard rate of 0.87 ($p = 0.29$).

The comparison of concomitant treatment with trastuzumab versus sequential treatment with trastuzumab was associated with a hazard rate of 0.64, which was significant ($p = 0.01$; [Perez 2005a]). It's not inappropriate for a medical oncologist to look at those data and say they are more impressed with data from the concomitant use of trastuzumab.

Are the results from NCCTG-N9831 inconsistent with the HERA data? Not necessarily. If you look at the hazard in the taxane-treated population in the HERA trial, the least impressive hazard rate occurred in those patients. So the question is whether or not this occurred because they received more cycles of chemotherapy, which delayed the administration of trastuzumab.

The data are not necessarily inconsistent with one another. I think these trials all show there is clearly a benefit of trastuzumab when given concomitantly with chemotherapy, and there may be a benefit sequentially.

3.3

Results from a Phase III Trial of Trastuzumab after Adjuvant Chemotherapy in Women with HER2-Positive Breast Cancer

	Trastuzumab (n = 1,694)	Observation (n = 1,693)	HR (95% CI)
2-year DFS	85.8%	77.4%	0.54 (0.43-0.67)
2-year distant DFS	90.6%	82.8%	0.49 (0.38-0.63)
2-year OS	96%	95.1%	0.76 (0.47-1.23)

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

Track 6

DR LOVE: What are your thoughts on the issue of delayed trastuzumab in patients who have received chemotherapy in the recent past — six months to two years ago. We've already been sensitized to this issue through our experience with the aromatase inhibitors and the time course of disease recurrence. Do you believe it makes sense to look at the risk of recurrence in relation to the continuum of disease course and assume that risk might be decreased if you administer trastuzumab, even if it is delayed?

DR WOLMARK: I think a conditional probability might be a good thing to utilize as a guide to determine whether trastuzumab should or should not be used in a delayed fashion. Would you administer trastuzumab to a patient with five positive nodes, who has completed chemotherapy a year ago knowing or, more specifically, not knowing what the effect is going to be at that point? The majority of clinicians would make that decision on an individual basis, and I would also.

Track 7

DR LOVE: There has been a lot of attention on the distant disease-free survival curve, which was dramatically better with trastuzumab. What are your thoughts about these data?

DR WOLMARK: When you see a curve of distant disease-free survival where the investigational arm — namely, in those patients who have received trastuzumab — is flat, it's dramatic, particularly so early on in follow-up (3.4). Does this mean that tumor cells have been eradicated? That's the great hope.

For distant disease-free survival, we are seeing a difference of 90 percent versus 74 percent at four years in the combined analysis — an absolute difference of 16 percent. These results are very impressive. Have we crossed the threshold for opportunities to treat the disease? I think we have.

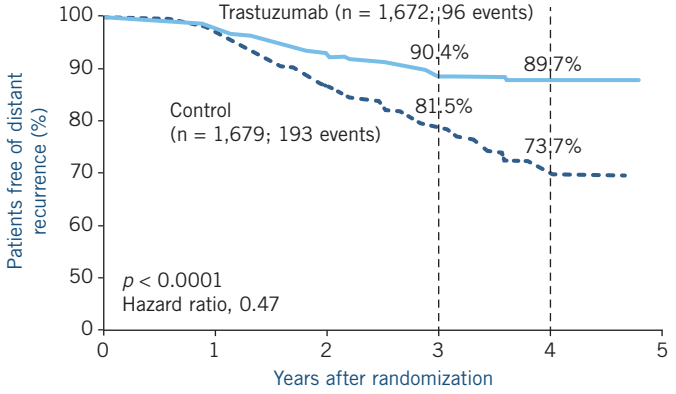
Track 10

DR LOVE: The initial data from BCIRG 006 have just been released. Do you think that a future data set from this study might show equivalent efficacy of TCH and AC → TH?

DR WOLMARK: That is the great hope, but I don't believe it is likely. We would have loved to have TCH show the same hazard rate as AC → TH — that would have made everything much more simple. You would have a noncardiotoxic regimen that shows efficacy in the same range as an anthracycline-containing regimen, so that would have rapidly become the preferred regimen.

3.4

Distant Disease-Free Survival in Patients Treated with Trastuzumab plus Chemotherapy versus Chemotherapy Alone



According to the press release (BCIRG 2005), the relative reduction in risk of relapse for AC → TH was 51 percent and was 39 percent for TCH, so we can't write eulogies for the AC → TH regimen, and we ought not. On the other hand, one is certainly not eliminating TCH as a template to which bevacizumab may be added. It is not unreasonable to consider that as a possibility.

DR LOVE: It's going to be interesting to see how oncologists and clinical investigators apply these findings to the clinical setting. Do you think it would be reasonable to consider using nonprotocol TCH based on the current data, particularly in the patient at lower risk or the older patient? The regimen clearly has efficacy.

DR WOLMARK: Medical oncologists are going to use the TCH regimen in a reasonable and logical way, as they should. The data that were disclosed relative to hazard rates from BCIRG 006 indicate that TCH is an effective regimen.

We would have liked for the hazard rate to have been the same as AC → TH, but it wasn't. We have seen a benefit when trastuzumab is added to the regimen, so if you have a patient who has cardiac compromise and you don't wish to use doxorubicin, I certainly think that TCH is a reasonable alternative.

Track 11

DR LOVE: Can you comment on the issue of monitoring cardiac toxicity? A common question is how to treat the patient who has a drop in ejection fraction after receiving AC. Can you discuss what was observed in the NSABP trial and how that translates into clinical practice?

DR WOLMARK: With AC alone, we saw a significant proportion of patients with decreases in ejection fraction. For those patients, I think medical oncologists will be making their decisions, which are going to be mainly driven by risk of recurrence. The higher the risk, the greater the likelihood that the patient is going to be treated. People are going to be innovative in the way they interpret ejection fraction or the algorithm they use.

Track 12

DR LOVE: Can you talk about the NSABP-B-41 neoadjuvant trial, which is being designed for patients with HER2-positive tumors?

DR WOLMARK: We were all certainly focused on Aman Buzdar's neoadjuvant study, which was a small trial indicating that paclitaxel followed by FEC with concomitant trastuzumab was associated with remarkable pCR rates (Buzdar 2005). This study caught our attention, so we would like to test that regimen in a larger clinical trial. That is what NSABP-B-41 is going to test: the Buzdar regimen compared to a more traditional sequential regimen of FEC followed by a taxane with trastuzumab.

DR LOVE: What is the endpoint of the study?

DR WOLMARK: The primary endpoint is pathologic complete response (pCR). We want to see if the pCR rate from the Buzdar study can be duplicated. Cardiac safety, of course, is another endpoint.

DR LOVE: What is the postsurgical therapy going to be in the B-41 study?

DR WOLMARK: Patients are going to receive trastuzumab for one year. Duplicating the Buzdar results will be a major step. Then — assuming that we do see that level of pCR — we will analyze the components of the regimen that led to the response. The Buzdar regimen was novel in that trastuzumab was administered concomitantly with both the taxane and the FEC.

DR LOVE: Can you discuss the NSABP-B-40 neoadjuvant study of three different arms of preoperative neoadjuvant chemotherapy?

DR WOLMARK: The novelty of B-40 is that we're using pCR as an endpoint with an emphasis on developing a molecular taxonomy to determine whether or not we can characterize patients who obtain a pCR as a surrogate marker to measure outcome. There is a definite interest in tissue collection in the B-41 study.

Disease-free survival and overall survival are not endpoints for the NSABP-B-40 protocol. We view it as a new mechanism to test promising agents in the neoadjuvant setting, and we think it is an appropriate direction to pursue, particularly with the number of agents that are available and the limited resources, both from a support standpoint and a population standpoint. ■

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INTERVIEW

Brian Leyland-Jones, MD, PhD

Dr Leyland-Jones is the Minda de Gunzburg Professor in the Department of Oncology at McGill University in Montreal, Quebec.

Tracks 1-14

Select Excerpts from the Interview

Track 2

DR LOVE: Can you describe the background of the HERA study?

DR LEYLAND-JONES: The design of the HERA study came about in a very pragmatic way. A group of us met on a Saturday in Frankfurt and spent a number of hours trying to come up with a common regimen. It became clear that it was impossible to agree upon one combined regimen.

The following morning, we simply drew the current trial design, in which we decided to include any prior chemotherapy regimen within reason, and mandated that eligible patients must have completed at least four cycles (Piccart-Gebhart 2005). We also decided to adopt the three-weekly trastuzumab regimen, which had been tested extensively worldwide.

Another factor that drove the trial design was the fact that it takes 18 weeks, either on the weekly or the three-weekly schedule, to reach steady-state levels of trastuzumab. So basically, with one year of therapy, you've devoted over a

third of the treatment time in achieving steady state. We decided to include a two-year arm also. That was supportive of the data that came from Rich Pietras and Dennis Slamon's group, which indicated that you need continuous attenuation of HER2 signaling to derive the most benefit (Pietras 1998).

So the four characteristics of the initial trial design were: patients had to receive adjuvant chemotherapy; trastuzumab was administered following the completion of all chemotherapy, radiation and surgery; the three-weekly trastuzumab regimen was adopted; and a three-arm design of observation versus one year of trastuzumab versus two years of trastuzumab was developed.

DR LOVE: What were the determinants of patient eligibility?

DR LEYLAND-JONES: There were many discussions about how patients with node-negative disease fared if they had poor pathology. So we decided to include anyone with a tumor size of greater than one centimeter, including patients with node-negative disease. We did not include patients with inflammatory breast cancer. One third of patients enrolled in the trial had node-negative disease.

Track 3

DR LOVE: Can you talk about the results that were observed?

DR LEYLAND-JONES: The findings were striking. The three-arm trial design mandated the accrual of more than 4,500 patients. In practice, accrual reached 5,070 women. The first interim analysis was planned at 475 events. That analysis showed a hazard ratio of 0.54 ($p < 0.0001$) for disease-free survival, which was remarkable after only one year of median follow-up (Piccart-Gebhart 2005).

DR LOVE: What about the survival data?

DR LEYLAND-JONES: Survival was not yet statistically significant after one year of median follow-up. That will be pursued, and additional data may be presented at the 2005 San Antonio Breast Cancer Symposium.

DR LOVE: When you look at different patient subsets, particularly according to status, age and other factors, what did you see in terms of relative risk reduction?

DR LEYLAND-JONES: As has been common across most of the trials, the data have not shown any huge differences between the subsets in general (4.1). However, the HERA study is the only trial in which one third of the patients had node-negative disease, and in this respect, the data are utterly striking.

Everything falls the same way, with exactly the same hazard ratio, whether it's a subgroup with negative nodal status, one to three positive nodes or four or more positive nodes. This gives us enormous confidence to treat node-negative disease with the same regimens that we utilize to treat node-positive disease.

4.1

HERA Trial (BIG-01-01) of Adjuvant Trastuzumab in Patients with HER2-Postive Breast Cancer: Analysis of Disease-Free Survival by Subgroup

	DFS Events*		
	Trastuzumab	Observation	HR† (95% CI)
All patients, n	127	220	0.54 (0.43-0.67)
Subgroups, n			
Age			
<35 years	12	23	0.47 (0.23-0.94)
35 to 49 years	55	95	0.52 (0.37-0.72)
50 to 59 years	39	73	0.53 (0.36-0.79)
≥60 years	21	29	0.70 (0.40-1.23)
Menopausal status			
Premenopausal	25	43	0.56 (0.34-0.92)
Uncertain	45	77	0.51 (0.36-0.74)
Postmenopausal	57	98	0.56 (0.41-0.78)
Nodal status			
Not assessed‡	25	39	0.53 (0.32-0.88)
Negative	20	40	0.51 (0.30-0.87)
1-3 positive nodes	26	48	0.51 (0.32-0.82)
≥4 positive nodes	56	93	0.53 (0.38-0.73)
Pathological tumor size			
Not assessed‡	25	39	0.53 (0.32-0.88)
0-2 cm	37	64	0.59 (0.39-0.88)
>2-5 cm	57	101	0.47 (0.34-0.65)
>5 cm	8	15	0.85 (0.36-2.03)
Type of adjuvant or neoadjuvant chemotherapy or both			
No anthracyclines	9	13	0.63 (0.27-1.47)
Anthracyclines, no taxanes	67	148	0.43 (0.32-0.57)
Anthracyclines and taxanes	51	59	0.77 (0.53-1.13)

* DFS events included any recurrences, contralateral breast cancer, second nonbreast malignant disease, and death.
† HR = Hazard ratios for one year of trastuzumab compared with observation
‡ Neoadjuvant chemotherapy

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

This is all a credit to the work of Dennis Slamon (Slamon 1987), who recognized that the expression of HER2 was critical to tumor biology and that this is a beautifully targeted therapy. In Melody Cobleigh's study of trastuzumab as a second- or third-line single agent in patients with HER2-positive disease, there was an objective response rate of approximately 15 percent (Cobleigh 1999). That objective response increased to almost 35 percent in Chuck Vogel's study, when it went into use as front-line therapy (Vogel 2002).

We've seen huge incremental gains with docetaxel/trastuzumab combinations and paclitaxel/carboplatin/trastuzumab combinations as front-line treatments. In many ways, we expected trastuzumab to be associated with increases

in efficacy during the adjuvant studies; however, I don't believe any of us thought it would be this dramatic.

DR LOVE: What did you see when you looked at the different chemotherapeutic regimens that patients received in the HERA trial? Were you able to tease anything out of that analysis?

DR LEYLAND-JONES: Around two thirds of the patients were treated with a straight anthracycline regimen: FAC, FEC or AC. Approximately six percent were treated with a nonanthracycline/nontaxane-containing regimen such as CMF. Around 25 percent were treated with an anthracycline/taxane.

So the anthracycline/taxane group appeared to do worse, although the confidence intervals are fairly wide because it's a smaller number (4.1). Patients treated with an anthracycline/taxane regimen tend to be a group with a worse prognosis. They tend to have large numbers of positive nodes, larger tumors and worse pathologies.

After essentially any adjuvant chemotherapy regimen with trastuzumab given sequentially, the hazard ratio is 0.54, and there was a significantly decreased incidence of distant metastases. So it shows the power of administering trastuzumab sequentially.

Track 4

DR LOVE: Can you discuss cardiac toxicity in the HERA trial?

DR LEYLAND-JONES: That is one of the key features of this trial. The entry criteria included completion of chemotherapy, surgery and radiation therapy prior to trastuzumab. Therefore, the randomization took place with trastuzumab starting either six weeks after completion of the radiation or surgery or seven weeks after the last cycle of chemotherapy.

This is a very clear separation, and what this resulted in was a difference in Grade III/IV cardiac toxicity, which was 0.54 percent in the trastuzumab group versus zero percent in the observation group (4.2).

We have to remember that the denominator is approximately 1,700 patients. In hard numbers, Grade III/IV CHF occurred in nine patients versus zero. In contrast, the Intergroup data reported CHF in 31 patients who received trastuzumab and in four patients from the control group (Romond 2005). So there was considerably less cardiac toxicity in the HERA trial if you're looking at cross-trial data.

The Intergroup study had a median follow-up of two years, whereas follow-up in HERA was one year. There are differences between the trials, of course. The LVEF cutoff criterion in the HERA study was 55 percent as opposed to 50 percent in the Intergroup trial. Having said that, at least looking at the HERA data, per se, there was a very low risk of cardiac toxicity.

DR LOVE: What is your current adjuvant treatment approach for patients with HER2-positive breast cancer?

DR LEYLAND-JONES: For our younger, fit patients, we use the current Intergroup/NSABP method: AC → TH, exactly as in NSABP-B-31. The NSABP and Intergroup trials showed that older patients or those who started post-AC with an LVEF in the 50 to 54 range were at a much higher risk for cardiac toxicity. Therefore, we tend to use a HERA type of regimen in the older patients or in patients who have a lower LVEF.

4.2

Cardiotoxicity During Phase III Trials of Trastuzumab Administered Sequentially or Concurrently with Adjuvant Chemotherapy in Patients with HER2-Positive Breast Cancer

HERA trial (Sequential trastuzumab)

Any chemo + XRT → H versus any chemo + XRT → observation

	Trastuzumab (n = 1,677)	Observation (n = 1,710)	*p*-value
Cardiac mortality	0	1 (0.06)	1.00
Severe CHF	9 (0.54%)	0	0.002
Symptomatic CHF, including severe CHF	29 (1.73%)	1 (0.06%)	<0.001
Decrease in LVEF	113 (7.08%)	34 (2.21%)	<0.001

NSABP-B-31 (Concurrent trastuzumab)*

AC → T+H → H versus AC → T

	Trastuzumab (n = 850)	Control (n = 814)
CHF (NYHA III or IV)	31	4
Cardiac mortality	0	1
Non-CHF cardiac dysfunction	43	8

* Cardiotoxicity reported in cohort of patients with normal cardiac function after AC therapy.

SOURCES: Tan-Chiu E et al. *J Clin Oncol* 2005;23:7811-19. **Abstract**; Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353:1659-72. **Abstract**

Track 5

DR LOVE: What are your thoughts about the NCCTG analysis, evaluating concurrent versus sequential trastuzumab therapy? The sequential treatment was similar to the HERA approach, yet there the NCCTG didn't see a statistically significant drop in relapse rate. You saw a 50 percent drop.

DR LEYLAND-JONES: It's an excellent question. All I can say is, the results are early, and the median follow-up is relatively short. If you look at the HERA

data, the hazard ratio is 0.54 for disease-free survival. The cardiac toxicity rate is low, and the efficacy and safety results are based on more than 1,600 patients per arm.

In the NCCTG study, the number of events in the concurrent versus sequential analysis is small — about 130 events (4.3). The complete number of events expected are 530, so they are only about a quarter of the way through the data. The idea that synergy between agents exists may well pan out in the end, and giving these drugs concurrently is perhaps better than giving them sequentially.

4.3

HERA (BIG-01-01), NCCTG-N9831 and NSABP-B-31 Adjuvant Trastuzumab Trials: Disease-Free Survival

	Number of events	Log rank *p*-value	HR (95% CI)
HERA analysis: Pairwise comparison			
Sequential versus control[1]	327	<0.0001	0.54 (0.43-0.67)
Joint analysis:* Pairwise comparison			
Concurrent versus control[2]	395	$3X10^{-12}$	0.48 (0.39-0.59)
N9831 analysis:* Pairwise comparison			
Sequential versus control[3]	220	0.2936	0.87 (0.67-1.13)
Concurrent versus sequential[4]	137	0.0114	0.64 (0.46-0.91)

* Stratified — nodal and receptor status

[1] H versus observation following any chemotherapy + HRT prior to study enrollment
[2] AC → T + H → H versus AC → T
[3] AC → T → H versus AC → T → H
[4] AC → T + H → H versus AC → T → H

H = trastuzumab; T = taxane

SOURCES: Perez EA et al. Presentation. ASCO 2005. No abstract available
Piccart-Gebhart MJ et al. *N Engl J Med* 2005;353:1659-72. **Abstract**

Track 8

DR LOVE: What was seen in the HERA trial in patients with ER-positive and HER2-positive tumors?

DR LEYLAND-JONES: The ER-positive population was half the population. Equal benefit from trastuzumab was seen in the ER-positive population. Again, I believe this is another indicator of the importance of HER2 biology.

DR LOVE: In the clinical setting, how do you approach the use of hormonal therapy with these patients? In the trials, patients received hormonal therapy together with trastuzumab after chemotherapy was completed. Is that your general approach?

DR LEYLAND-JONES: We utilize chemotherapy and trastuzumab followed by an aromatase inhibitor in patients who have HER2-positive and ER-positive disease. The original protocol for HERA included only tamoxifen. It was subsequently modified to include the aromatase inhibitors. As shown in the 2004 San Antonio presentation, many patients with ER-positive, HER2-positive disease have a downregulation of the PR, and the aromatase inhibitors are better in this treatment group (Dowsett 2005).

DR LOVE: So you start the aromatase inhibitor after the chemotherapy?

DR LEYLAND-JONES: Yes.

DR LOVE: In the metastatic setting, do you utilize a combination of hormonal therapy and trastuzumab?

DR LEYLAND-JONES: We are participating in a trial of anastrozole with or without trastuzumab (4.4). We already have first-hand experience with that combination; however, the data are not yet available for this trial. The natural biology drives the use of this combination, so we utilize trastuzumab and aromatase inhibitors in select patients in the clinical setting.

4.4

Phase II/III Randomized Study of Anastrozole with or without Trastuzumab in Postmenopausal Women with HER2-Positive Metastatic Breast Cancer

Protocol IDs: ROCHE-BO16216, CWRU-030118, GENETECH-H2223g, ROCHE-1100, ROCHE-B016216E, NCT00022672
Target accrual: 202 (Open)

Eligibility
At least 18 years of age with histologically or cytologically confirmed MBC; HER2 overexpression confirmed by IHC or FISH; postmenopausal; no CNS metastases; ER-positive and/or PR-positive; no prior anti-HER2 therapy and no prior chemotherapy for metastatic disease; at least six months since prior adjuvant treatment; ECOG PS 0-1

R

- Anastrozole PO once daily and trastuzumab IV once weekly × 2 years
- Anastrozole PO once daily × 2 years

SOURCE: NCI Physician Data Query, November 2005.

Track 9

DR LOVE: The patient with multiple positive nodes — five to 10 positive nodes — who is a year or two out from chemotherapy is still at substantial risk for subsequent recurrence. Do you think trastuzumab should be discussed with these patients?

DR LEYLAND-JONES: This is an agonizing situation. The evidence is the evidence, and national advisory committees everywhere use it. The general advice is to restrict the use of adjuvant trastuzumab to within six months of completing chemotherapy. One or two guidelines are taking it out to a year. At our center in Canada, however, we are restricted by the data, which support utilizing trastuzumab within six months of completing chemotherapy.

Track 10

DR LOVE: What about dose-dense chemotherapy and trastuzumab?

DR LEYLAND-JONES: We've treated patients with that regimen. A number of people question the best way of incorporating the trastuzumab. We do not have the appropriate pharmacokinetic data on this, but a number of doctors are administering a 4 mg/kg two-weekly regimen.

There is some evidence that using loading doses can help. Instead of giving the 2 mg/kg weekly dose, it makes sense to combine it with the dose-dense chemotherapy regimen using a 4 mg/kg two-weekly regimen, which makes it easier for the patient during the time of transition from AC to trastuzumab. In a clinical setting, it is natural that physicians would adopt trastuzumab into a dose-dense kind of regimen.

Track 13

Neoadjuvant trastuzumab

DR LOVE: What were your thoughts about the data from Aman Buzdar evaluating neoadjuvant trastuzumab/chemotherapy?

DR LEYLAND-JONES: This study had one of the most dramatic complete response rates ever seen in the neoadjuvant setting. The trial was discontinued after accruing 34 patients because it showed a huge difference between the two arms (Buzdar 2005). This causes a dilemma, because you can show patients a 67 percent pCR rate with the combined neoadjuvant regimen; however, the regulatory authorities look at this and say, "Well, you have 18 patients in the one arm and 16 in the other. Show us something that is more significant clinically."

Unfortunately, because the data are so compelling, I'm not sure whether we are going to have a large neoadjuvant trial. At the moment, the vast majority

of practicing oncologists are using trastuzumab in the neoadjuvant setting. The appropriate regimen is not well demonstrated, and we do not have a large trial confirming the benefit of trastuzumab. ■

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The three arms of the BCIRG 006 adjuvant trastuzumab trial were AC → docetaxel, AC → docetaxel + trastuzumab and _____.**
   a. AC → trastuzumab
   b. AC → paclitaxel + trastuzumab
   c. Docetaxel + cisplatin or carboplatin + trastuzumab

2. **The interim analysis of the BCIRG 006 trial showed that the addition of trastuzumab to docetaxel-based regimens significantly improved disease-free survival in early-stage HER2-positive breast cancer.**
   a. True
   b. False

3. **According to Dr Slamon, the HER2-positive population has higher VEGF levels, and, based on clinical and preclinical data, bevacizumab plus trastuzumab is a rational combination to evaluate in the adjuvant setting.**
   a. True
   b. False

4. **In the ECOG-E2100 trial, the addition of bevacizumab to paclitaxel had which of the following effects?**
   a. Prolonged progression-free survival
   b. Increased objective response rate
   c. Both a and b
   d. None of the above

5. **In the combined analysis of NSABP-B-31 and NCCTG-N9831, Romond et al reported an absolute difference of _____ in DFS at four years between the trastuzumab and control groups.**
   a. 15.3%
   b. 18.2%
   c. 10.5%

6. **In the HERA trial, the HR for two-year DFS was _____ for the comparison between trastuzumab and observation.**
   a. 0.54
   b. 0.76
   c. 0.64
   d. 0.86

7. **According to data from the HERA (BIG-01-01) trial, the risk of severe CHF was very low (0.54 percent) in patients who received trastuzumab following adjuvant chemotherapy.**
   a. True
   b. False

8. **In the HERA trial, the hazard ratio for disease-free survival in patients with four or more positive nodes was _____ the hazard ratio for disease-free survival in patients with node-negative disease or one to three positive nodes.**
   a. Greater than
   b. Less than
   c. Equal to

9. **In the neoadjuvant setting, trastuzumab and chemotherapy were associated with a _____ percent pCR rate in a small study of 34 patients with operable HER2-positive breast cancer.**
   a. 47
   b. 57
   c. 67
   d. 77

10. **The HERA trial had a three-arm design, which randomly assigned patients to either observation, one year of trastuzumab or _____ after initial chemotherapy.**
    a. Six months of trastuzumab
    b. Two years of trastuzumab
    c. Three years of trastuzumab
    d. Five years of trastuzumab

11. **The only adjuvant trastuzumab trial designed to evaluate concurrent chemotherapy with trastuzumab versus sequential chemotherapy and trastuzumab was _____.**
    a. HERA
    b. NCCTG-N9831
    c. NSABP-B-31
    d. BCIRG 006

Post-test answer key: 1c, 2a, 3a, 4c, 5b, 6a, 7a, 8c, 9c, 10b, 11b

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BCU NSABP Symposium, 2005

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5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	N/A = Not applicable to this issue of *BCU*

GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *BCU* address the following global learning objectives?

- Describe a clinical algorithm to optimally assess targets for adjuvant systemic therapy (HER2, ER/PR) at initial diagnosis of early breast cancer and the rationale for targeting these pathways. . . . . 5 4 3 2 1 N/A
- Describe results of recent clinical trials of adjuvant trastuzumab and counsel appropriate patients with HER2-positive early breast cancer about the absolute risks and benefits of adjuvant trastuzumab . . . . . 5 4 3 2 1 N/A
- Discuss a management strategy for use of adjuvant trastuzumab in combination with chemotherapy and/or endocrine therapy. . . . . 5 4 3 2 1 N/A
- Describe and implement a clinical algorithm for assessment of cardiac function in patients who are candidates for or are receiving adjuvant trastuzumab. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Charles E Geyer Jr, MD	5 4 3 2 1	5 4 3 2 1
Peter A Kaufman, MD	5 4 3 2 1	5 4 3 2 1
Brian Leyland-Jones, MD, PhD	5 4 3 2 1	5 4 3 2 1
Edward H Romond, MD	5 4 3 2 1	5 4 3 2 1
Dennis J Slamon, MD, PhD	5 4 3 2 1	5 4 3 2 1
Norman Wolmark, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity. . . . . 5 4 3 2 1 N/A
Related to my practice needs. . . . . 5 4 3 2 1 N/A
Will influence how I practice. . . . . 5 4 3 2 1 N/A
Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
Overall quality of material. . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
Avoided commercial bias or influence. . . . . 5 4 3 2 1 N/A

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.....

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Additional comments about this activity:

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As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

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Breast Cancer® UPDATE

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This program is supported by an education grant from Genentech BioOncology.

Breast Cancer® UPDATE

This program is supported by an education grant from Genentech BioOncology.

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Last review date: December 2005
Release date: December 2005
Expiration date: December 2006
Estimated time to complete: 6.25 hours