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How to use this monograph

This is a CME activity that contains both audio and print components. To receive credit, the participant should listen to the CD or tape, review the monograph and complete the post-test and evaluation form. This monograph contains edited comments, clinical trial schemas, graphics and references, which supplement the audio program and the website, **BreastCancerUpdate.com**, where you will find a full transcription of the audio program and 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 **red underlined text**. This regularly updated website also features an extensive breast cancer bibliography, clinical trial links, a "breast cancer web tour" and excerpts from interviews and meetings catalogued by topic.

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 utilizes 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.

Issue 8, 2002 of Breast Cancer Update consists of an in-depth interview with oncology research leader Dennis Slamon. This activity will review a variety of topics including the clinical development of trastuzumab, synergy between trastuzumab and chemotherapy, trastuzumab-related cardiotoxicity, combinations of trastuzumab with chemo/hormonal therapies, optimal duration of trastuzumab therapy, clinical trials and nonprotocol use of adjuvant trastuzumab, trials of trastuzumab in the neoadjuvant setting and the optimal method to assess HER2 status.

Educational Objectives

Upon completion of this activity, participants should be able to:

- More effectively utilize chemotherapy/trastuzumab combinations in appropriate patients with HER2-positive metastatic breast cancer.
- More effectively discern the risk of cardiotoxicity associated with various trastuzumab-containing regimens and apply this knowledge when choosing chemotherapeutic agents to minimize the potential for cardiotoxicity in your patients.
- Develop a more effective algorithm to assess HER2 status and utilize this in selecting appropriate candidates for trastuzumab therapy.

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Postgraduate Institute for Medicine and NL Communications, Inc. The Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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The Postgraduate Institute for Medicine designates this educational activity for a maximum of 1.5 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only credits that he/she actually spent in the activity.

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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals, LP
capecitabine	Xeloda®	Roche Laboratories, Inc.
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cisplatin	Platinol-AQ®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan®, Neosar®	Bristol-Myers Squibb Company, Pharmacia Corporation
docetaxel	Taxotere®	Aventis Pharmaceuticals
doxorubicin	Adriamycin®, Rubrex®	Pharmacia Corporation
etoposide	VePesid®	Bristol-Myers Squibb Company
5-fluorouracil, 5-FU	-	Various manufacturers
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals, LP
gemcitabine	Gemzar®	Eli Lilly and Co.
paclitaxel	Taxol®	Bristol-Myers Squibb Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals, LP
trastuzumab	Herceptin®	Genentech, Inc.
vinblastine	Velbe®	Eli Lilly & Co
vincristine	Oncovin®	Eli Lilly & Co
vinorelbine tartrate	Navelbine®	Glaxo Wellcome, Inc.

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Faculty Financial Interests or Affiliations

Neil Love, MD
Grants/Research Support: AstraZeneca Pharmaceuticals, LP, Roche Laboratories, Inc., Genentech, Inc., Cytyc Health Corporation

Dennis J Slamon, MD, PhD
Speakers' Bureau: Genentech, Inc., Aventis Pharmaceuticals

Editor's Note

Meet the Professor

"I love my work. I'm surrounded by incredibly talented people who constantly challenge me — and I challenge them. We have a great group, and we're really excited about our work, because it's the most exciting time in the history of oncology. I've also been fortunate enough to receive a number of awards, and those were all very nice. I was thrilled and honored, but the greatest reward I ever received was the Christmas after trastuzumab was approved. Melody Cobleigh — who participated in the registration trial and was the second leading accruer — asked her patients to write a one-page note to me about what it meant to have been on the trial and to have benefited from the study and respond. And so I got these personal notes from women whom I'd never seen, I'll never know, I've never met, talking about how we had impacted their lives. It was very moving — it brought me to tears. And it showed that while this is very interesting science, it goes way beyond that. If you can make things work, you really do impact people's lives."

— Dennis J Slamon, MD, PhD

The Breast Cancer Update series has provided me with the privilege of interviewing many "movers and shakers" in the oncology research leader community. My main mission is to ask questions that are not covered in journal articles or meeting presentations. By representing the practicing oncologist, I particularly want to push my interviewees to move away from standard algorithms and to tell us how they treat their own patients outside of a protocol setting. My other main objective is to have these research leaders predict what we might expect in the future, as data from ongoing clinical trials mature.

In 14 years of producing this series, I've had the opportunity to speak with many of the legendary figures in breast cancer clinical research, including Bernie Fisher, Gabriel Hortobagyi, Richard Peto, Michael Baum and Larry Norton. These leaders are united in a commitment to the application of the scientific method to improve patient care. They also maintain very close ties to preclinical research and often attempt to differentiate the hype from the hope of laboratory findings.

Because of their extensive knowledge and true love of their work, most of these visionaries can, and do, speak passionately for hours on the subject of breast cancer clinical research. The depth of their insight always makes it very challenging to edit

down these interviews. To offset this "problem", we are launching what we intend to be a regular annual feature — a special edition with an in-depth interview with a research leader who has played a crucial role in shaping the current breast cancer management paradigm.

The focus of our first "Legends in Oncology" program is Dr Dennis Slamon, whose pioneering laboratory and clinical research on the natural history and management of HER2-positive breast cancer has ushered in a new era of targeted biologic treatment. Like most visionary leaders, Dr Slamon unflinchingly "tells it like it is." In the enclosed program, he criticizes the designs of the two major adjuvant trastuzumab trials (NSABP B-31 and NCCTG-N9831) for including anthracyclines in all of the randomization arms. He also recounts, without apology, his nonprotocol use of adjuvant trastuzumab, a practice that most research leaders interviewed for this series do not support.

Dr Slamon also believes that FISH should be routinely utilized to assess a patient's HER2 status, calling the standard IHC assay archaic and ill advised. He predicts that the combination of a platinum agent, a taxane and trastuzumab will soon be standard therapy in the adjuvant and first-line metastatic setting for HER2-positive disease. A recent report by Dr Nicholas Robert* suggests that the second half of Dr Slamon's prediction is being borne by the initial results from a U.S. Oncology trial in the metastatic setting.

Last year during an interview at the San Antonio Breast Cancer Symposium, Michael Baum made one of my favorite and most-frequently cited comments in this audio series. Mike had just stunned a packed auditorium with the initial results from the ATAC adjuvant trial, which demonstrated an advantage for anastrozole compared to tamoxifen. Hours later, as he and I explored the clinical implications of these groundbreaking but early results, he shrugged and said, "There are always periods of uncertainty in the evolution of science and medicine."

Oncologists in clinical practice know that one productive way to face these "periods of uncertainty" is to obtain numerous perspectives, and determine areas of consensus and disagreement about the application of clinical trial results to patient care. However, we also need people like Dennis Slamon to challenge our conventional beliefs and make us think "outside of the box."

—Neil Love, MD

*Robert N et al. **Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer.** *Breast Cancer Res Treat* 2002;**Abstract 35.**

Dennis J Slamon, MD, PhD

Chief, Division of Hematology-Oncology.
Professor and Executive Vice Chair.
Department of Medicine;
Director of Clinical Research,
Jonsson Comprehensive Cancer Center

Director, Revlon/UCLA Women's Health
Research Program,
UCLA School of Medicine

2002	Jeffrey A Gottlieb Memorial Award, MD Anderson Cancer Center
2001	Bristol-Myers Squibb Milennium Award Brown-Hazen Award for Excellence in the Basic Sciences, Wadsworth Center, New York
2000	Appointed to the President's Cancer Panel Salk Award Translational Medicine, University of California, San Diego
1999	Albert B Sabin Heroes of Science Award, Americans for Medical Progress Education Foundation Richard and Hinda Rosenthal Foundation Award, American Association for Cancer Researchers (AACR) Women of Los Angeles, Highlight Award *GQ* magazine and General Motors, one of five "Men for the Cure"
1998	National Breast Cancer Coalition, Special Recognition, for Scientific Advances in Human Breast Cancer
Other Awards	Milken Family Medical Foundation Award for Cancer Research Upjohn Award in Internal Medicine

Edited comments by Dr Slamon

Initial phase I/II trastuzumab trials

In the first group of treated patients, we measured blood chemistries and vital signs every few hours to look for any changes in critical organ function. There was particular concern about the kidneys and lungs. Yet, we did not see any toxicity other than a couple of patients developing fevers from the drug infusion. Fever was treated with acetaminophen and chills with diphenhydramine.

When we got to the highest dose levels, we saw a couple of responders. The initial trials were conducted with a mouse monoclonal antibody. We had to test the humanized form of the drug, and those phase I studies were also done at UCLA.

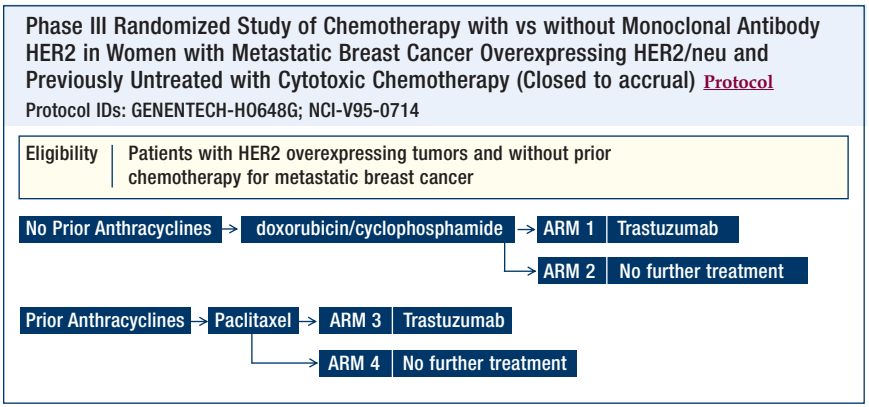
The phase II trials confirmed what the animal models predicted. Trastuzumab monotherapy, in refractory patients, appeared to have a 12% to 15% response rate.

Pivotal phase III trastuzumab trial

We used a combination of an anthracycline and cyclophosphamide, which was commonly used as first-line therapy in metastatic disease. For those patients who had received adjuvant doxorubicin, paclitaxel was utilized. Essentially, the patients were randomized to the best available standard chemotherapy plus or minus trastuzumab.

In the phase III trial, the addition of trastuzumab led to a significant improvement in response rate, response duration and time to progression, respectively. A little-known fact from that trial is that the highest response rate was seen in the anthracycline/cyclophosphamide/trastuzumab arm compared to the paclitaxel/trastuzumab arm. Paclitaxel/trastuzumab was ultimately included in the package label because of the toxicity encountered with the other arm.

We were very encouraged with the improvement in the median time to progression for the group receiving trastuzumab. Although it is only a three-month improvement, it translates, ultimately, into a survival advantage. At four years of follow-up, trastuzumab decreases the relative risk of death by 30% in women with truly HER2-positive breast cancer — those who are FISH-positive.



Clinical benefit, duration of response and cardiotoxicity in chemotherapy versus chemotherapy plus trastuzumab regimens

	AC (n=138)	AC + H (n=143)	Paclitaxel (n=96)	Paclitaxel + H (n=92)	Chemo (total) (n=234)	Chemo (total) + H (n=235)
Median time to progression (months)	6.1	7.8	3.0	6.9	4.6	7.4
Median duration of response (months)	6.7	9.1	4.5	10.5	6.1	9.1
Median survival (months)	21.4	26.8	18.4	22.1	20.3	25.1
Complete + partial response	58/138 42%	80/143 56%	16/96 17%	38/92 31%	74/234 32%	118/235 50%
Any cardiac dysfunction	8%	27%	1%	13%	5%	22%
Severe cardiac dysfunction	3%	16%	17%	2%	2%	10%

A=Anthracycline; C=cyclophosphamide; H=trastuzumab

Derived from Slamon DJ et al. *NEJM* 2001;344(11):783-792.**Abstract**

Duration of response to trastuzumab

We have patients who are five and six years out from their initial response to trastuzumab; some are still on it, and others are not. Those still on trastuzumab were allowed, if they responded on the trial, to continue. Many patients had very advanced disease so when they had a complete response, some were reluctant to stop the trastuzumab.

There are also patients who have had complete responses and now are off treatment. The longest living survivor treated with trastuzumab was a patient in those phase I studies at UCLA. Initially, she had 16 nodules throughout her lungs and positive lymph nodes above the clavicle. It is now about nine and a half years since she received about four and a half months of trastuzumab.

Preclinical data on trastuzumab/chemotherapy combinations

Preclinical studies demonstrated that trastuzumab in combination with certain chemotherapeutic agents worked better than trastuzumab alone. The drugs commonly used to treat breast cancer — doxorubicin, paclitaxel, gemcitabine, methotrexate, vincristine and vinblastine — tended to be additive with trastuzumab, and 5-FU was less than additive.

The platinum salts — cisplatin and carboplatin — appeared to be the most

synergistic. After the platinum salts came docetaxel, etoposide, vinorelbine and then the alkylating agents like cyclophosphamide. We wondered why there was a difference between paclitaxel and docetaxel since they both hit the same targets.

We learned that trastuzumab binds to the HER2 receptor and changes signaling so that there is a transient decrease in DNA repair. The platinum salts work by damaging DNA in a specific way, which is reparable by DNA repair mechanisms that are shut down significantly by trastuzumab. Docetaxel appears to be significantly superior to paclitaxel in the ability to induce programmed cell death. When trastuzumab and docetaxel are used together, the ability to induce programmed cell death is increased significantly. We do not see the same thing with paclitaxel.

In Vitro Drug Interactions Between Trastuzumab and Select Chemotherapeutic Agents

Synergistic	Additive	Antagonistic
cisplatin	doxorubicin	5-fluorouracil
docetaxel	paclitaxel	
thiotepa	methotrexate	
4-OH cyclophosphamide	vinblastine	
vinorelbine		
etoposide		

Pegram MD et al. *Sem Oncol* 2000;27(6suppl 11):21-5.

Phase II trials of trastuzumab/chemotherapy combinations

Trastuzumab plus chemotherapy — in particular the platinum salts — gave us an objective response rate of 25%. Cisplatin alone in refractory breast cancer is very inactive and not used very often. It has a reported response rate of about 7%. But when combined with trastuzumab, which has a response rate of about 12%, there was more than an additive effect.

Cardiotoxicity with different chemotherapy combinations

When trastuzumab was used in combination with an anthracycline, there was a significant increase in cardiotoxicity. In the pivotal phase III trial, about half of the patients with cardiotoxicity had class I and II, and the other half had class III and IV. Doxorubicin alone is known to cause a 9% incidence of cardiotoxicity. Patients with clinical cardiotoxicity can be treated with diuretics and ACE inhibitors. When they improve, they can continue on trastuzumab. Or, if the trastuzumab is discontinued, their cardiac function can improve.

We believe the cardiotoxicity associated with paclitaxel/trastuzumab was probably a recall phenomenon because of the data from Chuck Vogel's study in patients with HER2-positive disease who did not receive chemotherapy. Those patients were treated with trastuzumab alone, and the cardiac dysfunction rate was just under 4%. All were subclinical. Trastuzumab by itself, in a population of patients with minimal anthracycline exposure, was not a major cardiotoxin.

Phase II Trastuzumab Plus Chemotherapy Trials in Women with HER2-Positive Metastatic Breast Cancer

	Number of Subjects	Overall Response Rate
Weekly paclitaxel/trastuzumab		
Fountzilas G. *Ann Oncol* 2001;12:1545-51.	34	62%
Seidman AD. *JCO* 2001;19:2587-95.	50	67%-81%
Paclitaxel/gemcitabine/trastuzumab		
Miller KD. *Oncology (Huntingt)* 2001;15 (2 Suppl 3):38-40.	27	not reported
Docetaxel/trastuzumab		
Burris H. *Sem Oncol* 2001;28;38-44.	16	45%
Uber K. *Proc ASCO* 2001. #1949.	19	63%
Meden H. *Proc ASCO* 2001. #1987.	12	50%
Esteva FJ. *JCO* 2002;20:1800-8.	30	63%
Docetaxel/carboplatin/trastuzumab		
Slamon DJ. *Proc ASCO* 2001. #193.	14	64%
Docetaxel/cisplatin/trastuzumab		
Pienkowski T. *Proc ASCO* 2001. #2030.	34	76%
Weekly vinorelbine/trastuzumab		
Burstein HJ. *Proc ASCO* 2002. #211.	50	64%
Burstein HJ. *JCO* 2001;19:2722-30.	40	75%
Jahanzeb M. *Proc ASCO* 2001. #1986.	20	60%
Liposomal anthracycline/trastuzumab		
Theodoulou M. *Proc ASCO* 2002. #216.	33	58%

Biologic explanation for cardiotoxicity

Early studies looking at the distribution of HER2 receptors in human tissues found many in the fetal heart but very few in the adult heart. So we thought we would be okay in terms of the toxicity profile.

However, subsequently in the adult heart of laboratory animals, Ken Chien created a conditional knockout of the HER2 gene; he also stressed the animals and found that they developed a dilated cardiomyopathy. This

proved mechanistically that the HER2 receptor plays some role in maintaining cardiac performance and function. Therefore, if we inhibit the HER2 receptor and stress the heart, we see this cardiac problem.

Carboplatin or cisplatin plus docetaxel/trastuzumab (CTH)

The platinum salts in combination with docetaxel/trastuzumab have a robust response rate. Two different phase II trials (BCIRG 101 and 102) have treated 124 patients. The response rate for CTH is as good as that with an anthracycline/cyclophosphamide/trastuzumab or paclitaxel/trastuzumab. For cisplatin/docetaxel/trastuzumab, there is almost a five-month improvement in the median time to progression for patients with FISH-positive tumors. For carboplatin/docetaxel/trastuzumab the difference is even more dramatic.

This has been confirmed by Skip Burris in his study with carboplatin/docetaxel/trastuzumab. Skip's trial, the BCIRG trial and the UCLA trial are all nonrandomized. The US Oncology trial being reported at this year's San Antonio meeting is showing the same thing — the CTH combination is far superior to anthracycline regimens.

Results from BCIRG 101 and 102: First-line therapy in women with HER2-overexpressing metastatic breast cancer

	Cisplatin/docetaxel/trastuzumab BCIRG 101			Carboplatin/docetaxel/trastuzumab BCIRG 102		
Response Rate	**All (N=62)**	**FISH + (N=35)**	**FISH - (IHC 2+/3+) (N=19)**	**All (N=59)**	**FISH + (N=38)**	**FISH - (IHC 2+/3+) (N=19)**
Overall	79%	77%	84%	56%	64%	41%
Complete	5%	6%	5%	14%	19%	6%
Partial	74%	71%	79%	42%	44%	35%
Median Time to Progression (months)	**All (N=62)**	**FISH + (N=35)**	**FISH - (N=19)**	**All (N=59)**	**FISH + (N=38)**	**FISH - (N=19)**
	9.9	12.7	7.9	12	17	7.4

Nabholtz JM et al. **Results of two open label multicentre phase II pilot studies with Herceptin in combination with docetaxel and platinum salts (Cis or Carboplatin) (TCH) as therapy for advanced breast cancer (ABC) in women with tumors over-expressing the HER2-neu proto-oncogene.** *Eur J Can* 2001;37(suppl 6);190.**Abstract 695**

Preclinical data on trastuzumab/hormonal therapy combinations

Clinical data was emerging indicating that patients with HER2-positive breast cancer tended to be less responsive to tamoxifen. In fact, that is exactly what the preclinical model demonstrated. Adding trastuzumab significantly reverses tamoxifen resistance. This question still needs to be addressed in clinical trials.

Fulvestrant works at the level of the activated receptor, binding to the estrogen response element. Since fulvestrant does not allow the activated receptor to do its job, it does not matter how the estrogen receptor is activated. Fulvestrant might be effective in HER2-positive breast cancer because it works lower down in the pathway. Based on the available data, fulvestrant looks like the most promising hormonal agent used in combination with trastuzumab. But the aromatase inhibitors have not been tested as thoroughly as necessary.

PHASE II/III RANDOMIZED STUDY OF ANASTROZOLE WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN) IN POSTMENOPAUSAL WOMEN WITH HORMONE RECEPTOR-POSITIVE HER2-OVEREXPRESSING METASTATIC BREAST CANCER Open Protocol

Protocol IDs: ROCHE-BO16216, GENENTECH-H2223g

Eligibility	ER-positive, HER2-positive (IHC 3+ or FISH-positive) metastatic breast cancer
ARM 1	Anastrozole 1 mg qd + trastuzumab qw
ARM 2	Anastrozole 1 mg qd

Treatment continues in both arms for at least two years in the absence of disease progression or unacceptable toxicity

STUDY CONTACT
Bernd Langer, Chair. Ph: 41-61-68-80638
Roche Global Development-Palo Alto

Source: NCI Physician Data Query, November 2002

Duration of trastuzumab therapy

There are no data currently addressing the optimal duration of trastuzumab therapy. MD Anderson is trying to do a study of this, but the pharmacokinetics of trastuzumab may intercede with the results. After trastuzumab is discontinued, it is still on board when the next chemotherapeutic agent is given. Because of the unique half-life of the drug, these antibodies can be around for three to six months. In the MD Anderson trial, one group will stop trastuzumab, and another drug will be added, and the other group will continue the trastuzumab. The group that stops the trastuzumab and has a second drug added is still having that drug added in the presence of trastuzumab.

Based on preclinical data, our approach is to continue trastuzumab after the patient has progressed on their first trastuzumab/chemotherapy regimen and to add a different chemotherapeutic agent or I generally use a second

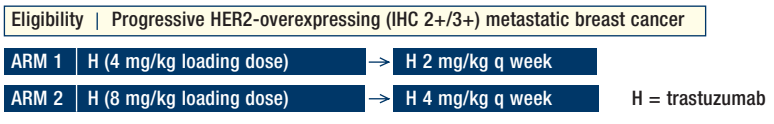
synergistic agent like vinorelbine. In the future, we will probably be switching to a different biologic therapy. If the patient is progressing rapidly on their second regimen of trastuzumab and chemotherapy, my own approach is to stop the trastuzumab. If the patient has a slow progression of their disease, I continue the trastuzumab. It is a matter of clinical judgment in the absence of clinical data.

Patients with HER2-positive, ER-negative metastatic disease

Systemic therapy is individualized to the patient. It depends on what she has received previously, her general health, comorbid diseases and a number of different factors. All things being equal and the patient being capable, I opt for the most optimum interactive combination of CTH. Trastuzumab can, however, be combined with vinorelbine, capecitabine or gemcitabine.

In terms of the response rate, trastuzumab monotherapy is inferior, but the survival data looks comparable to that with the trastuzumab/chemotherapy combination. Therefore, I am quite comfortable in a patient who cannot tolerate or does not want chemotherapy to offer trastuzumab monotherapy. It is not, however, my usual recommendation, which is to exploit any potential synergies. HER2-positive breast cancer is very aggressive, and we want to take our best shot at the disease.

Randomized Study of Standard versus Higher Dose Trastuzumab Monotherapy as First-line Therapy in Women with HER2-overexpressing Metastatic Breast Cancer



Response, clinical benefit and survival with first-line trastuzumab

Subset	Objective Response	Clinical Benefit*	Median Duration of Survival
All Patients	29/111 (26%)	42/111 (38%)	24 months
ER-positive	12/52 (23%)	19/52 (36%)	–
ER-negative	16/54 (30%)	21/54 (39%)	–
IHC 3+	29/84 (35%)	40/84 (48%)	–
IHC 2+	0/27 (0%)	2/27 (7%)	–
FISH +	27/79 (34%)	38/79 (48%)	–
FISH -	2/29 (7%)	3/29 (10%)	–

*Clinical Benefit = complete, partial or minor response or stable disease > 6 months.
Note: There was no evidence of a dose-response relationship for response, survival or adverse events.

DERIVED FROM: Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20:719-726.

Chemotherapy and trastuzumab in the metastatic setting

Oncologists: Which therapy would you utilize in the following patients with ER-negative, HER2-positive asymptomatic bone metastases who have not received prior adjuvant therapy?

Therapy	43-year-old	63-year-old	78-year-old
Chemotherapy alone	30%	40%	25%
Chemo + trastuzumab	55%	35%	30%
Trastuzumab alone	15%	25%	45%

Source: 2002 national survey of 100 oncologists

Use of trastuzumab for metastatic disease

It is shocking to think that patients with HER2-positive metastatic breast cancer would not be treated with trastuzumab up front. There is a survival advantage with trastuzumab — the only agent with a survival advantage in metastatic breast cancer. How can one justify not using it?

Adjuvant trastuzumab trials

I felt strongly that trastuzumab should not have been combined with anthracycline-based therapy when it moved into the adjuvant setting. Yet, two U.S. cooperative groups have insisted on developing this drug with anthracycline-based therapy.

In patients with HER2-positive metastatic breast cancer, which is very aggressive and uniformly lethal with the old treatments, taking risks makes sense as long as the patient and physician are aware and patients are monitored. In the adjuvant setting, some patients may be cured by the initial radiation and surgery.

Therefore, I think it is ill advised to put those HER2-positive women on an anthracycline-based regimen — with the risk of cardiac dysfunction — particularly if there are regimens that look superior in terms of their efficacy based on preclinical synergy.

BCIRG-006

I wanted only two experimental arms — doxorubicin/cyclophosphamide followed by docetaxel (AC → T) and cisplatin or carboplatin plus docetaxel/trastuzumab (CTH). But, there is a third arm with doxorubicin and cyclophosphamide followed by docetaxel/trastuzumab, which is very similar to the arms in the NSABP and the Intergroup trials. We have not seen any cardiotoxicity signal yet.

PHASE III RANDOMIZED STUDY OF DOXORUBICIN PLUS CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN) IN PATIENTS WITH HER2-OVEREXPRESSING NODE-POSITIVE BREAST CANCER **Open Protocol**

Protocol IDs: NCCTG-N9831, CLB-49909, E-N9831, GUMC-00224, SWOG-N9831

Eligibility | HER2-positive adenocarcinoma with ≥ 1 positive lymph node

ARM 1 | AC x 4 → T qw x 12

ARM 2 | AC x 4 → T qw x 12 → H qw x 52

ARM 3 | AC x 4 → (T + H) qw x 12 → H qw x 40

AC=doxorubicin/cyclophosphamide; T=paclitaxel; H=trastuzumab
All ER/PR-positive patients receive tamoxifen x 5 years.
Source: NCI Physician Data Query, November 2002

PHASE III RANDOMIZED STUDY OF DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN) IN WOMEN WITH NODE-POSITIVE BREAST CANCER THAT OVEREXPRESSES HER2 **Open Protocol**

Protocol ID: NSABP-B-31

Eligibility | HER2-positive adenocarcinoma with ≥ 1 positive lymph node

ARM 1 | AC x 4 → T x 4

ARM 2 | AC x 4 → T x 4 + H (qw x 52 weeks)

AC=doxorubicin/cyclophosphamide; T=paclitaxel; H=trastuzumab
ER/PR-positive patients receive tamoxifen for 5 years. Patients > 50 years old or who are ER/PR-negative or indeterminable or patients who have received prior chemopreventive tamoxifen may be treated with tamoxifen at investigator's discretion.
Source: NCI Physician Data Query, November 2002

PHASE III RANDOMIZED STUDY OF ADJUVANT DOXORUBICIN, CYCLOPHOSPHAMIDE AND DOCETAXEL WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN) VERSUS TRASTUZUMAB, DOCETAXEL AND EITHER CARBOPLATIN OR CISPLATIN IN WOMEN WITH HER2-NEU-EXPRESSING NODE-POSITIVE OR HIGH-RISK NODE-NEGATIVE OPERABLE BREAST CANCER **Open Protocol**

Protocol IDs: BCIRG-006, AVENTIS-TAX-GMA-302, NCI-G01-1978, UAB-0106, UCLA-0102006, UAB-F010326022

Eligibility | Node-positive or high-risk node-negative, HER2-overexpressing (FISH-positive) breast cancer

ARM 1 | AC x 4 → T x 4

ARM 2 | AC x 4 → T x 4 + H (qw x 12 weeks) → H (40 weeks for remainder of year)

ARM 3 | T + (cisplatin or carboplatin) x 6 + H (qw x 18 weeks) → H (34 weeks for remainder of year)

AC=doxorubicin/cyclophosphamide; T=docetaxel; H=trastuzumab
ER/PR+ patients receive tamoxifen

SOURCE: NCI Physician Data Query, November 2002

Neoadjuvant trastuzumab trials

Since we can obtain tissue, preoperative trials are a very good strategy to learn about the biology of the disease. From those tissues, we can hopefully learn which patients will be responders or nonresponders and the degree of response. I am most interested in learning about the downstream targets of the HER2 pathway and the intersecting targets with the HER2 pathway.

Phase II Study of Preoperative Trastuzumab (H) and Paclitaxel (T) for HER2-Overexpressing (HER2+) Stage II/III Breast Cancer

TRIAL SCHEMA

H + T x 3 months → Surgery → Adjuvant **AC** q3w x 4

↑	↑	↑	↑
LVEF SERA	LVEF SERA	LVEF	LVEF SERA

LVEF = Cardiac function assessment
SERA = Assessment of HER2 extracellular domain (ECD)
H= trastuzumab; T=paclitaxel; AC=doxorubicin/cyclophosphamide

PATIENT CHARACTERISTICS n=40

Age (median)	49
Clinical stage	
II	55%
III	43%
HER2 IHC	
2+	20%
3+	80%
ER +	65%

SUMMARY OF RESULTS

- Neoadjuvant H+T:
  - overall clinical response rate: 73%
  - HER2 IHC 3+ clinical response rate: 84%
  - pathological complete response rate: 18%
- HER2 expression persists in some patients after trastuzumab-based therapy, even in patients with clinical response
- Sequential neoadjuvant H+T followed by surgery and adjuvant AC:
  - grade 2 cardiac toxicity: 13%
- HER2 ECD in women with HER2-positive stage II/III breast cancer:
  - ECD elevated in 24% of cases, particularly among HER2 3+patients
  - may predict clinical response to trastuzumab-based therapy

Derived from Burstein HJ et al. **2001 San Antonio Breast Cancer Symposium**;Poster 507.

Assessing HER2 status

Immunohistochemistry (IHC)

IHC was all we initially had available for testing, but early on we saw that IHC was flawed. IHC has a false-negative rate of about 18%. In a good laboratory, the false-positive rate for IHC is probably a few percent; it goes up to 8% in general laboratories and was as high as 40% in some of the early

reported trials.

Mike Press has data demonstrating a 52% concordance with the Dako HercepTest™ among Dako-approved pathologists. The College of American Pathologists has done its own study, evaluating the concordance between a central laboratory and pathologists in the community. They are seeing similar trends.

Fluorescence in situ hybridization (FISH)

It has been consistently shown that FISH is superior to IHC. In the Genentech data set, which has been looked at very critically, the benefit with trastuzumab was not consistent in the patients with IHC-positive disease. When those cases were analyzed, the bulk of the benefit was seen in the patients with FISH-positive disease.

FISH is not a subjective test. If one can count dots, there should not be false-positives. If false-positive FISH results were a real phenomenon, the College of American Pathology (CAP) study should have detected it. CAP took cases it characterized and sent them to pathologists in community practice, not university pathologists. Ray Tubbs has done this study, and they are seeing great concordance.

Discordance between IHC and FISH

In two trials, the patients with IHC 3+ and FISH-negative disease had a response rate of zero to trastuzumab-based therapy. In one trial, two patients with IHC 3+ and FISH-negative disease responded; those cases need to be reanalyzed to make sure they are indeed FISH-negative. Since blocks were never kept, they had to use stained slides, take the cover slips off, unstain the slides and then do the FISH test.

Patients with IHC 0 or 1+ and FISH-positive disease are HER2-positive. By the traditional HercepTest™, those patients would have never gotten trastuzumab. This problem with IHC is a function of the fixation of the tumor when it goes into formalin.

Reason for false-negative IHC results

If we had frozen material on all patients at the time of diagnosis, IHC would be just fine. The problem occurs because formalin works by cross-linking proteins. HER2 is a protein that is progressively cross-linked. The longer the tissue is in the formalin, the more cross-linking and masking of the epitope occurs.

Cross-linking to other proteins covers up the HER2 epitope, which is detected by the antibody. Dako has tried to introduce antigen retrieval to make that better. Although one can put all kinds of fancy scanners onto the tissue, if one does not control the fixation of the tissue, there is no way one can control what is tested.

Benefit of FISH compared to IHC

If one wants to know whether a patient has the HER2 alteration, one should do FISH testing. One should not do a default IHC and only if they are 2+, then do a FISH. Using that algorithm, patients without the HER2 alteration will be treated with trastuzumab, and other patients with the HER2 alteration may not be treated. The BCIRG trial we are conducting was designed with FISH as the only criteria for assessing HER2 status.

Every patient should have their HER2 status assessed by FISH testing. We do not use or recommend IHC. I think the day when just FISH testing is used in the community is coming, and I hope it will be sooner, rather than later.

A chronology of select breast cancer publications by Dr Slamon

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Post-test

Questions *(please circle answer)*:

1. Preclinical studies indicate that trastuzumab is synergistic with:
- a. Paclitaxel
- b. 5-FU
- c. Docetaxel
- d. a and c
- e. All of the above

2. The platinum salts damage DNA. Trastuzumab is synergistic with the platinum salts since it causes a transient increase in DNA repair.
- a. True
- b. False

3. Which of the following is likely to be most synergistic with trastuzumab?
- a. Tamoxifen
- b. Megestrol acetate
- c. Fulvestrant
- d. All of the above

4. Cardiotoxicity was the dose-limiting toxicity encountered in the phase I trastuzumab trials.
- a. True
- b. False

5. BCIRG 101 and 102 assessed the efficacy of carboplatin or cisplatin in combination with docetaxel/trastuzumab.
- a. True
- b. False

6. In the pivotal phase III trastuzumab trial, which regimen had the highest response rate?
- a. Paclitaxel/trastuzumab
- b. Anthracycline/cyclophosphamide/trastuzumab
- c. Trastuzumab alone
- d. Capecitabine/trastuzumab
- e. Cisplatin/trastuzumab

7. In the pivotal phase III trastuzumab trial, which regimen had the highest incidence of cardiotoxicity?
- a. Paclitaxel/trastuzumab
- b. Anthracycline/cyclophosphamidel/trastuzumab
- c. Trastuzumab alone
- d. Capecitabine/trastuzumab
- e. Cisplatin/trastuzumab

Questions *(please circle answer)*:

8. Several ongoing adjuvant trials are evaluating trastuzumab-containing regimens. Which of the following trials is/are evaluating carboplatin in combination with docetaxel/trastuzumab?

a. Intergroup N9831
b. NSABP B-31
c. BCIRG-006
d. a and c
e. All of the above

9. Which of the following statements is/are correct about the methodologies for assessing HER2 status?

a. False-negative results with IHC may be the result of formalin cross-linking the HER2 protein.
b. The concordance among pathologists is high with the Dako HercepTest™.
c. According to the BCIRG, FISH is a very reproducible test.
d. a and c
e. All of the above

10. Clinical trials have determined the optimal duration of trastuzumab therapy to be one month after progressing on the first trastuzumab-containing regimen.

a. True
b. False

To obtain a certificate of completion and receive credit for this activity, you must complete the exam, fill out the evaluation form and mail or fax both to: Postgraduate Institute for Medicine, P. O. Box 260620, Littleton, CO 80163-0620, FAX (303) 790-4876.

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Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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Please answer the following questions by circling the appropriate rating:
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Extent to which program activities met the identified objectives
Upon completion of this activity, participants should be able to:

- More effectively utilize chemotherapy/trastuzumab combinations in appropriate patients with HER2-positive metastatic breast cancer. 5 4 3 2 1
- More effectively discern the risk of cardiotoxicity associated with various trastuzumab-containing regimens and apply this knowledge when choosing chemotherapeutic agents to minimize the potential for cardiotoxicity in your patients. 5 4 3 2 1
- Develop a more effective algorithm to assess HER2 status and utilize this in selecting appropriate candidates for trastuzumab therapy. 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
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

Will the information presented cause you to make any changes in your practice? ___Yes ___No
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_____

What other topics would you like to see addressed in future educational programs?

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