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Breast Cancer® UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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SPECIAL FEATURE:

Breast Cancer Journal Club

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Breast Cancer Update
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

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 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 patients with HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients.
- Counsel appropriate patients with metastatic disease about selection and sequencing of endocrine therapy and about the risks and benefits of combination versus single-agent chemotherapy.
- 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 9 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Burstein, Dresdner, Levine, Mamounas, Siegel and Vogel on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

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

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 4.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

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

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In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

Dr Burstein (interview conducted on July 8, 2005) — Speakers Bureau: Genentech BioOncology. **Dr Vogel** (interview conducted on July 8, 2005) — Grants/Research Support: Amgen Inc, AstraZeneca Pharmaceuticals LP, Biomira Inc, Bristol-Myers Squibb Company, Eli Lilly and Company, EMD Pharmaceuticals Inc, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis, TAIHO Pharmaceutical Co Ltd; Honorarium and Speakers Bureau: Amgen Inc, AstraZeneca Pharmaceuticals LP, Biomira Inc, Bristol-Myers Squibb Company, Eli Lilly and Company, EMD Pharmaceuticals Inc, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis. **Dr Mamounas** (interview conducted on February 26, 2005) — Consulting Fees: AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Novartis Pharmaceuticals, Pfizer Inc, Sanofi-Aventis; Honoraria: AstraZeneca Pharmaceuticals LP, Genomic Health Inc, Novartis Pharmaceuticals, Pfizer Inc, Sanofi-Aventis.

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UPCOMING EDUCATIONAL EVENTS

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

American Society of Clinical Oncology
2006 Gastrointestinal Cancers Symposium
January 26-28, 2006
San Francisco, California
Event website: **www.asco.org**

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

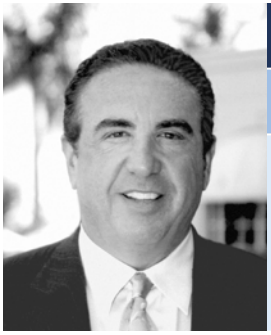
American Society of Clinical Oncology
2006 Prostate Cancer Symposium
February 24-26, 2006
San Francisco, California
Event website: **www.asco.org**

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

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

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

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



EDITOR'S NOTE

Neil Love, MD

Cheetos and raisins for dinner: The curse of Wilma and why a public sector that can't figure out a way to get electricity to gas stations seems unlikely to be victorious in the "war on cancer"

City without power: Darkened Miami skyline, October 25, 2005. The Research To Practice offices are located on the 36th floor of the building in the center with the antenna. (Reprinted with permission from *The Miami Herald*, photographer: Marice Cohn Band.)

Tuesday, October 25, 2005, 9:23 PM

At this moment — 36 hours after the storm — there is essentially no electricity available for the four million residents of Dade, Broward and Palm Beach Counties. None, nada, bupkis. It's as dark as a planetarium around here, and in fact, tonight many less fortunate South Floridians are seeing the stars through open roofs, praying there will be no rain. I have 54 minutes of battery time left on my laptop. With not much else to do, I begin to reflect on how the glacier-like response of most governmental agencies to Hurricane Wilma's recent visit to South Florida mimics what we've seen for decades in oncology research and practice, where important clinical trials take years to be approved and more years to execute.

Sitting on my breezy porch a while ago, listening with a remaining powered iPod to Harold Burstein's interview for this issue of *Breast Cancer Update*, I wondered how many cancer patients will suffer relapses and death as the US cooperative clinical trials process and mechanisms — which were verbally

crucified in a recent interview for our series by NSABP director Norman Wolmark — attempts to construct a new generation of adjuvant clinical trials incorporating the recent exciting breast cancer clinical trial findings with trastuzumab, bevacizumab, the aromatase inhibitors and various permutations of taxane-based therapy.

From Harold's profoundly knowledgeable perspective, it would be ideal if we could launch a new generation of adequately powered adjuvant breast cancer trials that would be individually designed for patients with HER2-positive, ER-positive and triple negative tumors and test a variety of strategies for each. Listening jealously to the monotonous drone of my neighbor's generator, I wonder if the same government that can't efficiently help people in a storm can set in place an infrastructure to follow Harold's very astute suggestions.

10:10 PM

My brave Mac is running on fumes, and it will soon be time to go back to staring at candles. Not having television, it's difficult to know what people think about this Wilma mess, but my guess is that we are not Geraldo-worthy and that the airwaves will be monopolized by media yes-men and women, profusely commending all the fine work being done under such trying conditions. The refrigerator is full of decaying food that my wife Adriana and I begin to toss out, but those Cheetos and raisins look safe and mighty tempting for a romantic, late-night candlelit dinner.

Thursday, October 27, 2005

It is now three full days after the storm and things actually seem worse than when it simply wasn't advisable to leave the "comfort" of your home. Apparently in all the post-Katrina teeth gnashing about being better prepared for a hurricane, no one figured out that electricity is required to pump gasoline, and since almost no South Florida gas stations have generators, the city is frozen; people are suffering, and businesses are hemorrhaging because no one can get to work or anywhere else.

Endless lines at the few open gas stations make us all feel like fools as we burn more fuel waiting with our engines idling than we are allowed to pump. With essentially no operational traffic signals, and trees all over the roads, those with gas venture out with extreme caution.

South Florida resident pundit Dave Barry — writing in *The Miami Herald* — likens our current situation to one of Mel Gibson's postapocalyptic *Road Warrior* movies, but notes that, "Mel did not have to deal with South Florida drivers, who simply do NOT grasp the concept of the four-way stop. Down here, when you come to an intersection with a nonworking stoplight, you have NO idea what any of the other drivers are going to do. Some slow down; some speed up; some make emergency U-turns to get behind you, in case you are forming a gas line. Mel wouldn't last 10 minutes out there."

To our amazement, the Research To Practice offices have power, and using the precious liquid gold in my shrinking tank to drive to work, I hear a cheery

news anchor "journalist" on the radio interviewing an equally imbecilic spokesperson for Florida Power and Light, who breathlessly announces that the number of homes in Broward County without electricity has dropped below the magic 700,000 level (695,000), while in Miami-Dade only 600,000 customers are in the dark. The deep-voiced Ted Baxter sound-alike on the radio announces with great encouragement that the President is doing his traditional Air Force One hurricane fly-over today. No doubt a series of empathetic photo-ops will be seen by the rest of the country, where the televisions work.

Texaco station just east of I-95 at 103 Street in Miami. *The Miami Herald* — a private sector entity that is performing admirably in this crisis — reports that many of the 10,000 downed utility poles were damaged extensively in prior hurricanes but repaired shoddily by Florida Power and Light. (Reprinted with permission from *The Miami Herald*, photographer: J Walter Michot.)

The value of water and electricity has a new meaning to many. (Reprinted with permission from *The Miami Herald*, photographer: Marsha Halper.)

I don't want to pick on W or his brother in Tallahassee any more than I would single out specific people at the NCI or Medicare or the FDA for their antiquated policies and procedures. In my mind, that sluggishness is the nature of bureaucracy and bean counting and why I run my own company rather than continuing on the faculty of the University of Miami, which like other academic centers, prides itself on obtaining good deli platters for their endless meetings.

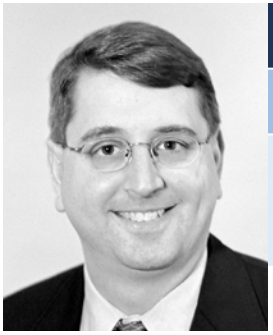
You can bet that Wal-Mart, Home Depot and Publix will be more efficient dealing with this Wilma mess than FEMA or George or Jeb B, just as corporate America took the lead after Katrina. The spirit of the private sector is also the reason that our CME group has not let the storm stop us. Right now, half of our staff is cooped up in a downtown hotel across the street from our offices because they can't obtain gas to drive in and have no electricity to work at home. Our dazed group started straggling in the day after the storm and has been cranking out content furiously all week, dedicated to their tasks because they believe that our products and services provide an important value to people whose physical and mental suffering makes the impact of hurricanes seem minimal — cancer patients and their families, who partner every day with their healthcare teams to combat what is often a relentless disease.

Maybe someday an innovative, functional oncologic private-sector entity (Wol-Mark?) will take control of clinical cancer research and practice and find answers quicker than our lights are expected to come back on.

Geraldo, where are you when we need you? ■

— Neil Love, MD
NLove@ResearchToPractice.net
December 5, 2005

Postscript, November 3, 2005: Ten days after Wilma, 600,000 South Floridians are still without electricity, and many have no running water. The impoverished and elderly — without adequate support to cope with their losses — continue to suffer deeply. (Reprinted with permission from *The Miami Herald*, photographer: Candace Barbot.)



INTERVIEW

Harold J Burstein, MD, PhD

Dr Burstein is an Assistant Professor of Medicine at the Dana-Farber Cancer Institute's Breast Oncology Center at Harvard Medical School in Boston, Massachusetts.

Tracks 1-19

Select Excerpts from the Interview

Track 2

DR LOVE: Would you comment on the rationale and design of the ECOG-2100 trial?

DR BURSTEIN: ECOG-2100 was a trial of chemotherapy alone or in combination with bevacizumab as first-line treatment for metastatic breast cancer. Patients were offered weekly paclitaxel three weeks out of four or that same regimen combined with bevacizumab given every two weeks (1.1).

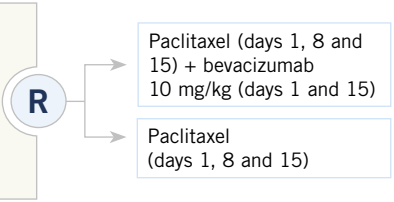
1.1

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

Protocol IDs: ECOG-2100, CTSU, NCT00028990, CAN-NCIC-E2100, NCCTG-E2100, NSABP-E2100
Accrual: 715 (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



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

The important thing about this study is that it followed a previous trial that looked at capecitabine with or without bevacizumab for anthracycline- and taxane-treated advanced breast cancer. In that study, which Kathy Miller presented at the San Antonio meeting in 2002 (Miller 2002) and published this spring in the *JCO* (Miller 2005b), there really had not been a dramatic benefit for adding bevacizumab to chemotherapy.

There has been a temptation to look through the retrospectoscope to say, "That previous study was a positive study because the response rate went from 19 to 30 percent; therefore, we should have known to expect more from bevacizumab." But those responses were very short lived, and there was no difference in progression-free or overall survival, so I think the question as to whether bevacizumab would be beneficial for advanced breast cancer was unanswered.

DR LOVE: In that study of capecitabine with or without bevacizumab, patients with HER2-positive disease were eligible. How did that differ from the ECOG-2100 trial?

DR BURSTEIN: ECOG-2100 ended up being a study principally of HER2-negative breast cancer. Patients with HER2-positive tumors were eligible if for some reason they could not receive trastuzumab, but because most patients can receive trastuzumab, that was a very small component of the study.

The other difference is that in ECOG-2100, patients had received less chemotherapy. It was a study for women who had not had any prior chemotherapy for advanced breast cancer. They could have had anthracycline-based chemotherapy or even taxane-based chemotherapy in the adjuvant setting if they were more than one year out from treatment.

DR LOVE: What were the key findings of the trial?

DR BURSTEIN: First, it showed that bevacizumab was reasonably well tolerated in the advanced breast cancer population. There is an increased risk of hypertension, which has been seen in some of the other trials. Fortunately, there were relatively few events such as thromboembolism or bleeding complications. A lot of patients had some minor degree of nosebleeds, or epistaxis, but for the most part, the drug proved quite well tolerated.

The second important finding was that the study met its primary endpoint, which was to show that adding bevacizumab did improve time to progression (1.2). The time to progression with chemotherapy alone was approximately five to six months, and that nearly doubled to about 11 months with the combination of paclitaxel and bevacizumab.

Associated with that gain in time to progression was an improvement in response rate. The response rate with chemotherapy alone was about 14 percent, and that increased to 28 percent by adding bevacizumab.

There was a suggestion, though it's very limited follow-up, of an improvement in survival on the order of a couple of months. That difference was statistically significant, though it must be acknowledged that these were preliminary data, and we'll hear more about that in San Antonio.

1.2

ECOG-E2100 Efficacy Results

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

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

Track 3

DR LOVE: It seems that in metastatic disease trials there has been a trend of focusing on progression-free survival rather than response rate or overall survival.

DR BURSTEIN: Yes, I think that's true, and the reason for that is complex. First, there is an appreciation that clinical improvement with response is a relatively soft endpoint for most patients. Patients would like to live longer and live free of cancer longer.

Secondly, there has been this theoretical argument that newer drugs that target the vasculature might not actually contribute to response as much as they may simply delay progression. So with some of the drugs that are thought to be inhibitors of tumor differentiation or drugs that might slow down angiogen-

esis, it has been argued that you might see improvement in progression-free survival without a difference in objective response.

For instance, with bevacizumab in the Phase II trials in renal cell cancer, there were hardly any responses, but there was a dose-dependent difference in time to progression, even though very few patients had objective response (Yang 2003). Interestingly, that has not, as yet, been the case with the more traditional solid tumors in the lung, colon and breast studies. The improvement in progression-free survival has been more or less matched by improvements in response rate.

What's lacking in all the bevacizumab studies to date is a predictive marker of which patients are likely to benefit and which are not. We don't have a marker like estrogen receptor or HER2 that would identify patients who are more likely to respond.

In the trial of capecitabine with or without bevacizumab, baseline levels of VEGF expression were evaluated (Miller 2005b). Those levels did not seem to correlate with response or outcome in that initial trial, but, of course, that was a negative trial, so it's hard to know what to infer.

Track 4

DR LOVE: What has been your clinical experience with bevacizumab?

DR BURSTEIN: We have a lot of clinical trial experience with bevacizumab. We conducted a Phase II study evaluating bevacizumab in combination with vinorelbine. These data were presented at the San Antonio meeting in 2002 and showed that the regimen was reasonably well tolerated and there was clinical activity (Burstein 2002).

There was a response rate of approximately 30 percent. However, at the time, the negative randomized trial with bevacizumab and capecitabine for the refractory patient population was reported, so our trial did not lead to a broad use of our particular combination.

What we've been doing more recently is a randomized Phase II study of so-called low-dose or metronomic chemotherapy, given either by itself or in combination with bevacizumab as first-line treatment for advanced breast cancer. We hope to present the data at the 2005 San Antonio meeting (Burstein 2005). We've found this regimen very interesting and hope to have some very nice clinical and correlative data to support it.

DR LOVE: What exactly is the regimen?

DR BURSTEIN: It is 2.5 milligrams of methotrexate twice daily for two days each week plus 50 milligrams of oral cyclophosphamide daily with or without bevacizumab. The argument here is that in laboratory models, the low-dose or metronomic chemotherapy actually provides very good tumor control in many systems and is thought to inhibit angiogenesis factors.

Very exciting data were presented at ASCO 2005 indicating that using low-dose oral cyclophosphamide with bevacizumab led to substantial response in platinum-refractory ovarian cancer (Garcia 2005; [1.3]). This is a very well-tolerated combination that I think is worth watching as the data evolve.

1.3

Phase II Clinical Trial of Bevacizumab and Low-Dose Metronomic Oral Cyclophosphamide in Recurrent Ovarian and Primary Peritoneal Carcinoma

Protocol ID: PH II-45
Accrual: 29 (Closed)

Eligibility
Ovarian or primary peritoneal carcinoma
Recurrent after initial platinum and paclitaxel chemotherapy

R → Bevacizumab 10 mg/kg IV q2wk + oral cyclophosphamide 50 mg qd*

* Treatment continues until tumor progression or toxicity occurs.

Interim efficacy data

Response rates	N	%
Complete response	0	0
Partial response	8	28
Stable disease	18	62

Survival data

6-month progression-free survival	57% ± 10%
Overall survival	+13.0 months

SOURCE: Garcia AA et al. Presentation. ASCO 2005;**Abstract 5000**.

DR LOVE: It appears bevacizumab is relatively patient friendly in the palliative setting, and hopefully we'll also see that with earlier stage disease.

DR BURSTEIN: So far that's been our experience. Bevacizumab doesn't make you sick to your stomach. It doesn't make your hair fall out. Patients who've been on it for months and months and months do have some hair thinning and some fatigue that accumulates.

DR LOVE: After you complete the Phase II trial of bevacizumab and low-dose oral cyclophosphamide and methotrexate, where do you see this regimen heading?

DR BURSTEIN: The study that we have activated now at Dana-Farber and Indiana University with my good friends Kathy Miller and George Sledge is a pilot study of bevacizumab in the adjuvant setting (1.4). The patient population is women who have had preoperative chemotherapy for breast cancer and who have residual cancer at the time of their surgery.

Those women will be offered one year of bevacizumab therapy to see if it's

feasible, and then a second cohort of the same type of patients will be offered one year of bevacizumab and six months of the metronomic chemotherapy.

We chose this patient population for a couple of very specific reasons. First, we know that women who have residual disease after preoperative chemotherapy constitute a very high-risk patient population for whom there is no standard treatment.

Secondly, these women have tumors that, by definition, have some resistance to chemotherapy, so instead of just treating them with more chemotherapy, we thought it would be interesting to bring in a biologic agent.

1.4

Phase II Pilot Trial of Adjuvant Bevacizumab with or without Cyclophosphamide

Protocol IDs: 05-055, NCT00121134
Target Accrual: 100 (Open)

Eligibility
Operable invasive breast cancer
Stage II-III
Residual invasive disease after completing neoadjuvant chemotherapy

R

Group A (60 patients)
Bevacizumab q3wk x 12mo

Group B (40 patients)
(Bevacizumab q3wk + cyclophosphamide qd + methotrexate BID x 2d qwk) x 6mo → bevacizumab q3wk x 6mo

Study contacts
Harold Burstein, MD, PhD, Principal Investigator
Nicole Brooke 617-632-6767
Dana-Farber/Harvard Cancer Center at Dana-Farber Cancer Institute

SOURCES: NCI Physician Data Query, November 2005; www.clinicaltrials.gov

DR LOVE: That's fascinating. Whenever we gather oncologists to discuss difficult cases, patients with residual disease after neoadjuvant chemotherapy are always among the first to be discussed.

DR BURSTEIN: Yes, so there is the temptation to say, "They've progressed on anthracyclines and taxanes in the neoadjuvant setting. They have lots of residual disease. What should we give them? Should we give them capecitabine? Should we give them gemcitabine?"

First, there are no data to suggest that more chemotherapy is beneficial in this setting. Secondly, there's reason to believe that women with tumors like that have disease that is more or less intrinsically resistant to chemotherapy. The temptation to offer more chemotherapy is understandable, but there are a lot of reasons to believe it's just not going to be very effective.

DR LOVE: What was the rationale for the bevacizumab-alone arm of that trial?

DR BURSTEIN: First, we don't know that bevacizumab alone would not be effective, and, of course, the adjuvant trials that are going to answer this

question ultimately will be large cooperative group studies of chemotherapy with or without bevacizumab. But bevacizumab alone has the advantage of being better tolerated, so when you start talking about extended periods of therapy, it probably is more feasible.

Secondly, we just wanted to see if it would be safe to give six to 12 months of bevacizumab in the adjuvant setting.

DR LOVE: That's a great trial. I think it's going to attract a lot of interest.

DR BURSTEIN: We also have some very handsome correlative studies built into it, taking advantage of the proteomics research for which Indiana University is very well known, and looking at some other markers of tumor recurrence and endothelial cell biology in which our group is very interested.

Track 5

DR LOVE: The key question oncologists have at this point about bevacizumab — assuming the reimbursement issues are resolved — is specifically how it should be utilized in practice. How are you using it clinically?

DR BURSTEIN: We now have data for bevacizumab in combination with paclitaxel. We certainly use a lot of weekly paclitaxel as first-line treatment for advanced breast cancer, so for patients who are already receiving paclitaxel, I believe this is clearly the regimen of choice.

The challenge is how to treat patients in the second- and third-line settings. At present, there really are only minimal data to indicate that bevacizumab is beneficial for such patients.

Another challenge is what to do for those women who received anthracyclines and taxanes in the adjuvant setting. Do you rechallenge them with paclitaxel and bevacizumab? There are two halves to that question. The first is, does bevacizumab actually help these women? We haven't seen the data as yet broken out as a function of prior taxane therapy.

The second half of the question is should you give the taxane again? Again, we don't have good answers. If it's been more than a year, it's probably reasonable to give the paclitaxel again. Occasionally, we recommend our vinorelbine regimen, because of our Phase II experience with vinorelbine plus bevacizumab (Burstein 2002).

Some people administer capecitabine plus bevacizumab, because, of course, there are safety data for that. On the other hand, those data don't really suggest that particular combination does all that much compared to capecitabine alone.

These are the types of issues that follow any exciting new drug introduction. We're all looking forward to more studies, more Phase II trials, to really try and understand how best to utilize this drug for metastatic disease.

DR LOVE: What about bevacizumab and docetaxel?

DR BURSTEIN: There are limited Phase II data on that combination from a preoperative study that Sandy Swain has done and a trial in the treatment of metastatic breast cancer conducted by Charlie Shapiro at Ohio State (Denduluri 2004; Wedam 2004; Ramaswamy 2003). There will be finite response rates and safety data from these Phase II trials. My personal preference, based on the ECOG-2100 data right now, is to use weekly paclitaxel with bevacizumab.

Track 6

DR LOVE: What about the combination of bevacizumab and nanoparticle albumin-bound *(nab)* paclitaxel?

DR BURSTEIN: What's interesting about *nab* paclitaxel is that it seems to have some convenience and safety advantages over paclitaxel — it has a lower rate of hypersensitivity reactions, so it eliminates the need for steroid premedication, and the infusion time is shorter.

One of the consequences of the way the drug was registered, though, is that it wasn't registered in a study that compared milligram-for-milligram equivalence of paclitaxel in the two formulations. The registration study was an every three-week treatment using paclitaxel at 175 mg/m^2 versus *nab* paclitaxel at 260 mg/m^2 (1.5).

A consequence of that is that we don't really have the data to substitute the drug into all the regimens that were discussed at ASCO this year (2005), in particular, weekly paclitaxel when combined with bevacizumab (Miller 2005a) and weekly paclitaxel or every three-week paclitaxel used in the adjuvant trastuzumab trials (Romond 2005a). We need the Phase II data for the safety and feasibility of those combinations and those schedules and we need to find the appropriate *nab* paclitaxel dose.

Obviously, those trials are being put together. Our group will be conducting a study of dose-dense AC followed by *nab* paclitaxel, and patients who have HER2-positive tumors will receive the *nab* paclitaxel with trastuzumab, so we can begin to characterize the safety and feasibility of these regimens. However, for the moment, I think that the data clearly suggest you should just go with paclitaxel.

DR LOVE: Some of the *nab* paclitaxel data suggest lower rates of neutropenia. Is that the case, and will you still use growth factors with dose-dense AC → *nab* paclitaxel?

DR BURSTEIN: There has been that suggestion of less neutropenia in the literature (Gradishar 2005; [1.5]), and so during our Phase II pilot study, we will be omitting the growth factors with *nab* paclitaxel for the taxane portion to see if it's feasible.

1.5

Phase III Randomized Trial Comparing *Nab* Paclitaxel to Paclitaxel as First-, Second-, Third- or Fourth-Line Therapy in Women with Metastatic Breast Cancer

	Nab paclitaxel 260mg/m^2 (n = 229)	Paclitaxel 175mg/m^2 (n = 225)	*p*-value
Complete response + partial response			
Overall	33%	19%	0.001
First-line therapy	42%	27%	0.029
Median time to tumor progression	23.0 weeks	16.9 weeks	0.006
Median survival			
Overall	65 weeks	55.7 weeks	0.374
≥Second-line therapy	56.4 weeks	46.7 weeks	0.024
Neutropenia (Grade IV)	9%	22%	<0.001
Sensory neuropathy (Grade III)	10%	2%	<0.001
Hypersensitivity (any grade)	<1%	2%	Not reported

"Despite a 50% increase in the dose of paclitaxel, patients treated with ABI-007 experienced significantly less neutropenia ($p < .001$). Polyethylated castor oil is believed to contribute to taxane-associated myelosuppression by inhibiting MDR1 P-glycoprotein in hematopoietic progenitor cells. Because of its low volume of distribution, polyethylated castor oil remains within the vasculature compartment in continuous contact with bone marrow and may enhance myelosuppression, while having less effect on MDR1 in tumor tissues.

In the CALGB trial [CALGB-9342], the incidence and severity of myelosuppression were markedly increased with the higher doses of standard paclitaxel. In contrast, with ABI-007 260 mg/m^2, the incidence of grade 4 neutropenia was markedly lower than that expected with high-dose paclitaxel (9% for ABI-007 v 53% for standard paclitaxel 250 mg/m^2 in the CALGB trial)."

SOURCE: Gradhishar WJ et al. *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

Track 10

DR LOVE: Can you summarize the adjuvant trastuzumab studies presented at ASCO and your take on the data?

DR BURSTEIN: The first presentation was a pooled analysis from the NSABP (NSABP-B-31) and Intergroup trials (NCCTG-N9831; [Romond 2005a]). The second presentation focused on the North American Intergroup study and tackled the question of sequential versus concurrent trastuzumab (Perez 2005). The third presentation was on the European HERA trial, which was a study of no therapy versus one or two years of trastuzumab after adjuvant chemotherapy (Piccart-Gebhart 2005a).

Dr Romond presented the pooled NSABP and Intergroup data. They combined these data because they realized that trial accrual was still ongoing

in the adjuvant trastuzumab studies in North America, and there was a sense of urgency to try and get some answers quickly. With the blessing of the National Cancer Institute, the NSABP and the Intergroup decided to pool two very separate trials into one, which would be analyzed for disease-free survival, and asked the question whether AC followed by paclitaxel with or without trastuzumab was better.

The results of the pooled analysis clearly showed that adding trastuzumab lowered the risk of recurrence by about half (1.6, 1.7). There was a very dramatic *p*-value — something like three times 10 to the negative 12th power — which everyone made a big deal out of, but suffice it to say this was not due to chance. And I think that the relative risk translated to a very substantial clinical gain. The risk of recurrence in the patients who received chemotherapy alone was actually quite high, 25 percent recurrence rate at three years — nearly 33 percent recurrence rate at four years — and, again, adding trastuzumab cut that risk in half.

The patients were randomly assigned to chemotherapy with or without trastuzumab, but half of the women had hormone receptor-positive tumors and presumably had received anti-estrogen therapy as well.

DR LOVE: Considering the fact that the patients had received adjuvant chemotherapy and, in addition, half of them had received adjuvant hormonal therapy, a 25 percent rate of relapse at three years is pretty impressive.

DR BURSTEIN: It is, and it just underscores how high-risk HER2-positive breast cancers really are. These data, as they were presented, were very clean, and you sit in the back of the amphitheater and say, "Now everything is different," because you're going to start offering adjuvant trastuzumab.

DR LOVE: What are your thoughts about the cardiac toxicity data?

DR BURSTEIN: There are still things we need to learn about this therapy. The price for using trastuzumab is a greater risk of cardiac toxicity, and we need to better understand that risk. That risk was about four percent in the NSABP experience with trastuzumab plus chemotherapy versus less than one percent with chemotherapy alone. It is true that in many instances the cardiac toxicity is reversible, but not always.

There was a suggestion that women who are older than age 50 and women whose baseline LVEF was borderline, between 50 and 55 percent, might be particularly at risk for cardiac toxicity. Clearly, ongoing cardiac surveillance and careful patient selection is still warranted when using this agent.

There were really two differences between the cardiac screening in the HERA trial and the North American trials. First, in the HERA trial, women were eligible after they'd finished all their chemotherapy, so if they had a major drop in their LVEF during their chemotherapy, they were ineligible for the trial.

Secondly, the threshold in the HERA trial was 55 percent, a little bit higher

than in the North American trials. If you actually look in the North American studies at the women whose ejection fractions were greater than 55 percent, the risk of cardiac toxicity looks to be about one to two percent, which is more or less what was seen in the HERA trial.

I don't know that we have compelling data suggesting that sequential therapy is safer than concurrent therapy with paclitaxel, and I don't think we know the window for which you need to be finished with your anthracyclines before you start the trastuzumab.

DR LOVE: The other impressive finding in the combined analysis was that it showed a survival benefit at just two years of follow-up.

DR BURSTEIN: There was a suggestion of a survival benefit in the pooled analysis. It was about a two to three percent difference at two to three years, and the difference was statistically significant. Neither study alone had a survival advantage, but the advantage of pooling the data was to observe enough events.

DR LOVE: I interviewed Ed Romond right after that presentation and asked him about the slide he showed of distant disease-free survival, in which there was a dramatic drop at three or four years of follow-up. What were your thoughts on that?

DR BURSTEIN: I think it is important that most of the events in these trials were distant metastatic events. In the hormone literature, particularly of late, we've included all breast cancer events — contralateral tumors, ipsilateral recurrences and distant metastases. That makes sense because hormone receptor-positive tumors have a much more indolent natural history, and these second breast cancer events matter. However, for HER2-positive disease, which is more virulent, really what you're talking about is preventing distant metastasis, and as you pointed out, even with the short follow-up and even with the availability of trastuzumab in the metastatic setting, there still was a survival difference emerging after just two to three years of follow-up.

1.6

Conclusions: Combined Analysis of NSABP-B-31/NCCTG-N9831

"Our conclusions for high-risk HER2-positive breast cancer: Trastuzumab, when given concurrently with paclitaxel following AC chemotherapy, reduces the risk of a first breast cancer event at three years by 52 percent. This benefit should change the standard of care. The relative risk reduction benefit was present and of similar magnitude in virtually all subsets of patients analyzed. There is not, however, statistical power to establish efficacy in the node-negative subset. The addition of trastuzumab reduced the probability of developing distant recurrence by 53 percent at three years and the hazard of developing distant metastases appears, thus far, to decrease over time. Early results at a median follow-up of two years show a statistically significant survival advantage, with a relative risk reduction of 33 percent."

SOURCE: Romond EH et al. Presentation. ASCO 2005. No abstract available

1.7

2005 ASCO Adjuvant Trastuzumab Data — Adjuvant Chemotherapy with or without Trastuzumab: Combined Analysis of NSABP-B-31/NCCTG-N9831 Efficacy Data

Parameters	AC → paclitaxel (n = 1,679)	AC → paclitaxel + trastuzumab (n = 1,672)	Hazard ratio	*p*-value
Disease-free survival			0.48	<0.0001
Three-year disease-free survival	75%	87%		
Four-year disease-free survival	67%	85%		
Time to first distant recurrence			0.47	<0.0001
Three years from randomization	81%	90%		
Four years from randomization	74%	90%		
Overall survival			0.67	0.015
Three years from randomization	92%	94%		
Four years from randomization	87%	91%		

SOURCES: Romond EH et al. Presentation. ASCO 2005. No abstract available; Romond EH et al. *N Engl J Med* 2005;353(16):1673–84. **Abstract**

Track 11

DR LOVE: What are your thoughts on the issue of concurrent versus sequential adjuvant chemotherapy and trastuzumab?

DR BURSTEIN: The context for that really is the global HERA trial, in which women finished all their chemotherapy and radiation therapy and then were randomly assigned to either no further treatment or one or two years of trastuzumab. The data presented were for one year of trastuzumab treatment (Piccart-Gebhart 2005).

This study also showed a dramatic lowering of the risk of recurrence, again cutting the risk by nearly 50 percent, again with very short follow-up, on average only one to two years, but a statistically and clinically apparent reduction in risk of recurrence. So trastuzumab works at preventing recurrence in the adjuvant setting. Because of the short follow-up, there was no survival advantage as yet reported in the HERA trial.

To circle back to the Intergroup experience, the three arms of the NCCTG-N9831 trial were chemotherapy alone, chemotherapy followed in sequence by trastuzumab, or chemotherapy where the patient began trastuzumab concurrent with paclitaxel. In comparing chemotherapy alone versus concurrent chemotherapy/trastuzumab, there was a big difference — a 50 percent risk reduction (Romond 2005a). By contrast, when they compared chemotherapy alone versus chemotherapy followed by sequential trastuzumab, there was a 13 percent risk reduction, which was not statistically significant.

Frankly, it is hard to square the results of the HERA trial with the results of the North American Intergroup study. The most likely explanation is that

there is some benefit for sequential trastuzumab therapy, but the benefit is modest. Perhaps the fact that everyone in the Intergroup study received a taxane, compared to the HERA trial in which most women did not receive a taxane, diminished some of the gains that you might see with trastuzumab. Perhaps it's just an artifact of small numbers of patients with very limited follow-up.

We don't really know how to optimally use adjuvant trastuzumab. I suspect in North America, most trials moving forward and in clinical practice most physicians will start with concurrent trastuzumab and paclitaxel, as was done in the NSABP and Intergroup studies. Whereas in Europe and around the world, I suspect clinicians will administer trastuzumab after the patient finishes chemotherapy, based on their experience to date.

Track 16

DR LOVE: The adjuvant trastuzumab data have generated many practical questions as to how to use this agent clinically. How are you using it in your practice?

DR BURSTEIN: The data were pretty straightforward and, while I think you can quibble with the margins, they're very simple data — you give patients with HER2-positive tumors trastuzumab. The studies consisted principally of patients with node-positive breast cancer, and so, on the issue of proportional risk reduction and absolute risk reduction, for women at lower risk who have node-negative or hormone receptor-positive breast cancer, we don't know in absolute terms how much benefit can be gained from adjuvant trastuzumab.

We know from the subset analyses in both the North American trials and the HERA trial that the proportional risk reduction was very similar regardless of nodal status or the number of positive nodes, the size of the tumor, the age of the patient or the hormone receptor status of the tumor (Romond 2005b; Piccart-Gebhart 2005b). All those lined up very similarly in the Forest plots; they all had an average of approximately a 50 percent risk reduction.

Still, that means that you don't know how much benefit a woman with a 1.2-centimeter, ER-positive, node-negative, HER2-positive tumor receives in absolute terms compared to one who has a three-centimeter, five-positive-node tumor. Those data will be generated, and people will start to weigh in on whether it makes sense or not.

DR LOVE: In the interim, I expect we will still probably rely on the relative risk reduction concept.

DR BURSTEIN: I would think so. The national guideline panels will be rapidly adopting these data. The NCCN has already evaluated the data. I sit on that panel, and they will recommend trastuzumab for all patients with node-positive breast cancer and, for patients with node-negative disease, they will recommend considering trastuzumab for those women who would

have met the eligibility criteria for the Intergroup study — a one-centimeter tumor if the tumor were ER-negative or a two-centimeter tumor if it were ER-positive.

They say "consider," as opposed to just do it, only because there are so few data from patients with node-negative disease. Patients with negative nodes comprised roughly five percent of the pooled North American clinical experience, approximately 10 percent of the entire Intergroup trial and about 30 percent of the HERA trial, so there are very little data on node-negative disease.

Track 17

DR LOVE: One of the most common questions to arise from the adjuvant trastuzumab data is how to treat the patient who is one, two or three years out from diagnosis. What are your thoughts on this?

DR BURSTEIN: In the North American trials, the risk of recurrence is very pronounced in the first two or three years. If the patient is beyond three years out, her risk is really quite different from what it was at baseline. So aside from the fact that there's no data on whether to give trastuzumab to women who are two or three years out, it's not clear that they need the trastuzumab.

For women with HER2-positive tumors who've just finished chemotherapy within the past several months, we have been suggesting they consider trastuzumab. Obviously, this is a time-limited problem. In patients who are more than six or 12 months out, we have not frequently gone back and added trastuzumab to their treatment regimen. I know that different centers have drawn the line in the sand at different places.

I think that a sobering experience from the Intergroup trial is that there is no statistically significant gain in the Intergroup study in the sequential arm. At best, we are offering a modest advantage to such patients. ■

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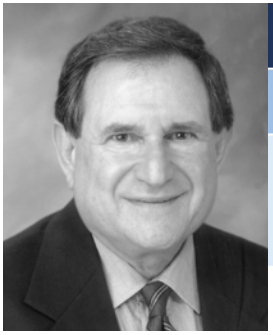


INTERVIEW

Charles L Vogel, MD

Dr Vogel is the Medical Director of Cancer Research Network Inc in Plantation, Florida.

Tracks 1-14

Select Excerpts from the Interview

Track 3

DR LOVE: Would you discuss the issue of quality control in hormone receptor testing?

DR VOGEL: I urge all oncologists to take a very close look at their patients with ER- and PR-negative disease because, unfortunately, pathology in the United States has really not kept pace in terms of quality control.

We started discovering these problems with one patient in our office who clinically didn't appear to have ER/PR-negative disease. We sent the slides to Craig Allred at Baylor, and lo and behold, the tumor was strongly ER-positive. So we sent a second and a third. In all, we sent 30 specimens — all read as

ER/PR-negative by immunohistochemistry in a broad array of laboratories. Thirty percent turned out to be positive.

DR LOVE: How much of the problem is technical performance of the assay as opposed to defining the limit for ER positivity?

DR VOGEL: There are technical problems in some laboratories, and there are cutoff problems in others. The oncologist sees a piece of paper that says "negative" and may not even look at the cutoff values. It is then written in stone in the oncologist's mind that this patient's disease is hormonally nonresponsive. We don't take receptor negativity at face value for any patient.

Track 4

DR LOVE: How do you utilize HER2 and PR status in approaching adjuvant hormonal therapy in postmenopausal patients with ER-positive disease?

DR VOGEL: A growing body of evidence indicates that tamoxifen may not be the best hormone therapy in a patient with HER2-positive disease (Ellis 2001). For that reason, I generally choose an aromatase inhibitor for those patients, in both the adjuvant and metastatic disease settings.

DR LOVE: What about those patients with ER-positive/PR-positive disease?

DR VOGEL: For those patients, we now have another bit of a problem, based on a retrospective subset analysis of the ATAC data from Mitch Dowsett, in which the group of patients with both estrogen and progesterone receptor-positive disease didn't seem to derive very much efficacy advantage from anastrozole compared to tamoxifen. The greatest benefit was seen in the patients with ER-positive, PR-negative disease (Dowsett 2003, 2005; [2.1]).

However, these same observations have not held up in three other major trials of aromatase inhibitors versus tamoxifen (Coombes 2004b; Jakesz 2005; Goss 2005).

2.1

Recurrence Rates in the ATAC Trial According to Estrogen and Progesterone Receptor Status

Receptor status	N	Hazard ratio for anastrozole versus tamoxifen (95% CI)*	Anastrozole	Tamoxifen
ER-positive, PR-positive	5,704	0.82 (0.65-1.03)	7%	8%
ER-positive, PR-negative	1,370	0.48 (0.33-0.71)	9%	17%
ER-negative, PR-positive	220	0.79 (0.40-1.50)	22%	26%
ER-negative, PR-negative	699	1.04 (0.73-1.47)	27%	27%

* Hazard ratios less than one indicate values in favor of anastrozole.

SOURCE: Dowsett M, on behalf of the ATAC Trialists' Group. *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6;**Abstract 4**.

Track 5

DR LOVE: Would you discuss the adjuvant management of ER-positive disease in the premenopausal patient?

DR VOGEL: Tamoxifen remains the mainstay of treatment for these patients. Certainly, in Europe there is a very strong feeling that the published data seem to indicate that the addition of ovarian ablation to tamoxifen is superior to either of those modalities alone. In Europe, it's very hard to convince the vast majority of oncologists that the question of treatment approach in these patients has not already been answered.

However, the fact that we have the SOFT, TEXT and PERCHE trials examining this very issue indicates that, at least in the minds of most North American oncologists, the question remains unanswered as to the best adjuvant therapy for premenopausal patients (2.2).

The answers are not in and won't be in for many years. In the meantime, oncologists are stuck deciding what to do. Do you or don't you believe that the addition of ovarian ablation adds to orally administered hormonal therapy? Certainly, you cannot use an aromatase inhibitor in premenopausal patients and expect it to work unless you render them postmenopausal.

DR LOVE: What about hormonal therapy for premenopausal women who stop menstruating during or after chemotherapy?

DR VOGEL: This must be viewed with considerable caution, especially related to the switching strategy of moving from tamoxifen to an aromatase inhibitor. It is very difficult to follow these women, because the LH and FSH levels are low in tamoxifen-treated patients. You have to rely on the estradiol level, which is fraught with methodological problems. These patients must be followed as closely as possible.

2.2 Trials of Adjuvant Endocrine Therapy with Ovarian Suppression

Study	N	Eligibility	Randomization
IBCSG-24-02 (SOFT trial)	3,000 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Tamoxifen x 5y OFS + tamoxifen x 5y OFS + exemestane x 5y
IBCSG-25-02 (TEXT trial)	1,845 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Triptorelin ± chemotherapy + tamoxifen x 5y Triptorelin ± chemotherapy + exemestane x 5y
IBCSG-26-02 (PERCHE trial)	1,750 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	OFS + tamoxifen or exemestane x 5y OFS + any chemotherapy + tamoxifen or exemestane x 5y

OFS = ovarian function suppression with triptorelin or surgical oophorectomy or ovarian irradiation

SOURCES: www.ibcsg.org; NCI Physician Data Query, November 2005.

If you want to use the switching strategy in a patient with chemotherapy-induced amenorrhea about whom you're concerned, you can put her on an LHRH compound and switch to an aromatase inhibitor. I would still monitor her estradiol level for a while.

Track 6

DR LOVE: Do you believe that five years of tamoxifen followed by an aromatase inhibitor is an acceptable therapy for a postmenopausal patient?

DR VOGEL: I personally might utilize this strategy in a patient with severe osteoporosis, where I am hoping for additional benefit to the bone. In general, however, up front I tend to use aromatase inhibitors as opposed to tamoxifen.

One of the big questions is, do you start with an aromatase inhibitor or do you give the patients two years of tamoxifen? Those who start with aromatase inhibitors are concerned that the first year and a half to two years is one of the major peak recurrence times, and consequently, if you don't start with an aromatase inhibitor, you will miss that peak recurrence time (Saphner 1996; [2.3, 2.4]). In general, I start with an aromatase inhibitor.

In my postmenopausal patients already on tamoxifen, I generally switch to an aromatase inhibitor after two years. Another unanswered question is, at five years, what do you do with the patients on an aromatase inhibitor? Theoretically and biologically, there is no real reason to discontinue the aromatase inhibitor at five years. We now have the MA17 data, indicating that five years of letrozole after five years of tamoxifen is beneficial (Goss 2003).

2.3

Annual Hazard Rates of Recurrence for Breast Cancer After Primary Therapy

"The pattern of recurrence for the entire population was that of a peak hazard of recurrence equalling 13.3% during the second year of follow-up, followed by a steady decrease in the hazard of recurrence until year 5. Beyond year 5, the hazard of recurrence slowly declined and averaged 4.3%. For the entire group, the annual hazard of recurrence has not reached zero through 12 years of follow-up."

SOURCE: Saphner T et al. *J Clin Oncol* 1996;14(10):2738-46. **Abstract**

Track 7

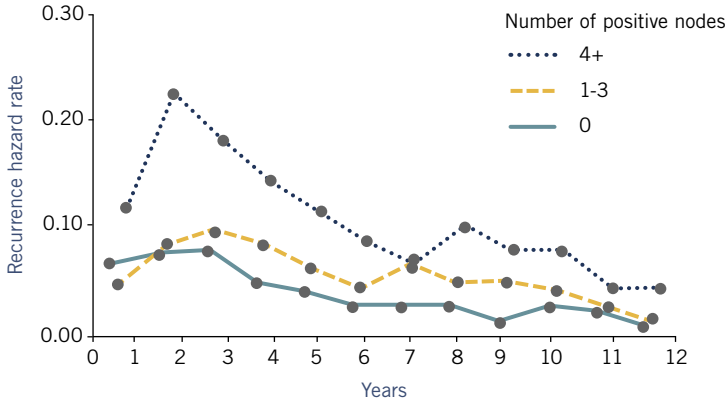
DR LOVE: What are your thoughts about the data on cardiac events in patients receiving aromatase inhibitors?

DR VOGEL: The first hint came from the BIG FEMTA trial with letrozole (Thürlimann 2005a, b), and they also observed this in the exemestane data (Coombes 2004a). I believe we will see much more in-depth analysis of all of the aromatase inhibitor trials to see just how real this issue is. I don't know

how big an issue the cholesterol problem in the BIG FEMTA trial is because those were not fasting specimens and it was not reproduced in the MA17 trial with the same drug. This is one of those areas where we're just going to have to wait.

2.4

Annual Hazard Rates of Recurrence for Breast Cancer After Primary Therapy



SOURCE: Adapted with permission from the American Society of Clinical Oncology. Saphner T et al. *J Clin Oncol* 1996;14(10):2738-46. **Abstract**

DR LOVE: Can you put the quantitative risk in perspective?

DR VOGEL: The risk appears to be very low, as we see it at the moment, and the benefits of the drugs appear to be quite high.

We all know about the risk of endometrial carcinoma with tamoxifen, and we have dealt with that. We know about the cardiac risk with adjuvant trastuzumab, and we have to deal with that. There will be many things we need to discuss with patients and document in our charts. For the moment, the cardiac toxicity and impact on lipid profiles with aromatase inhibitors remains to be resolved. More information should become available relatively soon because of the substudies in each of these very large-scale trials.

Track 9

DR LOVE: What is your approach to patients with ER-positive metastatic disease, both HER2-positive and HER2-negative?

DR VOGEL: To me, any patient with hormone receptor-positive disease is a candidate for hormonal therapy up front, regardless of HER2 status, except those patients with visceral crisis.

This will be controversial for patients with ER-positive, HER2-positive disease. There are those who feel that a combination of hormonal therapy and trastuzumab should be given up front. I do not fall into that camp, as yet.

To me, every available manipulation we have in metastatic disease is gold. If you use a combination of hormone therapy and trastuzumab, both of which are relatively nontoxic, and you have a two-year response, you really don't know what would have happened if you had given those agents sequentially. We're still arguing that point in the chemotherapy arena on the basis of the two Phase III combination chemotherapy trials that claim overall survival benefits without having had sequential arms (O'Shaughnessy 2002; Albain 2004).

DR LOVE: When you utilize hormonal therapy in metastatic disease, how do you approach the sequencing of the available options?

DR VOGEL: In postmenopausal patients, for the most part, I generally start with an aromatase inhibitor. There are nine lines of hormonal therapy for postmenopausal women, and there is no tried and true sequence — we don't have any consensus on a true hormonal cascade. Hormones can be manipulated, in some women, for years. I've had patients on hormonal therapy for 10 or 12 years before ever reaching cytotoxic chemotherapy.

Track 10

DR LOVE: What is your clinical experience with fulvestrant?

DR VOGEL: Fulvestrant is a very good drug that has minimal toxicity. We don't even encounter much in the way of buttock pain with a five-cc injection. We're also not seeing the degree of joint discomfort that we see with the aromatase inhibitors.

In terms of efficacy, fulvestrant seems to be equivalent to anastrozole (Robertson 2003). Based on data published this year in *Cancer,* there seems to be no difference in overall survival in the randomized trials of anastrozole versus fulvestrant (Howell 2005).

Fulvestrant is a good drug and a viable alternative to aromatase inhibitors in patients who have disease progression on tamoxifen. We do have to contend with the randomized trial of fulvestrant versus tamoxifen, where we expected a strongly beneficial effect for fulvestrant over tamoxifen, which was not forthcoming. There were some subsets where fulvestrant appeared to be better, but the overall results were about the same (Howell 2004).

Track 11

DR LOVE: Can you summarize your approach to first-line therapy in patients with HER2-positive metastatic disease?

DR VOGEL: First of all, if I don't have a FISH assay, I won't treat the patient. Many still feel that an IHC 3+ is absolute, but I disagree. Quality control is improving, but it is still nowhere near where it needs to be. I insist that my patients have a FISH assay before I embark on trastuzumab therapy in the metastatic setting.

Since I published the paper on single-agent trastuzumab (Vogel 2002), everybody thinks that that is my first-line treatment in every patient. It's not. Certainly, I believe a course of single-agent trastuzumab is not unreasonable in relatively asymptomatic patients with minimal disease burden. However, for more symptomatic patients, I tend to use a combination of chemotherapy and trastuzumab.

Track 12

DR LOVE: What do you consider an indication to discontinue trastuzumab in the metastatic setting?

DR VOGEL: It's difficult to get patients to stop trastuzumab. I tend to continue trastuzumab almost indefinitely as we switch from chemotherapy to chemotherapy.

Is that supportable by data? Absolutely not. Will continuation of trastuzumab beyond progression on first-line therapy ever be proven? My suspicion is not. This may be one of those questions that are never answered.

DR LOVE: How will you approach the new generation of patients who develop metastatic disease after receiving adjuvant trastuzumab?

DR VOGEL: I would use trastuzumab in these patients for the same reasons that we continue it in the metastatic setting. First, we're still hoping for therapeutic synergism with the next drug that we use. Second, it's relatively nontoxic and so relatively easy to continue. And the third reason is that preclinical data seemed to indicate that even in rats progressing on trastuzumab, the rate of progression was slowed in those who continued trastuzumab. ■

SELECT PUBLICATIONS

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Coombes RC et al. **The Intergroup Exemestane Study: A randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen — Updated survival analysis.** Presentation. San Antonio Breast Cancer Symposium 2004a;**Abstract 3**.

Coombes RC et al; Intergroup Exemestane Study. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004b;350(11):1081-92. **Abstract**

Dowsett M et al. **Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status: An hypothesis-generating study.** *J Clin Oncol* 2005;23(30):7512-7. **Abstract**

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Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802. **Abstract**

Howell A et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: A prospectively planned combined survival analysis of two multicenter trials.** *Cancer* 2005;104(2):236-9. **Abstract**

Howell A et al. **Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double-blind, randomized trial.** *J Clin Oncol* 2004;22(9):1605-13. **Abstract**

Jakesz R et al; ABCSG and the GABG. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005;366(9484):455-62. **Abstract**

O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results.** *J Clin Oncol* 2002;20(12):2812-23. **Abstract**

Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38. **Abstract**

Saphner T et al. **Annual hazard rates of recurrence for breast cancer after primary therapy.** *J Clin Oncol* 1996;14(10):2738-46. **Abstract**

Thürlimann B et al. **Letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. BIG 1-98: A prospective randomized double-blind Phase III study.** *Breast* 2005a;14(Suppl 1):3;S4.

Thürlimann BJ et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** Presentation. ASCO 2005b;**Abstract 511**.

Tripathy D et al. **Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression.** *J Clin Oncol* 2004;22(6):1063-70. **Abstract**

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26. **Abstract**

INTERVIEW

Eleftherios P Mamounas, MD, MPH

Dr Mamounas is an Associate Professor of Surgery at Northeastern Ohio Universities College of Medicine and is Medical Director of the Aultman Cancer Center in Canton, Ohio.

Tracks 1-12

Track 1	Introduction by Dr Love
Track 2	Background and rationale for development of the Onco*type* DX™ assay
Track 3	Onco*type* DX assay to predict prognosis for patients with early breast cancer
Track 4	Utilization of the Onco*type* DX assay in clinical practice
Track 5	Perspective on the economics of cancer treatment
Track 6	Recurrence score as a predictor of response to therapy
Track 7	Integration of Onco*type* DX assay into clinical practice guidelines
Track 8	Results of NSABP-B-32 sentinel node trial
Track 9	Sentinel lymph node biopsy: Clinical issues in utilization
Track 10	Clinical use of adjuvant aromatase inhibitors in postmenopausal women
Track 11	Planned NSABP trial evaluating optimal duration of aromatase inhibitors
Track 12	Aromatase inhibitors for chemoprevention and treatment of DCIS

Select Excerpts from the Interview

Track 2

DR LOVE: Can you discuss the first major presentation of the Onco*type* DX assay NSABP data by Dr Soon Paik at the 2003 San Antonio Breast Cancer Symposium?

DR MAMOUNAS: The initial study looked at the value of the recurrence score as it was developed based on the data sets from Rush-Presbyterian in Chicago (Cobleigh 2003), St Joseph Medical Center in California (Esteban 2003) and the tamoxifen-treated patients in NSABP-B-20 (Paik 2003).

By putting the data in a multivariate analysis, we found genes that were the most predictive of recurrence; 16 cancer-related genes and five reference genes ended up being the most predictive. So a 21-gene index was developed.

The next step was to validate the index prospectively in another data set. For that data set, we chose to evaluate the 668 tamoxifen-treated patients from NSABP-B-14. The goal was to see whether the recurrence score would separate patients at lower risk from those at higher risk for recurrence (Paik 2004).

DR LOVE: What specifically was seen when you looked at the tamoxifen arm of the NSABP-B-14 study in terms of the recurrence score?

DR MAMOUNAS: The recurrence score can range from zero to 100. We found that patients with a recurrence score of less than 18 had a 10-year distant recurrence rate of about 6.8 percent, with very narrow confidence intervals. Patients with a high recurrence score (31 or greater) had about a 30.5 percent 10-year distant recurrence rate. Patients with a recurrence score that fell in between 18 and 31 had an intermediate risk of 10-year recurrence, which was about 15 percent (Paik 2004a; [3.1]).

3.1

Estimates of Recurrence Rate Based on Multigene Assay in Patients Who Received Tamoxifen on NSABP-B-14 (N = 668)

Risk group	Percent of patients	10-year distant recurrence rate	95% confidence interval
Low (RS < 18)	51	6.8%	4.0-9.6
Intermediate (RS = 18-30)	22	14.3%	8.3-20.3
High (RS ≥ 31)	27	30.5%	23.6-37.4

RS = recurrence score
$p < 0.001$ for comparison between high- and low-risk groups

SOURCE: Paik S et al. *N Engl J Med* 2004;351(27):2817-26. **Abstract**

DR MAMOUNAS: The next step was to see whether the recurrence score went above and beyond prognosis; maybe it would provide a prediction of response to therapy. There was good reason to look at that, because the recurrence score index contains genes that have traditionally been associated with response to therapy.

For example, low ER positivity versus high ER positivity: We know from neoadjuvant chemotherapy studies that ER negativity has been associated with higher rates of pathologic complete response. Studies have shown that high proliferation and poor nuclear grade are factors associated with chemotherapy response. Therefore, we set out to assess the benefit from adjuvant tamoxifen and adjuvant chemotherapy according to the recurrence score.

We did that with the two studies we used to develop and validate the recurrence score. First, we looked at the NSABP-B-14 study. We ended up having approximately 645 patients for whom we had tissue blocks and who were randomly assigned to tamoxifen or placebo. The idea was to see whether the benefit from tamoxifen would be seen in patients with low, intermediate and

high recurrence scores or whether there would be a differential benefit from chemotherapy in these three groups.

Patients with a low recurrence score and those with an intermediate recurrence score benefit significantly from adjuvant tamoxifen. Patients with a high recurrence score seem to have no benefit from adjuvant tamoxifen (Paik 2004b). Now you can take these data with a grain of salt, because there is some uncertainty as the numbers are relatively small, and the threshold for using hormonal therapy is much lower than the threshold for using chemotherapy. I haven't changed my practice to avoid using hormonal therapy in patients with a high recurrence score.

DR LOVE: We should also clarify that this data set was looking at both premenopausal and postmenopausal patients.

DR MAMOUNAS: Exactly. And, of course, it was looking at tamoxifen. One can start questioning, based on this data, why patients have a high recurrence score. Well, they usually have low PR, high HER2, high nuclear grade. Therefore, these may be the patients who benefit from the aromatase inhibitors if they are postmenopausal. I'm not willing to give up hormonal therapy for these patients, but I would certainly think, at least for postmenopausal patients, it would be a good group to be more biased towards the aromatase inhibitors over tamoxifen.

Track 5

DR LOVE: In December 2004, Dr Paik presented the second data set in this project. Can you review that?

DR MAMOUNAS: That was the more important finding. We utilized a study the NSABP conducted following NSABP-B-14 — it was NSABP-B-20, which compared tamoxifen alone to tamoxifen plus one of two chemotherapy regimens, either methotrexate and 5-FU (MF) or CMF, in patients with node-negative, ER-positive disease. For all practical purposes, both chemotherapy regimens performed equally well and better than tamoxifen alone. So the overall trial had shown about a 30 percent reduction in risk of recurrence (Fisher 1997).

We looked at the benefit of adjuvant chemotherapy according to the recurrence score. It turns out that patients with a low recurrence score received no benefit from chemotherapy. In fact, at 10 years, the distant disease-free survival rate was 96 percent for patients on tamoxifen alone and 95 percent for patients on tamoxifen plus chemotherapy.

Patients with an intermediate recurrence score also did not seem to have much benefit. The 10-year distant recurrence-free survival was approximately 90 percent for both patients treated with tamoxifen alone and those treated with tamoxifen plus chemotherapy (Paik 2004b; [3.2]). However, in that group of patients, the confidence intervals around the estimates were somewhat wide,

so we could not exclude some benefit. In fact, the odds ratio was about 0.6, so it could be up to a 40 percent reduction.

What was very interesting was that the benefit was seen in the patients with a high recurrence score. In those patients, the absolute improvement in distant disease-free survival with chemotherapy was 28 percent, or a 75 percent relative reduction in the odds of recurrence. The group that received tamoxifen alone, at 10 years, had a 60 percent distant disease-free survival, and it was 88 percent when they received tamoxifen plus chemotherapy (Paik 2004b; [3.2]).

DR LOVE: Those numbers were shocking and, to many people, unexpected.

DR MAMOUNAS: We've never seen such differences in any subset of patients with breast cancer. I like to quote what George Sledge said when he saw these data. He said, "This makes CMF look like a targeted regimen." In fact, that's true. In other words, we found a signature that predicts a huge benefit from a regimen that otherwise was almost ready to become obsolete.

3.2

Ten-Year Distant Recurrence-Free Survival According to Recurrence Score in NSABP-B-20 (N = 651)

Risk group	Tamoxifen (n = 227)	Tamoxifen plus chemotherapy (n = 424)	*p*-value
Low (RS < 18)	96%	95%	0.76
Intermediate (RS = 18-30)	90%	89%	0.71
High (RS ≥ 31)	60%	88%	0.001*

Chemotherapy = MF or CMF; RS = recurrence score
* In patients with a high risk recurrence score

SOURCE: Paik S et al. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 24**.

Track 8

DR LOVE: Would you summarize the NSABP-B-32 sentinel node trial?

DR MAMOUNAS: NSABP-B-32 was a large randomized trial comparing sentinel node biopsy followed by standard axillary dissection to sentinel node biopsy alone, provided the sentinel node was negative intraoperatively or postoperatively. This was the largest randomized trial of sentinel node biopsy, with over 5,600 patients (Julian 2004; [3.3]).

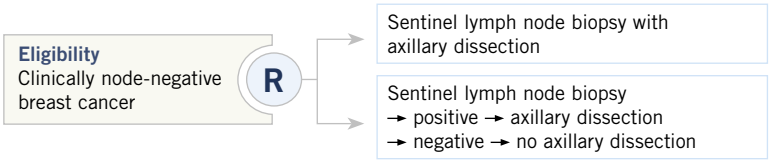
If the sentinel node were positive, then for both groups, an axillary dissection would take place. This was a study for patients with sentinel node-negative disease to evaluate complete axillary dissection. We presented a technical report comparing the identification rates for the sentinel node and false-negative rates. What we found was that the identification rate was about 97 percent, and it became better as surgeons performed more biopsies (Julian 2004; [3.3]).

The false-negative rate was about 9.7 percent (Julian 2004; [3.3]). Interestingly enough, false-negative rates did not seem to improve that much, or not significantly, with time and the more procedures that the surgeons performed. The false-negative rates appear to be inherent to the sentinel node biopsy procedure.

3.3

Phase III Randomized Study of Sentinel Node Dissection with or without Conventional Axillary Dissection in Women with Clinically Node-Negative Breast Cancer

Protocol ID: NSABP-B-32
Accrual: 5,611 (Closed)



If no sentinel node is identified, patients undergo axillary dissection. Patients with cytologically negative but histologically positive sentinel nodes undergo axillary dissection.

Preliminary Technical Results of NSABP-B-32

Sentinel node identification rate (Both arms, n = 5,210)	97%
Percent of identified sentinel nodes that were positive (Both arms, n = 5,058)	26%
SNB overall accuracy (Arm 1 only, n = 2,461)	97.2% (95% CI, 96.5-97.8)
SNB negative predictive value (Arm 1 only, n = 1,811)	96.1% (95% CI, 95.2-97.0)
SNB sensitivity (Arm 1 only, n = 720)	90.3% (95% CI, 88.1-92.4)
SNB false-negative rate (Arm 1 only, n = 720)	9.7% (95% CI, 7.6-11.9)

SNB = sentinel node biopsy

SOURCES: NCI Physician Data Query, December 2004; Julian TB et al. Presentation. San Antonio Breast Cancer Symposium, 2004;**Abstract 14**.

Track 10

DR LOVE: Can you summarize where we are right now with the adjuvant aromatase inhibitors in postmenopausal women — up front and after two, three years or after five years of adjuvant tamoxifen?

DR MAMOUNAS: There are a total of six randomized trials that have reported benefits with aromatase inhibitors either above and beyond tamoxifen or as

extended adjuvant therapy. The interesting pattern we are now seeing is that if we compare different aromatase inhibitors in the same setting, the results are pretty much consistent. We now have data looking at letrozole as up-front adjuvant therapy with a relative reduction in recurrence of about 19 percent (Thürlimann 2005; [3.4]), which was very similar to what was seen with the ATAC trial and anastrozole (Howell 2005; [3.4]).

There are three studies in which the aromatase inhibitors are introduced after two to three years of adjuvant tamoxifen, showing recurrence reductions in the range of about 30 to 40 percent. The ITA trial was a smaller study with 448 patients and about a 60 percent reduction with anastrozole (Boccardo 2005). The Intergroup Exemestane Study (IES) (Coombes 2004), as well as the ARNO/ABCSG trials (Jakesz 2005) have shown reductions in the range of 30 to 40 percent with anastrozole or exemestane.

Of course, we have a third setting, that of extended adjuvant therapy, in which letrozole also produced about a 40 percent reduction compared to placebo after five years of adjuvant tamoxifen (Goss 2005). Based on these results, clearly, aromatase inhibitors have entered the adjuvant therapy setting.

The bigger question nowadays remains: What is the best setting in which to introduce the aromatase inhibitors — up front or after two to three years or after five years of tamoxifen? Most oncologists and surgeons will switch a patient who is on two to three years of tamoxifen — and not necessarily wait the five years — or prescribe an aromatase inhibitor up front.

3.4 **BIG 1-98 (N = 8,010) and ATAC (N = 9,366) Efficacy Data**

Endpoint	BIG 1-98[1] hazard ratio (25.8 months)	ATAC[2] hazard ratio (33.0 months)	ATAC[3] hazard ratio (68.0 months)
Disease-free survival	0.81	0.83	0.87
Time to recurrence	0.72	0.79	0.79
Time to distant recurrence	0.73	NR	0.86
Time to breast cancer death	NR	NR	0.88
Overall survival	0.86*	NR	0.97*

* Not significant; NR = not reported

SOURCES: [1] Thürlimann B for the BIG 1-98 Collaborative Group. Presentation. St Gallen Breast Cancer Conference 2005. *Breast* 2005a;14(Suppl 1):3;S4.

[2] The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. *Lancet* 2002;359:2131-9. **Abstract**

[3] Howell A et al; ATAC Trialists' Group. *Lancet* 2005;365(9453):60-2. **Abstract**

Track 11

DR LOVE: What is the future direction of the NSABP in terms of the next generation of adjuvant endocrine therapy trials?

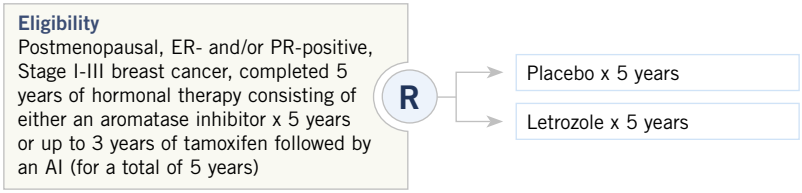
DR MAMOUNAS: We believe that this is an important time to study the question of duration of aromatase inhibitor therapy. So the NSABP has designed a study to take patients who complete five years of an aromatase inhibitor — either anastrozole, letrozole or exemestane — or patients who complete five years of hormonal therapy that consists of at least two to three years of an aromatase inhibitor and randomly assign them to an aromatase inhibitor — in this case, letrozole — versus placebo (3.5).

Essentially, we are repeating what was done in the NSABP-B-14 trial with tamoxifen, but now with aromatase inhibitors. I believe that this question should be studied prospectively, and the existing databases or continuation of current trials will not provide a definitive answer. We are planning on continuing the aromatase inhibitor therapy for five years. ■

3.5

Phase III Trial Evaluating Duration of Adjuvant Aromatase Inhibitor Therapy

Protocol ID: NSABP (under development*)
Target accrual: 3,840 patients over four years



* Expected to open early 2006

SOURCE: NSABP Group Meeting, September 2005, Protocol Summaries.

SELECT PUBLICATIONS

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Cobleigh MA et al. **Tumor gene expression predicts distant disease-free survival (DDFS) in breast cancer patients with 10 or more positive nodes: High throughput RT-PCR assay of paraffin-embedded tumor tissues.** *Proc ASCO* 2003;**Abstract 3415**.

Coombes RC et al; Intergroup Exemestane Study. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92. **Abstract**

Dowsett M et al. **Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status: An hypothesis-generating study.** *J Clin Oncol* 2005;23(30):7512-7. **Abstract**

Esteban J et al. **Tumor gene expression and prognosis in breast cancer: Multi-gene RT-PCR assay of paraffin-embedded tissue.** *Proc ASCO* 2003;**Abstract 3416**.

Esteva FJ, Hortobagyi GN. **Comparative assessment of lipid effects of endocrine therapy for breast cancer: Implications for cardiovascular disease prevention in postmenopausal women.** *Breast* 2005;[Epub ahead of print]. **Abstract**

Fisher B et al. **Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer.** *J Natl Cancer Inst* 1997;89(22):1673-82. **Abstract**

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**

Goss PE et al. **Updated analysis of NCIC CTG MA.17 (letrozole vs placebo to letrozole vs placebo) post unblinding.** San Antonio Breast Cancer Symposium 2005;**Abstract 16**.

Goss PE et al. **NCIC CTG MA17: disease free survival according to estrogen receptor and progesterone receptor status of the primary tumor.** San Antonio Breast Cancer Symposium 2005;**Abstract 2042**.

Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. **Abstract**

Ingle JN et al. **Analysis of duration of letrozole extended adjuvant therapy as measured by hazard ratios of disease recurrence over time for patients on NCIC CTG MA17.** San Antonio Breast Cancer Symposium 2005;**Abstract 17**.

Jakesz R et al; ABCSG and the GABG. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005;366(9484):455-62. **Abstract**

Jakesz R et al. **The benefits of sequencing adjuvant tamoxifen and anastrozole in postmenopausal women with hormone-responsive early breast cancer: 5 year-analysis of ABCSG Trial 8.** San Antonio Breast Cancer Symposium 2005;**Abstract 13**.

Jonat W et al. **Switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-responsive early breast cancer: A meta-analysis of the ARNO 95 Trial, ABCSG Trial 8, and the ITA Trial.** San Antonio Breast Cancer Symposium 2005;**Abstract 18**.

Julian TB et al. **Continued technical results of NSABP B-32: Does a positive sentinel node biopsy require an axillary dissection?** San Antonio Breast Cancer Symposium 2005;**Abstract 20**.

Mamounas EP et al. **Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: Results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27.** *J Clin Oncol* 2005;23(12):2694-702. **Abstract**

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004a;351(27):2817-26. **Abstract**

Paik S et al. **Expression of the 21 genes in the Recurrence Score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20.** Presentation. San Antonio Breast Cancer Symposium 2004b;**Abstract 24**.

Paik S et al. **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14.** San Antonio Breast Cancer Symposium 2003;**Abstract 16**.

The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *Lancet* 2002;359:2131-9. **Abstract**

Thürlimann BJ et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor positive breast cancer.** *Proc ASCO* 2005;**Abstract 511**.

Viale G et al. **Central review of ER, PgR and HER-2 in BIG 1-98 evaluating letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** San Antonio Breast Cancer Symposium 2005;**Abstract 44**.

BREAST CANCER JOURNAL CLUB NOTES

On CD 3 of the enclosed audio program, community oncologists David Mark Dresdner, MD; Leonard J Seigel, MD and Richard M Levine, MD present patients from their practices to clinical investigators Harold J Burstein, MD, PhD and Charles L Vogel, MD for discussion. The following Journal Club notes section provides expanded abstracts of the presentations and publications that are discussed.

39 Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.

Romond EH et al. *N Engl J Med* 2005;353(16):1673-84.

42 Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.

Piccart-Gebhart MJ et al; Herceptin Adjuvant (HERA) Trial Study Team. *N Engl J Med* 2005;353(16):1659-72.

45 E2100: A randomized Phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.

Miller KD et al. Presentation. ASCO 2005.

48 Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women.

Bajetta E et al. *J Clin Oncol* 2005;23(10):2155-61.

51 Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma. A prospectively planned combined survival analysis of two multicenter trials.

Howell A et al. *Cancer* 2005;104:236-9.

53 Patterns of care in medical oncology: A case survey comparing practices of breast cancer investigators and general oncologists: Section 1 — Adjuvant Endocrine Therapy.

Love N. *Patterns of Care in Medical Oncology* 2005;2(3).

Trastuzumab Plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN and Wolmark N.

Source

New England Journal of Medicine 2005;353(16):1673-84. **Abstract**

Purpose

Combine the results of two trials comparing adjuvant doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab

Patients and methods

- National Surgical Adjuvant Breast and Bowel Project trial B-31
  - AC → paclitaxel (n = 872)
  - AC → paclitaxel + trastuzumab (n = 864)
- North Central Cancer Treatment Group trial N9831
  - AC → paclitaxel (n = 807)
  - AC → paclitaxel + trastuzumab (n = 808)
  - AC/paclitaxel → trastuzumab (excluded from analysis)
- Eligibility
  - NSABP-B-31: HER2-positive (IHC 3+ or FISH-positive), node-positive disease in patients with LVEF ≥ low normal limit
  - N9831: HER2-positive (IHC 3+ or FISH-positive), node-positive or high-risk node-negative disease (tumor >2 cm if ER/PR-positive or >1 cm if ER/PR-negative) in patients with LVEF ≥ low normal limit
- Patients with protocol-defined history of cardiac disease excluded
- Endpoints
  - Primary: Disease-free survival
  - Secondary: Overall survival, time to distant recurrence, death from breast cancer, contralateral breast cancer and others

Results

4.1 NSABP-B-31/NCCTG-N9831 Combined Analysis

"The addition of trastuzumab to paclitaxel after a regimen of doxorubicin and cyclophosphamide reduced the rates of recurrence by half among women with HER2-positive breast cancer. The absolute decreases in distant recurrence were 8.8 percentage points after three years and 15.9 percentage points after four years, although the latter value had a wide confidence interval (11.1 to 20.8 percentage points). The reduction was similar among women with hormone-receptor-negative tumors and women with hormone-receptor-positive tumors. No subgroups that did not appear to benefit from trastuzumab therapy were identified...

The addition of trastuzumab reduced the mortality rate by one third (P = 0.015). Among eligible patients who continued treatment after doxorubicin and cyclophosphamide and who were HER2-positive on central testing, the relative reduction in the mortality rate associated with trastuzumab was 39 percent (P = 0.01)."

4.2 Adjuvant Chemotherapy with or without Trastuzumab: Combined Analysis of NSABP-B-31/NCCTG-N9831 Efficacy Data

Parameters	AC → paclitaxel (n = 1,679)	AC → paclitaxel with trastuzumab (n = 1,672)	Hazard ratio* [95% CI]	*p*-value†
Disease-free survival			0.48 [0.39-0.59]	$p < 0.0001$
Three-year disease-free survival	75.4%	87.1%		
Four-year disease-free survival	67.1%	85.3%		
Time to first distant recurrence			0.47 [0.37-0.61]	$p < 0.0001$
Three years from randomization	81.5%	90.4%		
Four years from randomization	73.7%	89.7%		
Overall survival			0.67 [0.48-0.93]	$p = 0.015$
Three years from randomization	91.7%	94.3%		
Four years from randomization	86.6%	91.4%		

* The hazard ratios are for the comparison of the trastuzumab group with the control group.
† All *p*-values were two sided.

4.3 Three-Year Cumulative Incidence of Protocol-Defined Cardiac Events

Trial	Arm of study	Cardiac event* rate
NSABP-B-31	AC → TH	4.1%
	AC → T	0.8%
NCCTG-N9831	AC → TH	2.9%
	AC → T	0%

* Cardiac event = NYHA Class III or IV cardiac dysfunction or death from cardiac causes.

4.4

Editorial: Perspective on the Development of Trastuzumab for HER2-Positive Disease

"The history of HER2 and trastuzumab treatment is a triumphal narrative of translational research. An oncogene, originally discovered in a rat model of chemically induced carcinogenesis, was found to have a sequence that resembled that of a normal cellular gene. The *HER2/neu* gene, when overexpressed, transforms normal cells into cancer cells. Next, overexpression of the gene was found in human breast cancers, where it was shown to contribute to a poor prognosis. A novel antibody therapy that targets the overabundant HER2 protein was developed, and this antibody now redefines the natural history of the disease and establishes a new standard of treatment for breast cancer. It is a dramatic story that epitomizes the often cited cliché of 'bedside to bench to bedside' research."

SOURCE: Burstein HJ. *N Engl J Med* 2005;353(16):1652-4. No abstract available

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Mamounas EP. **Can we approach zero relapse in breast cancer?** *Oncologist* 2005;10(Suppl 2):9-17. **Abstract**

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Tan-Chiu E et al. **Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31.** *J Clin Oncol* 2005;23(31):7811-9. **Abstract**

Trastuzumab After Adjuvant Chemotherapy in HER2-Positive Breast Cancer

Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Lang I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Ruschoff J, Suto T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS and Gelber RD; Herceptin Adjuvant (HERA) Trial Study Team.

Source

New England Journal of Medicine 2005;353(16):1659-72. **Abstract**

Purpose

- Evaluate the efficacy and safety of one year of trastuzumab compared to placebo following a variety of (neo)adjuvant chemotherapy regimens administered for four cycles
- Results of patients receiving two years of trastuzumab not reported

Patients and methods

- International, multicenter randomized trial
- Compared one or two years of trastuzumab given every three weeks to observation
- 1,694 women received one year of trastuzumab; 1,693 were assigned to observation
- Eligibility
  - Centrally verified HER2-overexpressed or amplified node-negative (tumor >1 cm) or node-positive breast cancer in patients who completed four or more cycles of approved (neo)adjuvant chemotherapy regimen and had baseline LVEF ≥ 55% (Echo or MUGA)
- Locoregional therapy and at least four cycles of (neo)adjuvant chemotherapy completed
- Patients with protocol-defined history of cardiac disease excluded
- Endpoints
  - Primary: Disease-free survival
  - Secondary: Cardiac safety, overall survival, site of first event and time to distant recurrence

Results

5.1 Conclusions from HERA

"This study shows that trastuzumab can benefit women with HER2-positive breast cancer when given after completion of adjuvant chemotherapy. As compared with observation after primary therapy (including surgery with or without radiotherapy and neoadjuvant or adjuvant chemotherapy), trastuzumab given after primary therapy reduced the rate of recurrence, particularly distant recurrence, by approximately 50 percent. This degree of benefit in early breast cancer is the largest to be reported since the introduction of tamoxifen in hormone-receptor-positive disease...

The results of the HERA trial should be widely applicable to women with HER2-positive breast cancer for the following reasons: different types of neoadjuvant or adjuvant chemotherapy were allowed before the initiation of trastuzumab; the schedule of administration of one dose every three weeks, which was shown in the metastatic setting to have efficacy, side effects, and pharmacokinetics similar to those of the weekly schedule, was used; and patients with node-negative disease were included."

5.2 Systemic (Neo)Adjuvant Therapy in HERA

Type of (neo)adjuvant chemotherapy	Trastuzumab	Observation
No anthracyclines or taxanes	6.0%	6.1%
Anthracyclines, no taxanes	67.9%	68.3%
Doxorubicin-based regimen	23.4%	24.6%
Epirubicin-based regimen	44.5%	43.7%
Anthrycyclines and taxanes	26.0%	25.6%
Concurrent	6.1%	6.2%
Sequential	19.9%	19.4%
Paclitaxel	15.1%	14.7%
Docetaxel	10.9%	10.9%

5.3 Cardiotoxicity in the HERA Trial

Cardiac event	Trastuzumab 1 yr	Observation	*p*-value
Death	0%	0.06%	1.00
Severe CHF*	0.54%	0%	0.002
Symptomatic CHF, including severe CHF†	1.73%	0.06%	<0.001
Decrease in LVEF‡	7.08%	2.21%	<0.001

* New York Heart Association functional class III or IV, confirmed by a cardiologist, and a decrease in ejection fraction of 10 percentage points or more from baseline to an LVEF of less than 50 percent at any time

† Severe CHF plus CHF considered symptomatic by a cardiologist

‡ Decrease in ejection fraction of 10 percentage points or more from baseline to an LVEF of less than 50 percent at any time

5.4

Editorial Commentary: Initial Reports of NSABP-B-31/NCCTG-N9831 and HERA

"Many recent phase 3 trials of adjuvant systemic therapy for breast cancer highlighted absolute benefits of 2 to 6 percent after four to six years of follow-up. In contrast, an absolute difference of 6 percent is evident in the HERA trial at two years, with a benefit of 8 percent observed in the joint analysis of the trials B-31 and N9831 during the same interval; by four years, these two trials project an absolute benefit of 18 percent, exceeding all previously reported therapeutic benefits in breast cancer...

Survival differences are also emerging from these comparisons. The most dramatic observation in these trials, however, is the comparison of hazard ratios in the joint analysis: the initial peak in recurrences that is generally expected during the first two to three years, and indeed, was observed in the control groups of the two trials, has been abrogated by trastuzumab, and the hazard ratio remains very low even a year after completion of trastuzumab therapy. This observation suggests a dramatic and perhaps permanent perturbation of the natural history of the disease, maybe even a cure."

SOURCE: Hortobagyi GN. *N Engl J Med* 2005;353(16):1734-6. No abstract available

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E2100: A Randomized Phase III Trial of Paclitaxel versus Paclitaxel Plus Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

Miller KD, Wang M, Gralow J, Dickler M, Cobleigh MA, Perez EA, Shenkier TN and Davidson NE.

Source

Oral Presentation. 2005 Proceedings of the American Society of Clinical Oncology Meeting, Orlando, Florida. No abstract available

Purpose

- Evaluate the addition of the anti-VEGF bevacizumab to paclitaxel as first-line therapy in patients with metastatic breast cancer

Patients and methods

- 715 patients without prior chemotherapy for metastatic breast cancer enrolled
  - 350 patients received paclitaxel 90 mg/m^2 qwk
  - 365 patients received paclitaxel + bevacizumab 10 mg/kg q2wk
- HER2-positive only if prior treatment with or contraindication to trastuzumab
- Adjuvant taxane only if disease-free interval >12 months
- No therapeutic anticoagulation, no CNS metastases

Results

6.1 **ECOG-E2100 Safety Results**

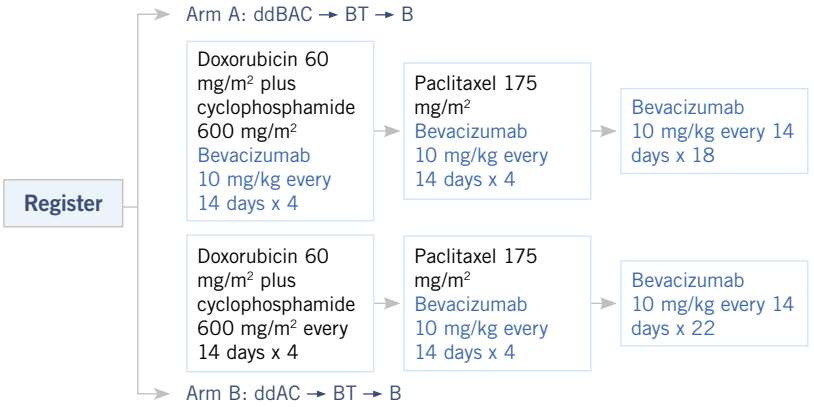
	Paclitaxel + bevacizumab (n = 342)	Paclitaxel (n = 330)
Hypertension*		
Grade III	13%	0%
Grade IV	0.3%	0%
Thromboembolic		
Grade III	1.2%	0.3%
Grade IV	0%	0.9%
Bleeding		
Grade III	0.6%	0%
Grade IV	0.3%	0%
Proteinuria†		
Grade III	0.9%	0%
Grade IV	1.5%	0%
Neuropathy‡		
Grade III	19.9%	13.6%
Grade IV	0.6%	0.6%

* $p < 0.0001$; † $p = 0.0004$; ‡ $p = 0.01$

6.2 ECOG-E2100: First Planned Interim Analysis of Primary and Secondary Efficacy Endpoints

	Paclitaxel + bevacizumab (n = 330)	Paclitaxel (n = 316)	*p*-value
Response rate			
All patients	28.2%	14.2%	<0.0001
Measurable disease	34.3%	16.4%	<0.0001
Progression-free survival	10.97 months Hazard ratio = 0.498	6.11 months (CI: 0.401-0.618)	<0.001
Overall survival	Hazard ratio = 0.674	(CI: 0.495-0.917)	0.01

6.3 E2104 Adjuvant Pilot Trial



Hormone therapy and radiation per standard care

6.4 Conclusions: Preliminary Results of ECOG-E2100

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

The next step in this process will activate soon in a trial known as E-2104. This adjuvant pilot trial will investigate the safety and feasibility of incorporating bevacizumab into standard adjuvant chemotherapy, using the dose-dense anthracycline followed by paclitaxel regimen, as used in the previous CALGB-9741 trial."

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Safety and Efficacy of Two Different Doses of Capecitabine in the Treatment of Advanced Breast Cancer (ABC) in Older Women

Bajetta E, Procopio G, Celio L, Gattinoni L, Della Torre S, Mariani L, Catena L, Ricotta R, Longarini R, Zilembo N, and Buzzoni R.

Source

Journal of Clinical Oncology 2005;23(10):2155-61. **Abstract**

Purpose

- Evaluate efficacy and tolerability of capecitabine in older women with ABC

Patients and methods

- 73 patients (median age: 73 years old)
- 30 patients received oral capecitabine 1,250 mg/m^2 BID on days one to 14 every 21 days
  - Due to two toxic deaths, capecitabine 1,000 mg/m^2 BID was administered to the remaining 43 patients

Results

- Dose reductions were required in 30 percent of patients in the standard-dose group, but capecitabine was given without a dose reduction to 95% of patients in the low-dose group.
- Capecitabine had a favorable safety profile.
  - Grade III/IV toxicities: ≤10 percent fatigue, diarrhea, dyspnea and nausea
- Efficacy
  - 1,250 mg/m^2 BID: response rate was 36.7 percent; 33 percent had disease stabilization at ≥24 weeks.
  - 1,000 mg/m^2: response rate was 34.9 percent; 46 percent had prolonged disease stabilization.
  - Median time to disease progression was four months in both groups.

7.1 **Response According to Dose in the Intention-to-Treat Analysis**

	1,250 mg/m^2 BID (n = 30)	1,000 mg/m^2 BID (n = 43)
Complete response	3%	2%
Partial response	33%	32%
Overall response	36.7%	34.9%
Stable disease	33%	46%
Progressive disease	30%	19%

7.2

Incidence of Grade III/IV Adverse Events According to Dose

	1,250 mg/m² BID	1,000 mg/m² BID
Anemia	0%	0%
Diarrhea	13%	2%
Dyspnea	10%	5%
Fatigue	7%	12%
Nausea	7%	5%
Neutropenia	0%	2%
Pain	0%	2%
PPE	0%	2%
Stomatitis	0%	0%
Thrombocytopenia	0%	0%
Vomiting	3%	0%

PPE = Palmar-plantar erythrodysaesthesia

7.3

Conclusions: Safety and Efficacy of Two Doses of Capecitabine in the Elderly

"To the best of our knowledge, this is the first report specifically dealing with the use of capecitabine in an elderly population with breast cancer...

Overall, efficacy of the two starting doses was similar to that reported in a previous trial, in which first-line monotherapy with capecitabine at the dose of 2,500 mg/m²/d resulted in an objective response rate of 30% in 61 women aged 55 years and older...

This study has shown in a large series that oral capecitabine is well tolerated and effective in older women with advanced breast cancer. Older patients may frequently exhibit diminished capacity to eliminate drugs, resulting in unusual sensitivity to standard dosing regimens. In light of this, the overall results of the study suggest that although the dose groups are small and nonrandomized, the capecitabine dose of 1,000 mg/m² twice daily merits consideration as standard for women aged 70 years and older who are candidates to cytotoxic therapy for metastatic breast cancer and do not have severely impaired renal function."

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Fulvestrant versus Anastrozole for the Treatment of Advanced Breast Carcinoma: A Prospectively Planned Combined Survival Analysis of Two Multicenter Trials

Howell A, Pippen J, Elledge RM, Mauriac L, Vergote I, Jones SE, MD, Come SE, Osborne CK and Robertson JFR.

Source

Cancer 2005;104(2):236-9. **Abstract**

Background

As second-line therapy, fulvestrant was as effective as anastrozole in terms of time to disease progression and objective response rates.

Methods

A prospectively planned, combined, overall survival analysis was performed on data from two Phase III trials that compared fulvestrant (250 mg monthly; n = 428) with anastrozole (1 mg daily; n = 423) in the treatment of postmenopausal women with advanced breast carcinoma who had disease progression after receipt of previous endocrine treatment.

Results

- Prolonged survival was observed with both drugs, with 10 to 20 percent of patients still alive >5 years after randomization.
- Median overall survival was 27.4 months and 27.7 months in fulvestrant and anastrozole-treated patients, respectively (hazard ratio, 0.98; $p = 0.809$).

8.1 **Incidence of Adverse Events**

Adverse event	Fulvestrant (n = 428)	Anastrozole (n = 423)	*p*-value
Gastrointestinal disorder*	48.7%	45.4%	0.40
Hot flashes	21.7%	22.2%	0.80
Joint disorder†	8.3%	12.8%	0.02
Thromboembolic disease	3.5%	4.5%	0.46
Urinary tract infection	8.7%	5.9%	0.13
Vaginitis	2.6%	1.9%	0.51
Weight gain	1.4%	2.1%	0.44

* GI disorder = anorexia, constipation, diarrhea, nausea and emesis
† Joint disorder = arthralgias, arthrosis and arthritis

8.2

Conclusions

"In conclusion, fulvestrant is at least as effective as anastrozole with respect to the efficacy end points TTP and objective response, and similar to anastrozole in terms of survival. Fulvestrant treatment is also well tolerated by patients. This, along with its unique mode of action and lack of cross-resistance with tamoxifen, means that fulvestrant is a valuable second-line treatment option for postmenopausal women with hormone-sensitive metastatic breast carcinoma experiencing disease progression or recurrence on tamoxifen."

SOURCE: Howell A et al. *Cancer* 2005;104(2):236-9. **Abstract**

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Patterns of Care in Medical Oncology: A Case Survey Comparing Practices of Breast Cancer Investigators and General Oncologists — Section A: Adjuvant Endocrine Therapy

Love NH.

Source

Breast Cancer Update Patterns of Care 2005;2(3).

Purpose

This publication reports the results of a Breast Cancer Patterns of Care survey, completed in August and September of 2005 by 45 breast cancer clinical investigators and 100 randomly selected United States–based medical oncologists, designed to compare how these two groups of medical oncologists integrate clinical research results into their practices. The adjuvant endocrine therapy section of this publication is reviewed here.

Results

9.1 Adjuvant Hormonal Therapy for ER/PR-Positive, Node-Positive Disease

- *Woman in average health*
- *1.2-centimeter, Grade II tumor*
- *ER/PR-positive, HER2-negative*
- *3 positive nodes*

Which endocrine therapy, if any, would you most likely recommend for this patient?

	Age 35 (premenopausal)		Age 55 (postmenopausal)	
Anastrozole	2%	6%	78%	80%
Letrozole	—	—	4%	—
Tamoxifen for 5 years and no further hormonal treatment	47%	54%	—	4%
Tamoxifen for 2-3 years and then switch to aromatase inhibitor	—	4%	16%	8%
Tamoxifen for 5 years and then switch to aromatase inhibitor	9%	10%	2%	8%
Aromatase inhibitor + LHRH agonist or ovarian ablation	22%	6%		
Tamoxifen + LHRH agonist or ovarian ablation	20%	20%		

Breast Cancer Specialists General Oncologists

9.2 Use of Adjuvant Aromatase Inhibitors

When you use an aromatase inhibitor in each of the following settings, what percentage of this use is with each aromatase inhibitor? (mean)

	Initial adjuvant		Adjuvant after 2-3 years of tamoxifen		After 5 years of adjuvant tamoxifen	
Anastrozole	86%	86%	17%	37%	5%	19%
Letrozole	11%	11%	12%	18%	90%	73%
Exemestane	3%	3%	71%	45%	5%	8%

Tolerability of adjuvant endocrine therapy

What percentage of your patients on adjuvant aromatase inhibitors have significant arthralgias? (mean)	28%	16%
What percentage of your patients on adjuvant aromatase inhibitors have significant arthralgias to the point that you consider discontinuation or switching agents? (mean)	10%	5%
What percentage of the patients you start on tamoxifen have significant vasomotor symptoms to the point that you consider interventions such as SSRI antidepressants? (mean)	25%	18%

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9.3 Approach to Adjuvant Endocrine Therapy for ER/PR-Positive, Node-Negative Disease

- *Woman in average health*
- *1.2-centimeter, Grade II tumor*
- *ER-/PR-positive, HER2-negative*
- ***Negative nodes***

Which endocrine therapy, if any, would you most likely recommend for this patient?

	Age 35		Age 55	
Anastrozole	—	—	63%	72%
Exemestane	—	—	—	2%
Letrozole	—	—	5%	—
Tamoxifen for 5 years and no further hormonal treatment	79%	64%	5%	4%
Tamoxifen for 2-3 years and then switch to aromatase inhibitor	—	2%	25%	16%
Tamoxifen for 5 years and then switch to aromatase inhibitor	4%	16%	2%	6%
Aromatase inhibitor + LHRH agonist or ovarian ablation	4%	4%		
Tamoxifen + LHRH agonist or ovarian ablation	13%	12%		
Would not recommend endocrine therapy	—	2%	—	—

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9.4 Sequencing Aromatase Inhibitors after Two Years of Tamoxifen

- *65-year-old woman in average health on **tamoxifen x 2 years**, tolerating tamoxifen as described below*
- *1.2-cm, Grade II tumor*
- *ER-positive/PR-positive, HER2-negative*
- *3 positive nodes*

How would you manage this patient's therapy?

	Without severe side effects		Complains of 20-pound weight gain		Complains of moderate hot flashes refractory to nonhormonal therapy	
Continue tamoxifen	5%	24%	2%	4%	5%	8%
Stop tamoxifen and switch to anastrozole	14%	26%	19%	40%	21%	44%
Stop tamoxifen and switch to letrozole	9%	12%	9%	14%	7%	12%
Stop tamoxifen and switch to exemestane	72%	38%	70%	40%	67%	36%
Stop tamoxifen and use no further hormonal therapy	—	—	—	2%	—	—

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9.5 Endocrine Therapy after Five Years of Tamoxifen

- *65-year-old woman in average health who has **completed 5 years of tamoxifen***
- *1.2-cm, Grade II tumor*
- *ER-positive/PR-positive, HER2-negative*
- *3 positive nodes*

How would you manage this patient's therapy at the following three time points?

	Has just completed 5 years of tamoxifen		Completed 5 years of tamoxifen 1 year ago		Completed 5 years of tamoxifen 3 years ago	
Continue tamoxifen	—	2%	—	—	—	—
Start anastrozole	2%	16%	2%	12%	—	6%
Start letrozole	98%	78%	88%	62%	20%	18%
Start exemestane	—	2%	—	2%	—	2%
Use no further hormonal therapy	—	2%	10%	24%	80%	74%

Breast Cancer Specialists General Oncologists

9.6 Use of Aromatase Inhibitors in Premenopausal Women

Which of the following best describes your use of aromatase inhibitors in the following premenopausal women?

	Have not used		Have used alone		Have used with ovarian suppression /ablation		Have used both alone and with ovarian suppression /ablation	
With contraindication to tamoxifen (clotting, etc) in the adjuvant setting	16%	18%	—	12%	84%	70%	—	—
Who cannot tolerate tamoxifen due to side effects in the adjuvant setting	43%	12%	—	18%	57%	70%	—	—
With multiple positive axillary nodes	40%	18%	—	12%	60%	70%	—	—
With locally advanced disease after local therapy	37%	24%	—	6%	63%	64%	—	6%
Other	56%	94%	—	—	44%	—	—	6%

Breast Cancer Specialists General Oncologists

9.7 Conclusions

"Clearly, there is a rapidly building consensus that five years of adjuvant tamoxifen is an inferior therapy for postmenopausal women compared to a treatment plan that includes or consists of an aromatase inhibitor. Our data reveal a dramatic shift in prescribing in this direction, with anastrozole now being the most common up-front endocrine therapy in postmenopausal women, most postmenopausal women on tamoxifen being switched to either exemestane or anastrozole and many patients being started on letrozole after five years of tamoxifen.

Our survey demonstrates that few investigators embrace the "tamoxifen first" approach in their clinical practices, although when the case is switched to a woman with a node-negative tumor, more researchers start with tamoxifen.

Four years after the first ATAC presentation, a number of other AI trials are reporting advantages for AIs over tamoxifen, and it is clear that an important change in practice has occurred. The minority of oncologists who still prescribe five years of tamoxifen in postmenopausal women should re-evaluate their positions in fairness to their patients.

Endocrine therapy for premenopausal women is much more heterogeneous, and although generally those patients are started on tamoxifen, a substantial number of case situations prompt oncologists to consider ovarian suppression and ablation — occasionally alone, but more commonly combined with either tamoxifen or an aromatase inhibitor — although most clinical investigators prefer entering patients on clinical trials evaluating these strategies."

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Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status Report 2004.** *J Clin Oncol* 2005;23(3):619-29. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In a pilot trial of bevacizumab in the adjuvant setting, one group of patients will also receive six months of _____.**
   a. Endocrine therapy
   b. Metronomic chemotherapy
   c. High-dose chemotherapy

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

3. ***Nab* paclitaxel has the following advantage(s) over standard paclitaxel:**
   a. Lower rate of hypersensitivity reactions
   b. Eliminates the need for steroid premedication
   c. Infusion time is shorter
   d. All of the above

4. **The combined analysis of the NSABP-B-31 and NCCTG-N9831 adjuvant trastuzumab trials showed statistically significant survival for women who received AC/paclitaxel plus trastuzumab versus AC/paclitaxel with no trastuzumab.**
   a. True
   b. False

5. **In Dowsett's retrospective subset analysis of the ATAC data, which subset of patients derived the greatest benefit with anastrozole versus tamoxifen?**
   a. ER-positive, PR-positive
   b. ER-positive, PR-negative
   c. ER-negative, PR positive
   d. ER-negative, PR-negative

6. **Studies comparing fulvestrant to anastrozole have demonstrated that with regard to efficacy as first line therapy of metastatic disease, fulvestrant appears to be _____ anastrozole.**
   a. Better than
   b. Equivalent to
   c. Worse than

7. **The Onco*type* DX assay, which involves 21 genes, can be used to predict which patients have a high, low or intermediate risk of 10-year distant recurrence.**
   a. True
   b. False

8. **Patients with node-negative, ER-positive disease and a low recurrence score according to the Onco*type* DX assay have been shown to benefit from adjuvant _____.**
   a. Tamoxifen
   b. Anastrozole
   c. Chemotherapy
   d. All of the above

9. **Patients with node-negative, ER-positive disease and a high recurrence score according to the Onco*type* DX assay have been shown to benefit from adjuvant _____.**
   a. Tamoxifen
   b. Anastrozole
   c. Chemotherapy
   d. All of the above

10. **According to the preliminary technical results from NSABP-B-32, the false-negative rate is approximately _____.**
    a. One percent
    b. Ten percent
    c. Fifty percent
    d. Ninety percent

11. **Which of the following trials compared aromatase inhibitor to tamoxifen as up-front adjuvant therapy?**
    a. ATAC
    b. BIG 1-98/BIG FEMTA
    c. IES
    d. Both a and c
    e. Both a and b

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

EVALUATION FORM

Breast Cancer Update — Issue 9, 2005

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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 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 patients with 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 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 appropriate patients with metastatic disease about selection and sequencing of endocrine therapy and about the risks and benefits of combination versus single-agent chemotherapy. . . . . 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
Harold J Burstein, MD, PhD	5 4 3 2 1	5 4 3 2 1
Charles L Vogel, MD	5 4 3 2 1	5 4 3 2 1
Eleftherios P Mamounas, MD, MPH	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

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.....

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UPDATE

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