

Breast Cancer[®]

U P D A T E

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

FACULTY

Larry Norton, MD

Hyman B Muss, MD

Joseph A Sparano, MD

ROUNDTABLE DISCUSSION

Harold J Burstein, MD, PhD

Stephen E Jones, MD

Peter M Ravdin, MD, PhD



Breast Cancer Update

A Continuing Medical Education Audio Series

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.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of switching to or sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions.
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment, nonanthracycline-based regimens and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients.
- Counsel appropriately selected patients with metastatic disease about selection and sequencing of endocrine therapy and chemotherapies and about the risks and benefits of chemotherapeutic agents and combinations.
- Evaluate the emerging data for biologic therapies and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease.
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions.

PURPOSE OF THIS ISSUE OF BREAST CANCER UPDATE

The purpose of Issue 1 of Breast Cancer Update is to support these global objectives by offering the perspectives of Drs Norton, Muss, Sparano, Burstein, Jones and Ravdin on the integration of emerging clinical research data into the management of breast cancer.

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Memorial Hospital for
Breast Cancer Programs
Norna S Sarofim Chair in
Clinical Oncology
Memorial Sloan-Kettering
Cancer Center
New York, New York

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Professor of Medicine
University of Vermont
College of Medicine
and Vermont Cancer Center
Burlington, Vermont

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Professor of Medicine
and Women's Health
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Associate Chairman
Department of Oncology
Montefiore Medical Center
Director, Breast Evaluation
Center
Montefiore-Einstein
Cancer Center
Bronx, New York

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Harold J Burstein, MD, PhD

Assistant Professor of Medicine
Harvard Medical School
Breast Oncology Center
Dana-Farber Cancer Institute
Boston, Massachusetts

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Director, Breast Cancer
Research, Charles A Sammons
Cancer Center
Baylor University Medical Center
Dallas, Texas
Chair, US Oncology
Breast Cancer Research
Medical Director
US Oncology Research
Houston, Texas

Peter M Ravdin, MD, PhD

Clinical Professor of Medicine
The University of Texas
Health Science Center
at San Antonio
San Antonio, Texas

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UPCOMING EDUCATIONAL EVENTS

NCCN 12th Annual Conference: Clinical Practice Guidelines and Quality Cancer Care

March 14-18, 2007

Hollywood, Florida

Event website: nccn.org

Preoperative Therapy in Invasive Breast Cancer: Reviewing the State of the Science and Exploring New Research Directions

March 26-27, 2007

Bethesda, Maryland

Event website: ctep.cancer.gov/bcmeeting

American Association for Cancer Research Annual Meeting

April 14-18, 2007

Los Angeles, California

Event website: aacr.org

NCCTG Semi-Annual Meeting

April 16-19, 2007

Rochester, Minnesota

Event website: nccctg.mayo.edu

NSABP Semi-Annual Meeting

April 27-30, 2007

Jacksonville, Florida

Event website: nsabp.org

SWOG Semi-Annual Meeting

May 2-6, 2007

Chicago, Illinois

Event website: swog.org

ASCO 2007 Annual Meeting

June 1-5, 2007

Chicago, Illinois

Event website: asco.org



EDITOR'S NOTE

Neil Love, MD

A tale of two trials

On this edition of *Breast Cancer Update*, Dr Joseph Sparano chats about two of the most important breast cancer clinical trials of the last decade, both of which are fortunate to have him as their principal investigator.

The first is ECOG-E1199, which was launched in 1999, at a time when the optimal use of taxanes as adjuvant therapy was an issue of great concern. Under Dr Sparano's able leadership, this simply designed trial quickly accrued more than 5,000 patients, who received AC followed by either docetaxel or paclitaxel every week or three weeks.

As discussed in the interview, like many other adjuvant trials in recent years, E1199 ended up having fewer recurrences and deaths than anticipated. After many months of waiting, the Data Safety and Monitoring Committee decided to recommend release of the results before the stipulated number of events had occurred.

ECOG-E1199 was first reported at the 2005 San Antonio Breast Cancer Symposium by Dr Sparano, causing a considerable stir. To many observers' surprise, this two-by-two design didn't demonstrate a great deal of difference between the regimens, but weekly paclitaxel seemed to have the best risk-benefit ratio, although every three-week docetaxel appeared comparable.

The problem is that, thankfully, in the seven years since the trial launched, a lot has happened in research on adjuvant therapy of breast cancer, particularly the release of results of CALGB-9741 and BCIRG 001, demonstrating advantages for dose-dense AC → paclitaxel and TAC, respectively. Another critical development in research on adjuvant chemotherapy was the US Oncology trial led by Steve Jones, which demonstrated superiority in efficacy and tolerability of TC (docetaxel/cyclophosphamide) compared to AC. These regimens are now frequently utilized by medical oncologists and have made the E1199 data somewhat less exciting than was hoped for when the trial was designed.

The recent availability of nanoparticle albumin-bound (*nab*) paclitaxel is another development that is interesting in light of E1199. I am starting to hear a consistent response when breast cancer investigators opine about *nab*. The bottom line is that many would throw old-fashioned paclitaxel (Pac) and its Cremophor[®] base right in the garbage if cost were not an issue. Of interest is our recent Patterns of Care survey, in which 83 percent of breast cancer investigators and

73 percent of practicing oncologists believe that *nab* has a greater antitumor effect than its close cousin, Pac, yet the same survey shows that not that much *nab* is being utilized — mainly because of cost. I wonder what patients would think about this.

Dr Sparano is also the principal investigator of another critical study that has been discussed and eagerly anticipated for several years. TAILORx (aka the PACCT-1 Trial) features a design that only five years ago would have seemed like science fiction. Following the landmark collaboration between Soon Paik of the NSABP and Steve Shak of Genomic Health, patients entering TAILORx will be randomly assigned to one of three study arms based on their *Oncotype DX*TM recurrence score (Figure 1).

1

TAILORx: A Phase III Randomized Trial of Adjuvant Combination Chemotherapy and Hormonal Therapy versus Adjuvant Hormonal Therapy Alone in Women with Previously Resected Axillary Node-Negative Breast Cancer with an Intermediate Score of the *Oncotype DX* Assay

Target Accrual: 10,046 (Open)
Date Activated: April 7, 2006

```

    graph LR
      G1[Group I (RS* < 11)] --> H1[Hormonal therapy†]
      G2[Group II (RS* 11-25)] --> R((R))
      R --> A1[ARM 1: Hormonal therapy†]
      R --> A2[ARM 2: Combination chemotherapy† + hormonal therapy†]
      G3[Group III (RS* > 25)] --> H2[Combination chemotherapy† + hormonal therapy†]
  
```

* *Oncotype DX* recurrence score
† Physician's choice for hormonal therapy and chemotherapy

Select Eligibility Criteria

- ER-positive and/or PR-positive breast cancer
- Negative axillary nodes
- Tissue from primary tumor available for *Oncotype DX* assay
- 18-75 years of age
- HER2-negative
- Tumor size 1.1-5.0 centimeters (tumors 5 mm to 1.0 cm allowed if intermediate or poor nuclear and/or histologic grade or lymphovascular invasion)

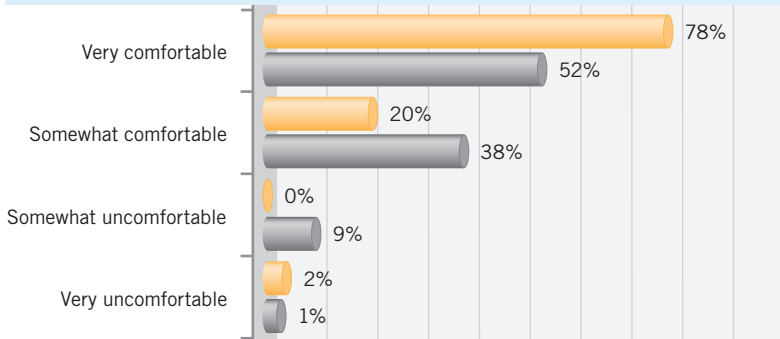
Study Contact

Eastern Cooperative Oncology Group
Joseph Sparano, MD
Tel: 718-920-4826

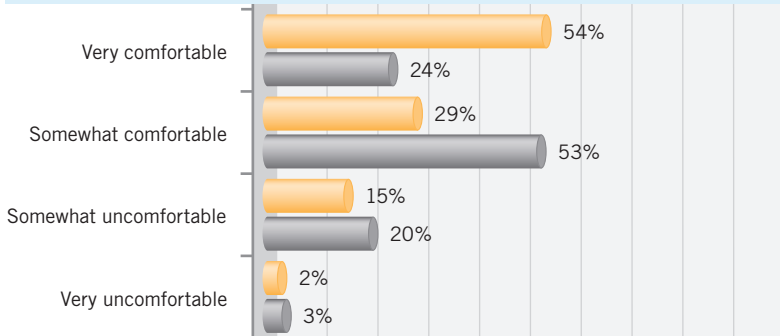
SOURCES: PACCT-1 Protocol, August 23, 2006; ecog.org.

With regard to the TAILORx trial, how comfortable are you with the major clinical paths of the three study groups?

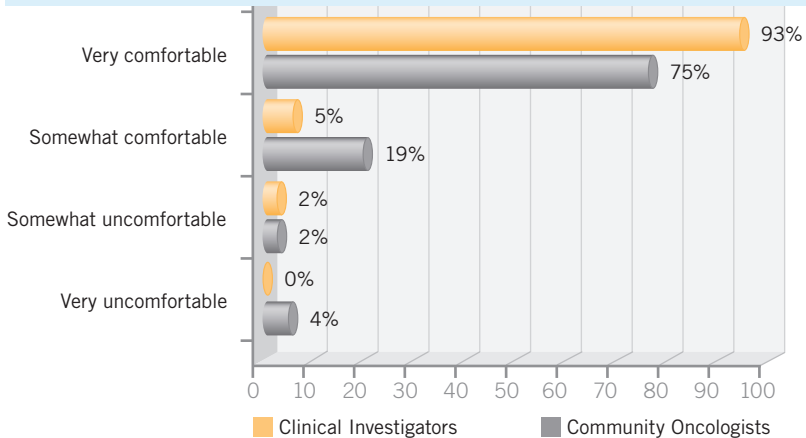
First group (low recurrence scores): Hormone therapy without chemotherapy



Second group (intermediate recurrence scores): Randomization to chemotherapy and hormone therapy or hormone therapy alone



Third group (high recurrence scores): Chemotherapy and hormone therapy



SOURCE: Love N; Research To Practice. *Patterns of Care in Medical Oncology* 2006;3(2).

For the first time in a long, long time, this adjuvant study uses a chemotherapy versus no chemotherapy randomization. Although this may seem controversial, our Patterns of Care study suggests that oncologists are mostly comfortable with the idea of entering patients on this landmark study (Figure 2).

We can only speculate about how TAILORx will be viewed five years from now, but for what it's worth, my bet is that even if the clinical questions being addressed become outdated (as sort of happened with E1199), the careful molecular study of tumors is here to stay, and the correlation with superbly documented follow-up as is being done in this study will provide biologic and therapeutic insights about breast cancer that will shape the next generation of interventions.

I recently spent 90 amazing minutes recording an interview with Soon Paik, and when it was over, my brain hurt. When I told Soon that he reminded me of a physics professor teaching a course I was destined to fail, he chuckled humbly and told me that he didn't understand genomics and proteomics either. Yeah, right.

Cancer patients and their loved ones are relying on geniuses like Soon and Steve Shak to jump-start oncologic research and on clinical leaders like Joe Sparano to take state-of-the-art technologies like *Oncotype* and rally our team to get trials done quickly, and maybe turn this nasty disease into a bad memory.

— Neil Love, MD
NLove@ResearchToPractice.com
January 15, 2007

SELECT PUBLICATIONS

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- Gradishar W et al. **A randomized phase 2 trial of qw or q3w ABI-007 (ABX) vs q3w solvent-based docetaxel (TXT) as first-line therapy in metastatic breast cancer (MBC).** San Antonio Breast Cancer Symposium 2006; [Abstract 46](#).
- Gradishar WJ et al. **Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-803. [Abstract](#)
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- Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26. [Abstract](#)
- Sparano JA et al. **Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: Results of North American Breast Cancer Intergroup Trial E1199.** San Antonio Breast Cancer Symposium 2005; [Abstract 48](#).



INTERVIEW

Larry Norton, MD

Dr Norton is Deputy Physician-in-Chief at the Memorial Hospital for Breast Cancer Programs and Norna S Sarofim Chair in Clinical Oncology at Memorial Sloan-Kettering Cancer Center in New York, New York.

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| Track 3 | Identification of site-specific metastasis genes and functions | Track 12 | Characteristics of molecules associated with metastasis |
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Select Excerpts from the Interview

Tracks 2-4

► **DR LOVE:** Can you discuss the Gompertzian growth hypothesis and how it relates to dose-dense chemotherapy?

► **DR NORTON:** We’ve been interested in Gompertzian growth for decades, which in addition to being interesting has clinical applications. The whole concept of dose density or the scheduling of chemotherapy drugs being at least as important as dose level is dependent on the fact that tumors grow in this Gompertzian fashion.

They start to grow exponentially, but growth eventually trails off and reaches a plateau phase.

No counterexamples have emerged, and everything that's ever been observed to grow in nature, including cancer tumors, follows this kind of growth pattern. Why things follow this growth pattern or why it's so ubiquitous in nature has never been clear.

Understanding why, obviously, could be of tremendous importance because it would not only explain why dose density works, which is derived from the mathematics of Gompertzian growth, but it would also potentially provide some therapeutic targets.

► **DR LOVE:** Can you discuss your self-seeding hypothesis (Norton 2006)?

► **DR NORTON:** I received a phone call from one of my collaborators, Joan Massagué, who has been studying metastasis. He took human breast cancer cells, grew them in appropriate animal models and found cells that were metastasizing to the lung. He then took those cells, reimplanted them in the mammary fat pad of the recipient mice, and developed cell lines that had a high potential for lung metastasis (Minn 2005).

The cell lines with a high probability of metastasizing to the lung grew very rapidly in the mammary fat pad, the primary site in which they were implanted. Also, the genes that were overexpressed in the cell lines with potential for lung metastasis — compared to the genes in the parental cell line — were not associated with cell division, apoptosis or cell loss. They were the genes associated with matrix dissolution, angiogenesis, cell adhesion, et cetera (Minn 2005).

In that discussion, it became evident that one way of explaining the phenomenon of the tumor growing faster in the mammary fat pad was not that the cells were dividing more rapidly but that they were metastasizing back to themselves. In other words, the cells leave the mammary fat pad, and some go to the lung, but some go into circulation and come back to the tumor where they originated.

It's logical from a biologic point of view because that is the organ they're most comfortable in and that is where they were growing in the first place. It would also explain a lot about cancer that, right now, is mysterious. Why is cancer so disorganized histologically? Maybe it's disorganized because tumors are not one entity but a collection of little entities (ie, little metastases). Maybe they're growing quickly because a tumor is not one big mass but a collection of little masses.

The bottom line is that we're convinced aggressive cancers attract their own cells that go out into circulation. We've termed this "self-seeding" because it's reminiscent of the way weeds take over your garden (Norton 2006; [1.1]).

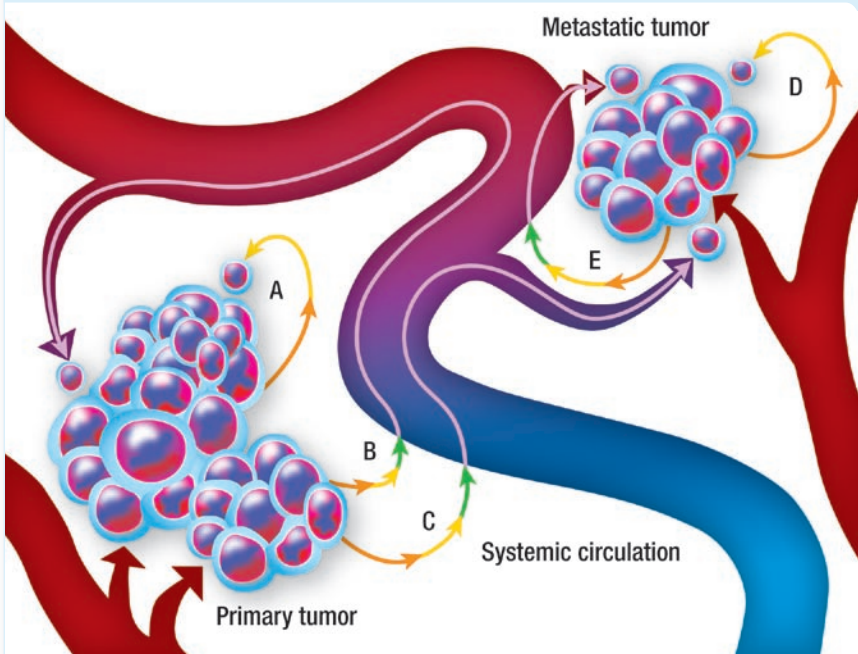
A weed takes over your garden by seeding other weed plants. Each weed plant is not particularly fast growing or large. It's not the weed that takes over your

garden — it's the weed bed. Weeds are invasive — they invade the normal plants in your garden — and they are metastatic because the same seeds that can fall in your garden can fall in your neighbor's garden.

It ties together closely with the stem cell theory because the seeds may indeed be stem cells. That's why they are causing continued growth wherever they're found, because each one is a nidus of another tumor focus.

1.1

Self-Seeding Concept of Cancer Growth and Metastasis



Self-seeding may take place along the following paths: (A) dislodging and reattachment of a primary tumor cell at the primary site; (B) dislodging, intravasation, circulation, then extravasation back to the primary site; (C) dislodging, intravasation, circulation, then extravasation to a metastatic site; (D or E) self-seeding from a metastatic site following path A or B.

SOURCE: Reprinted by permission from Macmillan Publishers Ltd: *Nature Medicine*. Norton L, Massagué J. **Is cancer a disease of self-seeding?** *Nat Med* 2006;12(8):875-8, copyright 2006. No abstract available

Tracks 5-7

▶ **DR LOVE:** Can you discuss the clinical and therapeutic relevance of this hypothesis?

▶ **DR NORTON:** From a therapeutic perspective, the self-seeding concept is

fascinating because we have no drugs to interfere with that process. However, that process should be a rich source of targets because the ability to migrate through the tissues, break away from the primary tumor mass, go into a blood vessel, travel and survive in the blood vessel, come out of the blood vessel, reanchor itself and start to divide involves molecules that must be located on the surface of the cell.

These are all cell-surface phenomena related to adhesion and trying to find a niche in which to grow and develop. It may be that antibodies or small molecules that work against cell-surface molecules are important. All of these are potential areas for drug development.

I can say for sure that I know the phenomenon occurs. How important it is and how it relates proportionally, in terms of malignancy, to other characteristics of cancer remains to be determined. Self-seeding, however, is a truth, and it is a potential target for intervention.

► **DR LOVE:** Are there agents that interfere with this cycle?

► **DR NORTON:** Actually, we believe that the seeding of the metastasis is not the primary problem. The primary problem is growth in metastatic sites. If a “shower” of cancer cells occurred to somebody’s entire body and each cell only divided two or three times to form a microscopic focus that never became any larger, cancer would not be a problem.

The important factor is the growth in the metastatic sites, and we have to consider the possibility that the growth in metastatic sites is also a result of self-seeding in the metastatic sites. The recent paper we published in *Nature Medicine* provides an illustration of this (Norton 2006; [1.1]).

This fascinates me as a biomathematician. If you hypothesize that self-seeding occurs, then self-seeding occurs from the outside in. In other words, cancer grows from the outside inward. The surface area of a mass is related to its diameter squared, whereas the volume of a mass is related to its diameter cubed. Because growth is occurring from the outside in, growth is proportional to the diameter squared, but you’re going to lose cells by spontaneous cell death related to the diameter cubed. The ratio of growth to death will drop over time, and that will give you the Gompertzian phenomenon.

If the hypothesis is true and the curve is an accurate representation of tumor growth, then we don’t have to kill cancer cells, necessarily, to be able to cure patients. We have to affect growth parameters so that each tumor doesn’t grow large — for example, increase cell death slightly or increase the spatial arrangement of the cells on the periphery of the tumor where the growth occurs.

I’m encouraged by the experts in cancer stem cells who have assured me they find cancer stem cells on the periphery of tumors, not in the core of tumors. If we can somehow make these stem cells deposit themselves in the tumor in a more diffuse pattern, rather than such a dense pattern, that may be enough to convert a malignant tumor to a benign mass.

Track 9

► **DR LOVE:** At another level, any speculation about how effective bevacizumab will be in the adjuvant setting? How does that tie into the self-seeding hypothesis?

► **DR NORTON:** Bevacizumab and other anti-angiogenic agents should be studied in the adjuvant setting. In fact, if the self-seeding hypothesis is correct, the earlier you use these agents the more effective they will be because the metastatic process is dependent on seeding.

Early breast cancer, when it's micrometastatic, might be the best time to intervene with the ability of seeds, which have already spread, to attract a blood supply. If anything, the self-seeding theory would suggest that anti-angiogenic therapy should be more active in the adjuvant setting than against advanced disease.

Track 14

► **DR LOVE:** Theoretically, how does dose-dense therapy tie into the self-seeding hypothesis?

► **DR NORTON:** I believe it ties into it because the concept of dose density derives mathematically from the Gompertzian phenomenon. Tumors grow and respond to therapy in a Gompertzian fashion — meaning if they grow fast, they shrink fast and if they grow slowly, they shrink more slowly, which is the Norton-Simon hypothesis (1.2).

1.2

Norton-Simon Hypothesis

“Chemotherapy results in a rate of regression in tumor volume that is proportional to the rate of growth for an unperturbed tumor of that size.”

SOURCE: Simon R, Norton L. *Nat Clin Pract Oncol* 2006;3(8):406-7. No abstract available

If you plug into your thinking Gompertzian growth and regression proportional to rate of growth, then dose density stands out. It implies that the big problem is to kill cancer cells, but you have to come back in with another dose of therapy before they have a chance to regrow. So you pick the dose of the drug that provides the optimal response, and you administer it as often as you can.

Track 15

► **DR LOVE:** How does the concept of dose density relate to the work your group at Memorial has been doing with capecitabine?

► **DR NORTON:** We designed some experiments to observe the growth curves of tumors in mice that were being treated with capecitabine. We found that six,

seven, eight or nine days was the point at which the ratio of the regression to its anticipated growth rate was maximum. If you kept treating at eight, nine, 10, 11, 12, 13 or 14 days, the tumor continued to shrink, but it was shrinking more gradually than it was shrinking on day seven.

To optimize that schedule, one has to stop capecitabine at day seven and then come back with another seven days of therapy as soon as possible, which is the dose-dense concept. You pick the optimal dose and schedule and administer it as often as possible.

We explored, in animal models, capecitabine administered seven days on and seven days off. It is remarkable that we could drive the dose level much higher. If you don't have to worry about the second week of therapy, you can push the dose level higher, which causes even more regression. We obtained fantastic results in the animal models.

Based on that evidence, Maria Theodoulou, Cliff Hudis and Tiffany Traina have been conducting at Memorial Sloan-Kettering a Phase I/II trial of capecitabine administered seven days on and seven days off. The trial is still ongoing because we can't reach the maximum tolerated dose.

We've gone much higher with the capecitabine dose than we ever could have imagined. Responses are terrific, and the toxicity is greatly minimized. Just as we discovered with the use of filgrastim or pegfilgrastim with AC → paclitaxel every two weeks (Citron 2003; Hudis 2005; Burstein 2005), we have greater efficacy with less toxicity. The seven days on, seven days off with capecitabine seems to be efficacious. In addition, it's less toxic than 14 days on and seven days off.

► **DR LOVE:** Are we moving toward adjuvant dose-dense AC → paclitaxel followed by capecitabine?

► **DR NORTON:** People are talking about that regimen now, especially in the setting of preoperative dose-dense AC → T, because not all patients will have a pathologic complete remission. If you use dose-dense AC → T and you don't obtain a pathologic complete remission, then you have residual cells that are probably resistant to those agents. Therefore, dose-dense capecitabine at that point would be a reasonable idea. We're also considering combinations of dose-dense capecitabine with antivascular agents, such as bevacizumab, and anti-HER2 agents.

Track 17

► **DR LOVE:** Where are we with dose-dense AC → paclitaxel/trastuzumab?

► **DR NORTON:** Chau Dang, in our program, has completed a study, and we're still following the last patient out far enough to be able to publish definitive results. We have, however, presented mature preliminary results several times (Dang 2006, 2005).

The major observation we've made is that cardiotoxicity is extremely acceptable (Dang 2006; [1.3]). We're certainly not seeing any more cardiotoxicity with dose-dense AC → paclitaxel/trastuzumab than with the nondose-dense use of those agents. We might be seeing less cardiotoxicity with dose-dense therapy than we saw before.

In CALGB-9741, dose-dense AC produced less cardiotoxicity than every three-week AC (Citron 2003; Hudis 2005). If the chemotherapy itself had less cardiotoxicity, then the additional incremental impact of trastuzumab would be less as well.

Currently, dose-dense AC → paclitaxel/trastuzumab is our standard of care for adjuvant therapy in HER2-positive disease. ■

1.3

Preliminary Cardiac Safety Results of Dose-Dense Doxorubicin/ Cyclophosphamide Followed by Paclitaxel with Trastuzumab

Timing of MUGA*	N	Median LVEF	LVEF range
Baseline	70	68%	55%-81%
Month 2	70	67%	58%-79%
Month 6	67	66%	56%-75%
Month 9	41	65%	57%-72%

* MUGA obtained at baseline and repeated at months 2, 6, 9 and 18

SOURCE: Dang C et al. Presentation. *Proc ASCO* 2006; [Abstract 582](#).

SELECT PUBLICATIONS

Burstein HJ et al. **Efficacy of pegfilgrastim and darbepoetin alfa as hematopoietic support for dose-dense every-2-week adjuvant breast cancer chemotherapy.** *J Clin Oncol* 2005;23(33):8340-7. [Abstract](#)

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9. [Abstract](#)

Dang C et al. **Updated cardiac safety results of dose-dense (DD) doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) with trastuzumab (H) in HER2/neu overexpressed/amplified breast cancer (BCA).** *Proc ASCO* 2006; [Abstract 582](#).

Dang C et al. **Preliminary cardiac safety results of dose-dense (DD) doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) with trastuzumab (H) in HER2/neu overexpressed/amplified breast cancer (BCA).** Poster. San Antonio Breast Cancer Symposium 2005; [Abstract 2041](#).

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Norton L. **Conceptual and practical implications of breast tissue geometry: Toward a more effective, less toxic therapy.** *Oncologist* 2005;10(6):370-81. [Abstract](#)



INTERVIEW

Hyman B Muss, MD

Dr Muss is Professor of Medicine at the University of Vermont College of Medicine and Vermont Cancer Center in Burlington, Vermont.

Tracks 1-17

- | | | | |
|----------------|---|-----------------|---|
| Track 1 | Introduction | Track 10 | Evaluating schedule, dose and chemotherapy combinations of capecitabine in the adjuvant setting |
| Track 2 | Toxicity in older and younger patients treated with adjuvant chemotherapy: The CALGB experience | Track 11 | Use of capecitabine with bevacizumab as first-line therapy |
| Track 3 | Mortality comparison of the CALGB elderly population to a matched national population | Track 12 | Upcoming and ongoing adjuvant clinical trials |
| Track 4 | CALGB adjuvant trial 49907: Capecitabine versus AC or CMF in elderly patients | Track 13 | Incorporation of nanoparticle albumin-bound (<i>nab</i>) paclitaxel into the adjuvant setting |
| Track 5 | Quality of life and compliance subprotocols in CALGB-49907 | Track 14 | Offering clinical trial participation to elderly patients |
| Track 6 | Correlative science and toxicity studies on CALGB-49907 | Track 15 | Selection of elderly patients for treatment with adjuvant chemotherapy |
| Track 7 | Effect of adjuvant chemotherapy on cardiac function | Track 16 | Selection of adjuvant chemotherapy for patients with hormone receptor-negative, node-positive disease |
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| Track 9 | Adjuvant docetaxel/cyclophosphamide (TC) versus AC | | |

Select Excerpts from the Interview

Track 2

► **DR LOVE:** Can you discuss data from your toxicity analysis of chemotherapy in older patients who participated in CALGB studies?

► **DR MUSS:** We analyzed data from three Cancer and Leukemia Group B clinical trials that were conducted over a span of years (Muss 2006), including CALGB-9344, which compared AC with or without paclitaxel. We previously had shown that older women in these studies derived the same proportional

benefit as the younger patients in terms of relapse-free survival and overall survival (Muss 2005).

For instance, a woman older than 65 years of age who was receiving the paclitaxel-containing regimen after AC experienced similar benefits from paclitaxel to those the younger patients experienced in this study, in aggregate. Therefore, we feel that age was not a variable predictive of benefit from chemotherapy. These trials all comprised highly selected patients with node-positive disease.

We went back and assessed detailed toxicity in three of the clinical trials. Of approximately 6,500 patients, only seven percent were 65 years and older and only three percent were 70 and older. It sounds as if those numbers were small, but when you consider what's out there, these are some of the largest numbers of patients analyzed prospectively in a trial.

► **DR LOVE:** How many treatment-related deaths did you find?

► **DR MUSS:** Approximately 24 deaths were attributed to therapy (2.1). When you run a large clinical trial and a patient gets neutropenic fever and dies in the hospital, it's a catastrophe. It's obviously therapy related. But if someone dies of heart trouble four years after receiving an anthracycline-containing therapy, is that related? The 24 deaths attributed to therapy were coded by the principal investigator. It was his or her decision whether or not a death was treatment related.

Comparing those numbers with the size of the groups being treated, we found treatment-related death occurred in 1.5 percent of women age 65 and older, but the confidence interval was wide.

If you calculate trend statistics, the older patients have a higher probability of dying as a result of treatment. We also wanted to see if we could figure out a way to determine whether older people could be dying later on of treatment-related toxicity, such as cardiac disease, leukemia, et cetera.

For leukemia, it's interesting. Of the 24 deaths, we didn't have one septic death attributed to treatment in these three trials. That was probably good luck because in larger trials, one or two patients always die as a result of a defined, well-used adjuvant program, but we didn't see it here.

We saw a substantial number of patients with acute leukemia, and they tended to be older patients. The leukemia tended to fit in the right time range — five to 10 years, which is when you expect treatment-related leukemia to occur. Factoring this out, the elderly had a higher risk of leukemia than the younger patients. Of the seven older patients who died of treatment-related causes, five deaths were from leukemia.

► **DR LOVE:** If a 70-year-old woman who is receiving dose-dense AC and paclitaxel asks you her chances of developing treatment-related leukemia, what do you say?

► **DR MUSS:** It's about a half to one percent. In Dr Hudis's update (Hudis 2005)

of CALGB-9741, which compared the dose-dense regimen with the every three-week regimen, the incidence of AML/MDS was 0.7 percent, which is substantial.

2.1

Grade III/IV Toxicity and Mortality Rates According to Age in Women Who Participated in Adjuvant CALGB Trials That Included Intensive Chemotherapy Regimens

Toxicity (%)	Age < 50 years N = 3,676	Age 51 to 64 years n = 2,480	Age 65 years+ n = 486
WBC*	16	17	17
Platelets*	3	4	4
Nausea	8	6	5
Vomiting	2	1	2
Stomatitis	5	5	5
Diarrhea	<2	3	<5
Neurologic	<9	9	<9
Treatment-related death	0.19	0.32	1.4
AML/MDS death	0.03	0.20	1.0
CHF death	0.14	0.12	0.21

* Grade IV

SOURCE: Muss H et al. *Proc ASCO* 2006; **Abstract 559**.

 **Track 4**

► **DR LOVE:** Would you discuss CALGB-49907?

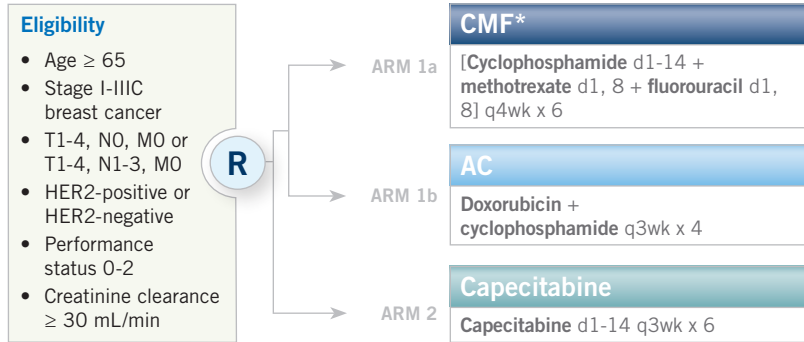
► **DR MUSS:** We’re conducting a clinical trial through the Intergroup, CTSU with CALGB, evaluating chemotherapy with the oral agent capecitabine versus standard therapy for women age 65 years and older. Standard therapy in this trial is either CMF using an oral cyclophosphamide regimen for six months or AC for four cycles. Capecitabine is administered at a dose of 2,000 mg/m² for 14 days out of every 21 days for six cycles (2.2).

We’ve enrolled 600 patients, which is our first cutoff for a Bayesian analysis to assess whether to continue the trial or stop it. The Data Safety Monitoring Board will evaluate the data and the event rates.

If it seems highly improbable that the capecitabine regimen will be less effective than standard therapy, the study will be stopped. If it’s a “slam dunk” that either AC or CMF is better than capecitabine, then the study will be stopped. If the results are in the middle, we will go on to accrue several hundred more patients. We hope this analysis will be completed over the next several months and that the data will be helpful.

CALGB-49907: Randomized Phase III Study of Adjuvant Chemotherapy in Elderly Women

Target Accrual: 1,800 within 2-6 years



* Patients with insufficient left ventricular ejection fraction (LVEF) are assigned to CMF. Patients with normal LVEF are assigned to CMF or AC based on physician/patient choice.

Use of Trastuzumab

Adjuvant trastuzumab will be allowed following protocol chemotherapy only for patients whose tumors are HER2-positive by either IHC 3+ staining or gene amplification by FISH.

A 52-week course of trastuzumab will be permitted for all patients with HER2-positive disease after completion of protocol chemotherapy.

The concurrent use of chemotherapy and trastuzumab is not acceptable.

Study Contacts

Cancer and Leukemia Group B
Hyman Muss, MD, Protocol Chair
Tel: 802-847-3827; 800-358-1144

Eastern Cooperative Oncology Group
Antonio Wolff, MD, Protocol Chair
Tel: 410-614-4192

Southwest Oncology Group
Julie Gralow, MD, Protocol Chair
Email: pink@u.washington.edu

NCIC-Clinical Trials Group
Debjani Grenier, MD, Protocol Chair

SOURCES: CALGB 49907/CTSU 49907 Protocol, May 15, 2006; cancer.gov.

Track 10

► **DR LOVE:** What are your thoughts about the work that's coming out of Memorial Sloan-Kettering, evaluating capecitabine one week on and one week off — the so-called dose-dense capecitabine?

► **DR MUSS:** I've seen some of the preclinical data, and they're intriguing. Maybe the dose-dense approach is a better way to administer capecitabine. I believe capecitabine is extremely effective.

We've used a fixed dose of capecitabine. I believe there's a lot more we can learn about this drug. For instance, would capecitabine be a good choice for metronomic low-dose chemotherapy to administer over a long period? I'm not sure we know the optimal dose or threshold dose of capecitabine.

I treated one woman with metastatic disease who was in her eighties with 500 milligrams BID because she said, "If I get the least bit sick from your treatment, I'm never coming back to see you." She had extensive pulmonary metastases, so I figured I could risk it.

She had a response that lasted about nine months, and when she came back without toxicity, I said maybe if we pushed up the dose, we'd do better. Of course, she was logical and said, "Why? Why would you want to do it?"

We still have a lot of fundamental biology to learn about capecitabine, and there may be better ways to administer it. Perhaps the dose-dense approach, which follows much of Larry Norton's work and mathematic models, will be a better way.

► **DR LOVE:** What about the research question of adding capecitabine to some of the existing regimens — for example, following dose-dense AC → paclitaxel?

► **DR MUSS:** Trials are in progress that utilize capecitabine in addition to taxanes. There is a US Oncology trial of AC followed by docetaxel or capecitabine/docetaxel, which leans on the Phase III data that have been published by Joyce O'Shaughnessy (O'Shaughnessy 2002).

When you're talking about response and potentially curable patients in the adjuvant setting, the combination makes a lot of sense.

So that's a great setting in which to explore capecitabine up front, in addition to other agents, and perhaps to consider nonanthracycline/capecitabine regimens with taxanes or gemcitabine or with other agents that we traditionally haven't used but that could be highly effective.

Track 11

► **DR LOVE:** Prior to the presentation of the paclitaxel/bevacizumab data at ASCO 2005 (Miller 2005a), we were seeing capecitabine used by clinical investigators a lot more in metastatic disease as first-line therapy compared to practicing oncologists. Now questions have arisen because of the paclitaxel/bevacizumab data. How have you sorted through that?

► **DR MUSS:** That's a great question. Kathy Miller reported a trial comparing capecitabine/bevacizumab to capecitabine alone (Miller 2005b), but for virtually all those patients, it was second-line or later therapy.

The response rate was a little bit better with bevacizumab (2.3), but we didn't see impressive changes in time to progression or survival in the long run, which we saw in the paclitaxel/bevacizumab trial.

The paclitaxel/bevacizumab data are impressive and demonstrate improvements in response rate (2.4), doubling the time to progression to about 11 months — and in randomized trials with large numbers, that’s among the best time to progression data you will see.

Toxicity, hypertension and other side effects are of concern with bevacizumab, but these are manageable compared to what you see with a lot of the other chemotherapy agents.

Those data have made our decisions more difficult. Before the paclitaxel/bevacizumab trial (Miller 2005a), I would have used capecitabine as first-line treatment for most patients. The truth is, whether you’re 25 years old with metastatic breast cancer or 85 years old, it’s palliative therapy.

For someone who’s been through adjuvant therapy, who has incurable disease and who is getting used to the fact that she has a serious problem, using a drug that doesn’t cause hair loss, doesn’t usually cause myelosuppression and allows her to maintain a pretty good quality of life — when she’s just been hit with the terrible news that she has an incurable metastatic breast cancer — seems like a good way to take care of a patient.

The bevacizumab data are intriguing, but I still believe, for many patients, capecitabine has a potential role up front.

2.3

Phase III Randomized Trial of Capecitabine with or without Bevacizumab in Patients with Previously Treated Metastatic Breast Cancer: Efficacy and Conclusions

	Bevacizumab + capecitabine (n = 232)	Capecitabine (n = 230)	p-value
Objective response rate			
Investigator	30.2%	19.1%	0.006
IRF	19.8%	9.1%	0.001
Median PFS			
IRF	4.86 months	4.17 months	0.857
Median duration of response			
IRF	5.0 months	7.6 months	—
Median overall survival	15.1 months	14.5 months	—

IRF = independent review facility; PFS = progression-free survival

“The addition of bevacizumab to capecitabine clearly increased response rates, whether assessed by the IRF or the investigators, without significantly adding to the overall toxicity of the treatment regimen. Despite improvement in ORR, the duration of the responses was short with respect to PFS, and the proportion of long-term responders was similar in the two groups.”

SOURCE: Miller KD et al. *J Clin Oncol* 2005b;23(4):792-9. [Abstract](#)

ECOG-E2100: Phase III Randomized Trial of Paclitaxel with or without Bevacizumab as First-Line Therapy for Patients with Locally Recurrent or Metastatic Breast Cancer

Protocol IDs: ECOG-2100, CTSU, NCT00028990, CAN-NCIC-E2100, NCCTG-E2100, NSABP-E2100
Accrual: 680 (Closed)

Eligibility

- Locally recurrent or metastatic breast cancer
- HER2-positive only if prior treatment with or contraindication to trastuzumab
- No prior chemotherapy for metastatic disease
- Adjuvant taxane allowed if disease-free interval > 12 months; PS 0 or 1; no CNS metastases

R

BT

Paclitaxel (d1, 8 and 15) + bevacizumab 10 mg/kg (d1 and 15) q4wk

T

Paclitaxel (d1, 8 and 15) q4wk

	Paclitaxel + bevacizumab (n = 341)	Paclitaxel alone (n = 339)	Hazard ratio (95% CI)	p-value
Response rate				
All patients	29.9%	13.8%	—	<0.0001
Measurable disease	37.7%	16.0%	—	<0.0001
Progression-free survival	11.4 months	6.1 months	0.51 (0.43-0.62)	<0.0001
Overall survival	28.4 months	25.2 months	0.84 (0.64-1.05)	0.12

CI = confidence interval

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005a; [Abstract 3](#).

Track 13

► **DR LOVE:** At the 2006 San Antonio Breast Cancer Symposium, we tried something new called “Design A Trial” ([DesignATrial.com](#)), in which we asked people to put forth ideas about trials they’d like to see in breast cancer — setting aside the issue of funding. What trials would you like to see if you had the funding?

► **DR MUSS:** Well, I’m biased toward the elderly. I’d like to see some nonanthracycline regimens evaluated. If capecitabine turns out to be as good as standard therapy, or perhaps even better, I’d like to add it to a taxane and evaluate that up front, maybe against capecitabine alone. I also believe that studying some of the new taxane preparations, such as *nab* paclitaxel, which minimizes toxicity, would be exciting.

► **DR LOVE:** What are your thoughts about *nab* paclitaxel as opposed to paclitaxel in the elderly?

► **DR MUSS:** *Nab* paclitaxel is intriguing because it decreases the time of treatment and complexity of nursing care and premedication, which is a big deal in many offices. Biologically, it uses a better delivery system.

Minimizing the risk of hypersensitivity reactions is important. All of us have seen that occasional serious reaction, even after weeks and months of taxane therapy or carboplatin. They're why we have crash carts in clinics. I don't want to overstate the case, but it's important. ■

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Citron ML et al. **Dose-dense AC followed by paclitaxel is associated with moderate, frequent anemia compared to sequential and/or less DD treatment: Update by CALGB on Breast Cancer Intergroup Trial C9741 with ECOG, SWOG, & NCCTG.** *Proc ASCO* 2005; [Abstract 620](#).

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9. [Abstract](#)

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Hurria A et al. **Geriatric assessment for oncologists: Rationale and future directions.** *Crit Rev Oncol Hematol* 2006;59:211-7. [Abstract](#)

Jones SE et al. **Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer.** *J Clin Oncol* 2006;24(34):5381-7. [Abstract](#)

Jones SE et al. **Final analysis: TC (docetaxel/cyclophosphamide, 4 cycles) has a superior disease-free survival compared to standard AC (doxorubicin/cyclophosphamide) in 1016 women with early stage breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005; [Abstract 40](#).

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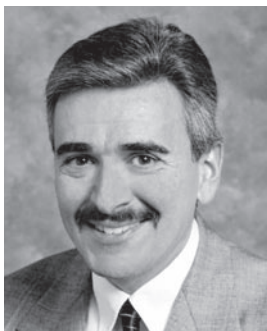
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Simon R, Norton L. **The Norton-Simon hypothesis: Designing more effective and less toxic chemotherapeutic regimens.** *Nat Clin Pract Oncol* 2006;3:406-7. No abstract available



INTERVIEW

Joseph A Sparano, MD

Dr Sparano is Professor of Medicine and Women's Health at Albert Einstein College of Medicine, Associate Chairman of the Department of Oncology at Montefiore Medical Center and Director of the Breast Evaluation Center at Montefiore-Einstein Cancer Center in Bronx, New York.

Tracks 1-16

- | | | | |
|-----------------|--|-----------------|---|
| Track 1 | Introduction | Track 11 | Selection of adjuvant chemotherapy for patients with HER2-positive disease |
| Track 2 | Background and design of ECOG adjuvant trial E1199 evaluating AC followed by paclitaxel or docetaxel every three weeks or weekly | Track 12 | Program for the Assessment of Clinical Cancer Tests (PACCT) |
| Track 3 | ECOG-E1199: Efficacy results | Track 13 | Use of the <i>Oncotype</i> DX multigene breast cancer assay in TAILORx |
| Track 4 | ECOG-E1199: Side effects and toxicity | Track 14 | TAILORx: Hormonal therapy with or without chemotherapy for node-negative breast cancer with various levels of risk for recurrence |
| Track 5 | ECOG-E1199: Conclusions | Track 15 | Rationale for the recurrence score criteria for patients randomly assigned to chemotherapy or not in TAILORx |
| Track 6 | Patient and treatment characteristics in E1199 | Track 16 | Microarray In Node negative Disease may Avoid ChemoTherapy (MINDACT) |
| Track 7 | Impact of hormone receptor status on response to adjuvant chemotherapy | | |
| Track 8 | Selection of adjuvant chemotherapy for patients with node-positive disease | | |
| Track 9 | Docetaxel/cyclophosphamide as an alternative to adjuvant AC | | |
| Track 10 | Use of <i>nab</i> versus standard paclitaxel in clinical practice | | |

Select Excerpts from the Interview

Track 3

► **DR LOVE:** Can you describe the background to the release and presentation of the ECOG-E1199 data?

► **DR SPARANO:** The design called for the data to be released if differences in the two primary comparisons emerged in any of the Data Monitoring Committee (DMC) analyses. Initially it was anticipated that full information would be available after about 1,042 events. The DMC finally elected to release the data after about 850 events. They felt that with continued follow-

up, it was unlikely that a difference would surface, at least with regard to the primary comparisons.

At San Antonio 2005, we presented data that constituted the fourth interim analysis and included 5,052 patients (Sparano 2005). Investigators recorded 856 disease-free survival events, which included relapse, second primary breast cancer or death from other causes. The results indicated no difference whatsoever with regard to the primary comparisons: Paclitaxel versus docetaxel and the every three-week versus weekly schedule (3.1).

However, comparing the individual arms, a difference seemed to emerge for the weekly paclitaxel compared to the every three-week paclitaxel arm. Approximately a 20 percent reduction in the risk of a disease-free survival event was evident in the weekly paclitaxel group, with a *p*-value of 0.06. No such difference appeared for the other arms — the weekly docetaxel group or the every three-week docetaxel arm compared to the every three-week paclitaxel arm.

► **DR LOVE:** So do you believe that weekly paclitaxel was more favorable in terms of antitumor effect?

► **DR SPARANO:** I believe that’s a very reasonable conclusion. Comparing the every three-week docetaxel arm to every three-week paclitaxel, about a 13 percent reduction in the risk of recurrence is evident with docetaxel, but the *p*-value is not statistically significant.

Among disease-free survival events, an equivalent number of relapses occurred in the every three-week docetaxel arm compared to the weekly paclitaxel arm. They looked the same, but slightly fewer nonbreast cancer deaths and slightly fewer second primary breast cancers occurred in the every three-week docetaxel arm. The aggregate disease-free survival outcome for the every three-week docetaxel arm was not evaluated as statistically better than the every three-week paclitaxel arm.

3.1

ECOG-E1199: AC Followed by Docetaxel or Paclitaxel Every Three Weeks (3) or Weekly (1) in Node-Positive or High-Risk Node-Negative Breast Cancer (Median Follow-Up = 46.5 Months)

Disease-free survival (DFS), primary comparisons	HR	95% CI	<i>p</i> -value
Paclitaxel (Pac) vs docetaxel (Doc)	0.985	0.84-1.15	0.83
Q3wk vs weekly	1.043	0.89-1.22	0.54
DFS, secondary comparisons	HR	95% CI	<i>p</i> -value
Pac3 vs Pac1	1.20	0.99-1.46	0.06
Pac3 vs Doc3	1.13	0.94-1.36	0.20
Pac3 vs Doc1	1.03	0.85-1.23	0.78

SOURCE: Sparano JA et al. Presentation. San Antonio Breast Cancer Symposium 2005; **Abstract 48**.

Track 4

▶ **DR LOVE:** Can you discuss side effects and toxicities in E1199?

▶ **DR SPARANO:** Docetaxel clearly brought more toxicity, whether administered every three weeks or weekly. With the every three-week schedule, substantially more neutropenia and infectious complications occurred, as would be expected from the dose of docetaxel that was used in the trial.

▶ **DR LOVE:** If you were to repeat the trial with preventive growth factors, would neutropenia be less of an issue?

▶ **DR SPARANO:** No question. Consistent with ASCO guidelines at the time, colony-stimulating factors were permitted as secondary prophylaxis but not as primary prophylaxis. In the every three-week docetaxel arm, the dosing schedule would now be consistent with ASCO guidelines for using a colony-stimulating factor for primary prophylaxis. In the every three-week docetaxel arm, we would certainly have seen much less neutropenia — as has been shown by other trials — if G-CSF had been used as primary prophylaxis.

For the weekly paclitaxel arm, as one would expect, there was more neurosensory toxicity. And for the weekly docetaxel arm, there was tearing and onycholysis.

Tracks 5-6

▶ **DR LOVE:** What were the conclusions from these data?

▶ **DR SPARANO:** The event rate was lower than anticipated, and this was likely exacerbated by two factors. First, given that a concurrent trial was studying HER2-positive disease, patients who were at higher risk of relapse and more likely to benefit from taxane therapy were not included in this study. Second, the aromatase inhibitors were approved in the adjuvant setting during this time, which further lowered the event rate.

▶ **DR LOVE:** How would you answer a clinician who asks, “What does this mean to my practice?”

▶ **DR SPARANO:** I believe weekly paclitaxel following AC represents another option for patients who have lymph node-positive breast cancer who may not be optimal candidates for dose-dense therapy.

Track 8

▶ **DR LOVE:** In your practice, what options do you present for 40- to 60-year-old patients in good health with several positive nodes who are not eligible for a study?

▶ **DR SPARANO:** For that type of patient, the usual options that I would discuss

would include TAC, dose-dense sequential AC followed by paclitaxel administered every two weeks or AC followed by weekly paclitaxel. Once I describe the options, toxicity profiles and duration of therapy, many patients choose the dose-dense, every two-week approach for eight cycles because of the shorter duration of therapy and the generally more favorable toxicity profile.

► **DR LOVE:** For patients at lower risk, do you ever use dose-dense AC every two weeks without a taxane?

► **DR SPARANO:** Yes I do, even though we don't have efficacy data to suggest that this approach is superior to AC administered every three weeks. However, we do have substantial long-term safety data suggesting that this approach may be safer in the short term and appears safe in the long term. It is also completed sooner, so for that reason it is a reasonable approach to the treatment of a patient at relatively low risk.

Track 9

► **DR LOVE:** What are your thoughts on docetaxel/cyclophosphamide (TC) as an alternative to adjuvant AC?

► **DR SPARANO:** We now know that TC administered every three weeks is superior to AC administered every three weeks (Jones 2005). Therefore, I believe that represents a reasonable evidence-based option for patients who have lower-risk early-stage breast cancer. Before the US Oncology study (Jones 2005), I would commonly use AC administered every two weeks, not necessarily because I thought it would be more effective — particularly in estrogen receptor-positive disease — but because the treatment was finished in a shorter period of time.

► **DR LOVE:** Has your perception of the risk of adjuvant regimens with an anthracycline, specifically AC, changed in light of recent data on cardiac toxicity (Shepherd 2006)?

► **DR SPARANO:** I believe it's a real complication. We can identify who's at high risk, but we can't identify who will develop a problem with any degree of certainty. For the patients at high risk, if we have alternatives to AC, then those options should be seriously considered.

Tracks 12-13

► **DR LOVE:** Can you discuss the background of the TAILORx study?

► **DR SPARANO:** This trial had its genesis in a program at NCI called PACCT (Program for the Assessment of Clinical Cancer Tests), which was designed to meet the challenge of integrating molecular proteomic and epigenomic markers into clinical practice and clinical decision-making. Of course, many molecular markers are available, and a variety of cancer types would be eligible for refining what patient subgroups are benefiting from specific treatments.

The time and the data seem to be right for targeting ER-positive, lymph node-negative breast cancer and for using the *Oncotype DX* test as part of that evaluation for several reasons. First, ER-positive, lymph node-negative breast cancer accounts for about half of all breast cancer diagnosed in North America each year. Second, the majority of these patients would be considered eligible for receiving chemotherapy based on current practice guidelines, such as the NCCN and St Gallen guidelines.

However, we know that 80 to 85 percent of these patients would be adequately treated with endocrine therapy alone and that the absolute benefit from chemotherapy is in the range of three to five percent. We're obviously overtreating the great majority of the patients whom we treat with adjuvant chemotherapy.

The question was whether we could use a molecular diagnostic test to provide a clear treatment path for patients who didn't require adjuvant chemotherapy and one for those who did. The trial was also an opportunity to refine the utility of the test and determine whether other subsets of patients were deriving benefit from chemotherapy. Because TAILORx (Trial Assigning Individualized Options for Treatment) was the first trial to emanate from the PACCT program, it has also been called the PACCT-1 trial.

At the time that TAILORx was being designed, a handful of externally validated molecular tests were available. The *Oncotype DX* was chosen to be integrated into this trial because, first, it was validated for patients with ER-positive, node-negative disease, for whom we believed integrating a molecular test would be most beneficial.

Second, the test can be performed on routinely processed paraffin-embedded tissue, a huge advantage compared to some of the other molecular diagnostic tests. Third, the work that led to the CLIA (Clinical Laboratory Improvement Amendments) approval of this test was done through the Cooperative Group system, building on the work done by the Cooperative Groups and the Inter-group (Paik 2003).

From a panel of about 250 genes believed likely to be clinically relevant, the scientists at Genomic Health evaluated three data sets that included patients with a mixture of clinical features: node-positive, node-negative, HER2-positive, HER2-negative, ER-positive and ER-negative disease.

They honed these down to 16 genes that cluster into various groups: an ER group, a proliferation group, a HER2 group and others. With that information, they developed the algorithm that was used to develop the recurrence score.

The algorithm was prospectively validated in the NSABP-B-14 trial for patients who had ER-positive, lymph node-negative disease (Paik 2003). The recurrence score predicted outcome, whether evaluated as a trinary variable with low, intermediate or high risk or as a continuous variable. In the NSABP-B-20 trial, which compares tamoxifen to tamoxifen with CMF, only patients who had a high recurrence score seem to be benefiting from the

administration of CMF (Paik 2004).

▶ **DR LOVE:** Do you believe that this assay should be utilized in clinical practice?

▶ **DR SPARANO:** Absolutely. I believe that this assay can and should be used in the clinical decision-making process if the result of the test is likely to influence a treatment decision.

For example, if you have a patient for whom endocrine therapy alone is the only option, the test can provide more precise prognostic information, but it's not going to alter your management. I would use the test in circumstances in which the results could potentially alter management.

Tracks 14-15

▶ **DR LOVE:** Would you describe the TAILORx study design (1)?

▶ **DR SPARANO:** The study is targeting patients up to age 75 who have ER-positive, axillary lymph node-negative breast cancer. The tumor must be at least 1.1 centimeters in size, or it could be between six millimeters and 11 millimeters if unfavorable histologic features are present, such as intermediate or poor nuclear grade or lymphovascular invasion. Patients must also have HER2-negative disease, determined by their local laboratory and defined as either FISH-negative or 0 to 1+ by the DAKO HercepTest™ or another FDA-approved test.

Given that the study will evaluate 10-year outcomes, patients must have a life expectancy of at least 10 years, making those with significant comorbid medical conditions ineligible. Of course, patients need to be acceptable candidates for chemotherapy, and they need to agree in principle to receive chemotherapy.

▶ **DR LOVE:** Can patients receive any type of chemotherapy, or is it specified?

▶ **DR SPARANO:** Physicians can choose from a range of standard chemotherapy regimens in the protocol. Generally these are consistent with NCCN guidelines and also now include docetaxel/cyclophosphamide as an option (Jones 2005). Patients can enroll on another CTSU trial, provided it is consistent with TAILORx-assigned treatment.

▶ **DR LOVE:** Patients at lower risk receive only hormone therapy according to physician choice. The focus, then, is the patients at intermediate risk, who are randomly assigned to chemotherapy or not?

▶ **DR SPARANO:** Yes. This is defined a little differently than in the original descriptions by Genomic Health and NSABP. We're targeting patients with a recurrence score of 11-25, who will be randomly assigned to either chemotherapy and hormonal therapy, which is considered the standard treatment arm, or hormonal therapy alone, which is considered the experimental arm. It is designed as a noninferiority trial, powered to detect a three percent or

greater reduction in disease-free survival by the omission of chemotherapy.

► **DR LOVE:** Why was 11 to 25 chosen for the midrange recurrence score?

► **DR SPARANO:** First, at the upper end, we dialed down from 31 to 25 because we wanted to minimize the potential for undertreating patients in the upper range. In fact, when the NSABP reanalyzed the data, the treatment effect of chemotherapy in patients with a recurrence score of 31 or higher was similar to that in patients who had a recurrence score of 26 or higher.

Second, at the lower end of the range, a recurrence score of 11 was chosen because, with that score, the risk of both distant and local recurrence is in the range of five to 10 percent, and that's the threshold at which we typically recommend chemotherapy.

Third, the B-20 trial assessed the risk of recurrence as a continuous variable for patients treated with tamoxifen or tamoxifen with chemotherapy. In that trial, the curves begin to separate at about 10 or 11, and by about 25 they are quite divergent (Paik 2006).

Yet the 95 percent confidence intervals in that range of 11 to 25 completely overlap. These are the principal reasons why we chose to use a different range of recurrence scores than were originally reported. ■

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Sparano JA et al. **Clinical application of molecular profiling in breast cancer.** *Future Oncol* 2005;1(4):485-96. [Abstract](#)

Sparano JA et al. **Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: Results of North American Breast Cancer Intergroup Trial E1199.** Presentation. San Antonio Breast Cancer Symposium 2005; [Abstract 48](#).

Harold J Burstein, MD, PhD, Stephen E Jones, MD, Peter M Ravdin, MD, PhD

Tracks 1-26

- Track 1** Introduction
- Track 2** NSABP-B-40: Randomized trial of six neoadjuvant regimens for patients with operable HER2-negative disease
- Track 3** Pathologic complete response as a clinical trial endpoint
- Track 4** Correlative science programs in neoadjuvant studies to develop molecular profiles for response to specific agents
- Track 5** Proposed NSABP preoperative HER2 trial: AC → paclitaxel with trastuzumab, lapatinib or the combination
- Track 6** Evaluating molecularly defined subsets and targeted therapies in clinical trials
- Track 7** Adjuvant docetaxel/cyclophosphamide versus dose-dense AC
- Track 8** Toxicity and costs of adjuvant TC versus dose-dense AC chemotherapy
- Track 9** Congestive heart failure in older women treated with anthracyclines
- Track 10** Considerations in the incorporation of *nab* paclitaxel into clinical practice
- Track 11** Neuropathy associated with standard versus *nab* paclitaxel
- Track 12** Impact of hormone receptor status on responsiveness to chemotherapy
- Track 13** Benefits of adjuvant chemotherapy in hormone receptor-positive versus hormone receptor-negative disease
- Track 14** Congestive heart failure in older women treated with anthracycline chemotherapy: Analysis of the SEER-Medicare database
- Track 15** Case discussion: A 44-year-old woman with a 1.1-cm, ER-positive, PR-negative, HER2-negative, node-negative breast tumor
- Track 16** Use of the *Oncotype* DX assay for patients with lower-risk disease
- Track 17** Use of other tumor markers versus the *Oncotype* DX assay in treatment decision-making
- Track 18** Discordance between *Oncotype* DX and other treatment decision-making algorithms
- Track 19** Clinical utility of the *Oncotype* DX recurrence score in treatment decision-making
- Track 20** Case discussion: A 42-year-old woman with a 1-cm, ER-positive, PR-negative, HER2-positive breast tumor with apparent benign mechanical tumor transport to a node
- Track 21** Differentiation and treatment of micrometastatic versus benign mechanically transported tumor to a lymph node
- Track 22** Case discussion: A 77-year-old woman with a 3-cm, ER-negative, PR-negative, HER2-positive, node-positive tumor
- Track 23** Trastuzumab as monotherapy or combined with single-agent chemotherapy
- Track 24** Age and trastuzumab-associated risk of cardiac toxicity
- Track 25** BIG 2-06 adjuvant HER2 trial of trastuzumab, lapatinib, the sequence or the combination
- Track 26** Therapeutic relevance of circulating tumor cells

Select Excerpts from the Meeting

Track 2

► **DR LOVE:** Norm, can you discuss NSABP-B-40?

► **DR WOLMARK:** In two previous preoperative chemotherapy trials, NSABP-B-18 (Wolmark 2001) and NSABP-B-27 (Bear 2006), we demonstrated that those individuals who have a pathologic complete response have, by far, the best outcome.

In NSABP-B-27, the addition of docetaxel to AC doubled the pathologic complete response rate, but it did not do much for distant disease or survival. It did, however, lower the rate of local recurrences. Nonetheless, those individuals who had a pathologic complete response had the best outcome relative to disease-free and overall survival (Bear 2006).

For NSABP-B-40, we decided to power the trial based on pathologic complete response and to use it to develop a molecular taxonomy. We also switched the sequence of the drugs, and we started with the taxane. The three chemotherapy arms are docetaxel followed by AC, a doublet of docetaxel/capecitabine followed by AC and a doublet of docetaxel/gemcitabine followed by AC. These chemotherapy regimens are administered with or without bevacizumab. It's a three-by-two factorial trial design (4.1).

The novelty of NSABP-B-40 is that we're using pCR as an endpoint with an emphasis on developing a molecular taxonomy to determine whether we can characterize patients who obtain a pCR as a surrogate marker to measure outcome. Disease-free and overall survival are not primary endpoints for NSABP-B-40.

We view it as a new mechanism to test promising agents in the neoadjuvant setting, and we believe 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.

Track 7

► **DR LOVE:** Steve, can you review your trial comparing docetaxel/cyclophosphamide (TC) to AC?

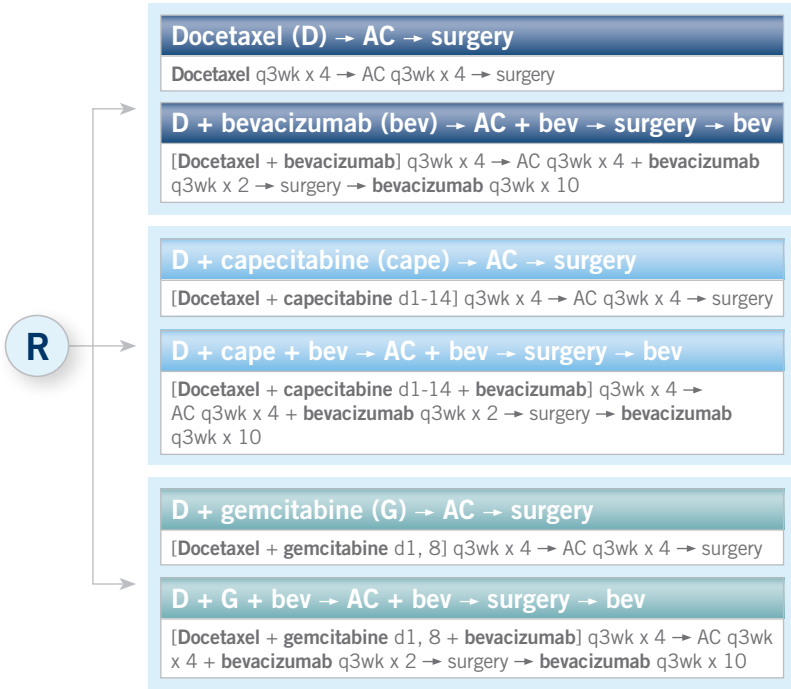
► **DR JONES:** The objective of the trial was to compare the disease-free survival between AC and TC for women with operable breast cancer. About half of the women had node-negative disease and half had node-positive disease. We recruited about 1,000 patients and had 5.5 years of median follow-up (Jones 2006; [4.2]).

We conducted a preliminary analysis at about three years, in which a difference in favor of TC was emerging (Jones 2003). At five years, however, this had become a significant difference, with a p -value of 0.015. We saw a one

Phase III Randomized Trial of Six Neoadjuvant Regimens in Patients with Palpable and Operable HER2-Negative Breast Cancer

Protocol ID: NSABP-B-40

Target Accrual: 1,200



Eligibility

- Tumor \geq 2 cm
- HER2-negative breast cancer

Patients with ER-positive and/or PR-positive disease receive a minimum of five years of hormonal therapy.

SOURCE: NCI Physician Data Query, December 2006.

third reduction in the risk of a breast cancer event among the patients who received TC, which is a significant impact and translates into a six percent absolute difference at five years (Jones 2006; [4.2]).

We conducted an exploratory analysis because of the interest in the differences in response to adjuvant chemotherapy between patients with hormone receptor-positive and receptor-negative disease. About 75 percent of the women had hormone receptor-positive disease. No obvious difference appeared between receptor-positive and receptor-negative disease with respect to benefit from TC (Jones 2006; [4.2]).

A trend toward an overall survival benefit ($p = 0.131$) and nearly a 25 percent lower chance of dying were evident among the patients treated with TC

(Jones 2006; [4.2]). If you present it that way to patients, most will opt for TC. I believe if this trial were larger or we had longer follow-up, we might see a survival difference. The conclusion from the trial was that TC is a new standard nonanthracycline adjuvant regimen.

Personally, I would use TC in the population of patients we studied in this trial: Those with node-negative disease or those with one to three positive nodes. It provides a good reduction in the risk of recurrence.

We don't have many data for women with four or more positive nodes, so I probably wouldn't pick TC in those situations, but I would for the patients with lower-risk disease or those with cardiac compromise.

► **DR BURSTEIN:** For the most part, for patients with high-risk disease, I'm using both anthracyclines and taxanes. The most common regimen we use is dose-dense AC followed by paclitaxel. For patients with lower-risk disease, the arguments are, do they need chemotherapy at all and what is the role of chemotherapy?

While I find Steve's trial very provocative and well done, I continue to use, principally, AC. We have such an enormous wealth of experience with AC, and it's the foundation for most of the modern treatment regimens. I find it to be less toxic than TC in the short term. In addition, the side effects that most

4.2

Docetaxel and Cyclophosphamide (TC) versus Doxorubicin and Cyclophosphamide (AC) for Women with Early Breast Cancer (Median Follow-Up = 5.5 Years)

	TC (n = 506)	AC (n = 510)	Hazard ratio	p-value
Five-year disease-free survival	86%	80%	0.67	0.015
ER-/PR-	HR = 0.64 (95% CI: 0.38-1.04)			
ER+ or PR+	HR = 0.71 (95% CI: 0.47-1.08)			
Node-positive	HR = 0.67 (95% CI: 0.45-0.98)			
Node-negative	HR = 0.73 (95% CI: 0.42-1.27)			
Five-year overall survival	90%	87%	0.76	0.13

Hazard ratios < 1 indicate values in favor of TC.

“We conclude that our study has established a new standard nonanthracycline regimen, TC, for the adjuvant treatment of early-stage breast cancer.”

Toxicities (Grades III/IV)	TC	AC	p-value
Neutropenia	61%	55%	
Neutropenic fever	5%	2.5%	0.07
Nausea	2%	7%	<0.01
Vomiting	<1%	5%	<0.01

SOURCE: Jones SE et al. *J Clin Oncol* 2006;24:5381-7. [Abstract](#)

worry patients are alopecia and hospitalization risk. I think those are pretty comparable between AC and TC.

We don't use the AC schedule used in Steve's trial. We typically use a dose-dense schedule every two weeks. Whether that is better, I don't know. TC is a nice option for patients for whom you want to use chemotherapy and there's a true contraindication to an anthracycline — someone who previously received CHOP for lymphoma or had a preexisting cardiomyopathy. But it is not a regimen I use in daily practice.

► **DR LOVE:** What's behind your decision to use dose-dense AC without a taxane as opposed to nondose-dense AC?

► **DR BURSTEIN:** It's based on the assumption that it has the same efficacy and is easier for the patients. It's a shorter course of therapy — eight versus 12 weeks. One of the things we learned while doing the adjuvant trastuzumab trials, in which patients received every three-week AC, is how challenging that regimen is to administer. In probably five to 15 percent of patients, the counts hadn't recovered by week three.

Tracks 8-9

► **DR LOVE:** Steve, your data suggest that TC is less toxic.

► **DR JONES:** Our experience — and I treated a lot of patients on this trial — was that TC was better tolerated. Many patients don't have much nausea or vomiting with TC (4.2), which is a big factor. A little more neutropenia does occur.

► **DR RAVDIN:** I believe TC should be a more popular regimen. Although we see a lot of enthusiasm for dose-dense AC, this has never been compared to q3wk treatment. We don't know from the dose-dense trials which part of the therapy is being improved. We do know that changing the schedule of the taxanes does improve a therapy. So it may be that the additional benefit for dose-dense therapy in CALGB-9741 came from the dose densification of the taxane, not the anthracycline.

Tracks 10-11

► **DR LOVE:** Hal, can you discuss your trial of dose-dense *nab* paclitaxel?

► **DR BURSTEIN:** We recently finished accruing more than 60 patients to a trial of AC followed by dose-dense *nab* paclitaxel. We had an early stopping rule evaluating whether you could use *nab* paclitaxel without growth factor support, and you cannot use *nab* paclitaxel every two weeks consistently without growth factor support. Our protocol was amended so that all the patients receive growth factor support. We'll show these data at ASCO 2007.

► **DR LOVE:** Bill, what are your thoughts about *nab* in breast cancer?

► **DR HARWIN:** If *nab* paclitaxel were proven to have less neuropathy down the road, that would be much more important than the premedications. Many patients who receive paclitaxel for breast cancer and other diseases are bothered by numbness in their extremities many months and even years later. If *nab* paclitaxel were found in a large trial not to cause that, then that might be a worthwhile advantage.

► **DR LOVE:** Steve, it's been said that the neuropathy associated with *nab* paclitaxel resolves more quickly.

► **DR JONES:** That does appear to be the case. It has been reported to be relatively rapidly reversible compared to the neuropathy associated with paclitaxel or docetaxel, which doesn't go away (Gradishar 2005). However, I believe the jury is still out.

Track 16

Case Discussion 1

A 44-Year-Old Premenopausal Woman with Node-Negative Breast Cancer (from the Practice of Scott Lunin, MD)

"This is a 44-year-old premenopausal woman, in otherwise excellent health, who was found to have a 1.1-cm invasive ductal carcinoma that was ER-positive, PR-negative and HER2-negative. Her sentinel node biopsy was negative. According to Adjuvant! Online, the odds were overwhelmingly in her favor.

However, my sense is that she and her family are more frightened of breast cancer than of chemotherapy. She came in with the attitude that she wanted to do everything possible to treat her disease. My job was to discuss what the data looked like in terms of Adjuvant! Online and what type of benefit we'd expect from adjuvant chemotherapy."

SOURCE: Track 15.

► **DR LOVE:** Peter, would the *Oncotype* DX assay fit into this patient's situation?

► **DR RAVDIN:** I believe the *Oncotype* DX assay could be used for a patient like this. It's designed for patients with node-negative disease with whom you're going to be using hormonal therapy, specifically tamoxifen.

The great hope for the *Oncotype* DX test is that it will be useful in identifying those patients who might benefit in more than an average way from chemotherapy. That story is, I believe, incomplete at this point. They only have data from the NSABP-B-20 adjuvant trial using CMF or M-F (Paik 2006).

► **DR LOVE:** Hal, would you consider obtaining an *Oncotype* DX recurrence score for a patient like this?

► **DR BURSTEIN:** I love the *Oncotype* DX test for these kinds of patients because this is exactly the patient population for whom we all have strongly suspected, for a long time, that the benefits of chemotherapy are very small. She has a

favorable overall prognosis. The tumor is small (less than two centimeters), and it is estrogen receptor-positive.

A number of observations of late have made us question the role of chemotherapy. Retrospective analyses suggest that most of the gains are in hormone receptor-negative disease (Berry 2006). Prospective studies have shown modest benefits under any circumstance. If you look at NSABP-B-20, for which this patient would have been a perfect candidate, you see that the benefits of chemotherapy on top of tamoxifen alone are estimated at only about four percent (Fisher 1997). And most women in that trial had larger tumors with a higher grade than she had.

We know from other work that grade is an important predictor of the benefits of chemotherapy. So this is the situation in which you're talking about administering chemotherapy for an extremely small benefit, some of which might even be accomplished with ovarian suppression, especially in someone with a hormone receptor-positive, low-grade tumor.

Historically, the dilemma has been that the models of risk or the clinical practice guidelines from the NCCN say, "She has a tumor that is greater than one centimeter. Give her chemotherapy," yet we all know the gain is small.

The way out of this box is a test like the *Oncotype DX* assay. We've had all this information in front of us for a long time, and yet many of us have lacked the courage of our convictions to say to a woman who has a low-risk tumor, "You don't need chemotherapy." That is the crux of the issue.

Tracks 20-21

Case Discussion 2

A 42-Year-Old Woman with a 1-mm Focus of Invasive Breast Cancer (from the Practice of Martin F Nicolau, MD)

"This is a 42-year-old premenopausal woman who was initially diagnosed with a multifocal ductal carcinoma in situ. She decided to undergo a bilateral mastectomy. At the time of surgery, they found a 1-mm focus of invasive ductal carcinoma, which was Grade II disease, and her sentinel lymph node showed a 0.8-mm focus of disease.

She was subsequently seen at an academic center. They thought the node was the result of benign mechanical transport (BMT) and that it wasn't a positive lymph node. Her disease was ER-positive, PR-negative and HER2-positive by FISH.

It's hard to know what to do with this micrometastatic lymph node when the disease measured only one millimeter in her breast. I had them go back and extensively examine the breast. They could not find any other occult disease."

SOURCE: Track 20.

► **DR BURSTEIN:** Sometimes it's helpful to look carefully at the lymph nodes microscopically because the worry about these cases is that they are artifacts and not biologically significant metastatic disease.

Sometimes you can get a feel for that based on how it appears in the lymph node and if other lymph nodes are positive. The first thing I would do is an axillary dissection. If she had extensive residual disease in her other lymph nodes, then I would be far more inclined to consider this breast cancer as opposed to an artifact.

► **DR NICOLAU:** She had an axillary lymph node dissection, and no other lymph nodes were involved.

► **DR BURSTEIN:** Now you're stuck. You have to decide, in your heart of hearts, whether you think this is biologically, clinically real cancer in the lymph node. The current guidelines parse these micrometastatic deposits in various ways: More than two millimeters is a real involvement, less than two millimeters but more than 0.2 millimeters is of unknown significance and less than 0.2 millimeters is considered node-negative (Singletary 2006).

She would have a 0.2- to 2.0-mm deposit of unclear significance. The most important treatment for her would be tamoxifen. The second most important might be ovarian suppression. The third and fourth most important might be chemotherapy and/or trastuzumab.

Track 22

Case Discussion 3

A 77-Year-Old Woman with HER2-Positive, Node-Positive Breast Cancer (from the Practice of Scott Lunin, MD)

"This is an otherwise healthy 77-year-old white woman who was found to have a 3-cm invasive ductal carcinoma that was ER-negative, PR-negative and HER2-positive by FISH. Two out of 12 nodes were positive in her regional lymph node dissection. She came to me for discussion of adjuvant therapy. This particular patient was more terrified of chemotherapy than she was of breast cancer."

SOURCE: Track 22.

► **DR RAVDIN:** A 77-year-old woman will have approximately a 25 percent 10-year risk of competing mortality, even if she's in good health. However, she has node-positive, HER2-positive, ER-negative disease, and she has a more substantial risk of dying of breast cancer than of something else.

This is the type of patient for whom one might seriously consider chemotherapy despite her age. Uncertainties exist about how good chemotherapy is in older patients. However, we have no biological reason to believe it isn't effective. The temptation arises in what to do in terms of administering trastuzumab if she refuses chemotherapy.

Track 23

► **DR LOVE:** Steve, would you consider trastuzumab without chemotherapy for this patient?

► **DR JONES:** Yes, I would. You've indicated she's terrified of chemotherapy. She's also older and much more likely to develop toxicity from chemotherapy. A year of trastuzumab by itself, however, might be relatively benign. We do not have data, but we all see the effect of adding trastuzumab to adjuvant chemotherapy. You could come up with a less-than-standard regimen if you wanted to and use 12 weeks of weekly paclitaxel, which is fairly nontoxic, in addition to trastuzumab. I believe you'd probably avoid AC.

TC with docetaxel and cyclophosphamide might be an alternative, but an older patient may potentially have a little more toxicity. We will be conducting a pilot safety study of TC with trastuzumab, and I know a few oncologists have used that regimen for patients with lower-risk disease. I believe there are a number of choices, and I'd like to use trastuzumab at the minimum.

► **DR BURSTEIN:** We have planned a multicenter trial, in which patients with HER2-positive, Stage I breast cancer receive 12 weeks of paclitaxel and trastuzumab concurrently followed by an additional 40 weeks of trastuzumab. The goal is to set a relatively low bar — a risk of recurrence of no more than five or six percent after five years, demonstrating in 300 to 400 patients that you can achieve a very low risk of recurrence with a reasonably well-tolerated regimen. ■

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Singletary SE, Connolly JL. **Breast cancer staging: Working with the sixth edition of the AJCC Cancer Staging Manual.** *CA Cancer J Clin* 2006;56(1):37-47. [Abstract](#)

Wolmark N et al. **Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18.** *J Natl Cancer Inst Monogr* 2001;(30):96-102. [Abstract](#)

QUESTIONS (PLEASE CIRCLE ANSWER):

- According to the Gompertzian growth model, tumors begin growing exponentially and eventually reach a plateau.
 - True
 - False
- The Norton-Simon hypothesis states that the rate of tumor regression associated with a therapy is proportional to the rate of tumor growth without therapy.
 - True
 - False
- Researchers at Memorial Sloan-Kettering have been conducting a Phase I/II trial of capecitabine administered on a _____ schedule.
 - Seven days on and seven days off
 - 14 days on and 14 days off
 - Five days on and two days off
 - None of the above
- An analysis of women with breast cancer who were treated with adjuvant chemotherapy during CALGB trials showed that the incidence of _____ increased as age increased.
 - Stomatitis
 - Treatment-related death
 - AML/MDS death
 - All of the above
 - Both b and c
- An Intergroup trial (49907) is evaluating the use of adjuvant CMF or AC versus oral capecitabine in _____ women with operable adenocarcinoma of the breast.
 - Young
 - Elderly
 - Both a and b
- The primary comparison of the ECOG-E1199 trial showed a difference between _____.
 - Paclitaxel and docetaxel
 - Every three-week and weekly schedules
 - Both a and b
 - None of the above
- The self-seeding hypothesis involves a tumor seeding itself and distant sites as well.
 - True
 - False
- A trial comparing TC (docetaxel/cyclophosphamide) to AC (doxorubicin/cyclophosphamide) in women with early operable breast cancer demonstrated that the absolute increase in five-year disease-free survival was _____ among those who received TC compared to those who received AC.
 - Three percent
 - Six percent
 - 10 percent
 - Nine percent
- TAILORx will include patients with a _____ recurrence score according to the Oncotype DX assay.
 - Low
 - Intermediate
 - High
 - All of the above
- In the TAILORx study, a midrange recurrence score is defined as _____.
 - 11-25
 - 11-35
 - 25-35
- NSABP-B-40 will compare which of the following neoadjuvant chemotherapy regimens administered with or without bevacizumab?
 - Docetaxel → AC
 - Docetaxel/capecitabine → AC
 - Docetaxel/gemcitabine → AC
 - Both b and c
 - All of the above
- In the adjuvant trial comparing TC to AC, patients treated with TC experienced less _____.
 - Nausea
 - Vomiting
 - Neutropenia
 - Both a and b
 - All of the above

EVALUATION FORM

Breast Cancer Update — Issue 1, 2007

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

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?

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings. 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of switching to or sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. 5 4 3 2 1 N/A
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment, nonanthracycline-based regimens and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients. 5 4 3 2 1 N/A
- Counsel appropriately selected patients with metastatic disease about selection and sequencing of endocrine therapy and chemotherapies and about the risks and benefits of chemotherapeutic agents and combinations. 5 4 3 2 1 N/A
- Evaluate the emerging data for biologic therapies and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease. 5 4 3 2 1 N/A
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions. 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Larry Norton, MD	5 4 3 2 1	5 4 3 2 1
Hyman B Muss, MD	5 4 3 2 1	5 4 3 2 1
Joseph A Sparano, MD	5 4 3 2 1	5 4 3 2 1
Harold J Burstein, MD, PhD	5 4 3 2 1	5 4 3 2 1
Stephen E Jones, MD	5 4 3 2 1	5 4 3 2 1
Peter M Ravdin, MD, PhD	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

Which of the following audio formats of this program did you use?

- Audio CDs Downloaded MP3s from website

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REQUEST FOR CREDIT — please print clearly

Name: Specialty:

Degree:

MD DO PharmD NP BS RN PA Other

Medical License/ME Number: Last 4 Digits of SSN (required):

Street Address: Box/Suite:

City, State, Zip:

Telephone: Fax:

Email:

Research To Practice designates this educational activity for a maximum of 4.25 AMA PRA Category 1 Credit(s)[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: Date:

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

Yes No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

.....

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

.....

What other faculty would you like to hear interviewed in future educational programs?

.....

Additional comments about this activity:

.....

FOLLOW-UP

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:

Yes, I am willing to participate in a follow-up survey. No, I am not willing to participate in a follow-up survey.

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at BreastCancerUpdate.com/CME.

Breast Cancer®

U P D A T E

Editor/CME Director	Neil Love, MD
Managing Editor	Kathryn Ault Ziel, PhD
Scientific Director	Richard Kaderman, PhD
Writers	Lilliam Sklaver Poltorack, PharmD Douglas Paley Marie Bialek, PharmD Anne Jacobson, MPH
Continuing Education Administrator for Nursing	Sally Bogert, RNC, WHCNP
Content Validation	Margaret Peng John H Brebner Ginelle Suarez Erin Wall
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Web Master	John Ribeiro
Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@ResearchToPractice.com Email: CME@ResearchToPractice.com
For CME Information	

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