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Breast Cancer® UPDATE

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

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INTERVIEWS

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Breast Cancer Update
A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 4 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Perez, Swain, Pritchard, Piccart-Gebhart and O'Regan 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 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs, 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. **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 Perez — Consulting Fees: Genentech BioOncology, GlaxoSmithKline; Contracted Research: Bristol-Myers Squibb Company, Eli Lilly and Company, Genentech BioOncology, GlaxoSmithKline, Roche Laboratories Inc, Sanofi-Aventis. **Dr Swain** — No financial interests or affiliations to disclose. **Dr Pritchard** — Consulting Fees: AstraZeneca Pharmaceuticals LP, Roche Laboratories Inc. **Dr Piccart-Gebhart** — Consulting Fees: Boehringer Ingelheim GmbH, DiaGenic ASA, Ipsen, Novartis AG, Onyx Pharmaceuticals Inc, Sanofi-Aventis, Schering-Plough Corporation. **Dr O'Regan** — Speaker: Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc.

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UPCOMING EDUCATIONAL EVENTS

ASCO 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Website: **www.asco.org**

The 2007 Breast Cancer Symposium
September 7-8, 2007
San Francisco, California
Website: **www.asco.org**

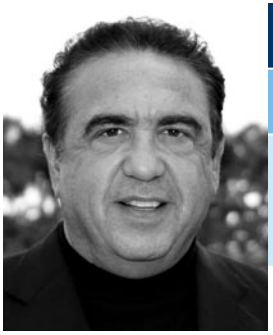
2007 California Breast Cancer Research Symposium
September 7-9, 2007
Los Angeles, California
Website: **www.cbcrp.org**

14th European Cancer Conference (ECCO)
September 23-27, 2007
Barcelona, Spain
Website: **www.fecs.be**

SWOG Semi-Annual Meeting
October 3-7, 2007
Huntington Beach, California
Website: **www.swog.org**

The Clinical Trials Workshop
October 26-28, 2007
Denver, Colorado
Website: **www.asco.org**

30th Annual San Antonio Breast Cancer Symposium
December 13-16, 2007
San Antonio, Texas
Website: **www.sabcs.org**



EDITOR'S NOTE

Neil Love, MD

Family disease

Agree, disagree, or in between?

Breast cancer has a more adverse impact on children and families than any other disease in contemporary Western society.

Every day, oncology infusion rooms across this country are filled with our mothers and daughters spending time away from their families, work and everyday lives to receive adjuvant chemotherapy — and hopefully a cure — for invasive breast cancer. In spite of this considerable personal and psychological sacrifice, perhaps a quarter to a third of these women will eventually succumb to the disease.

On a recent issue of our *Colorectal Cancer Update* audio series, GI investigator Dr John Marshall tells us what it's like to be the husband of a woman receiving adjuvant chemotherapy for breast cancer. What our listeners cannot see is the gaunt but determined look that spread across John's face when he verbalized his realization that after years of prescribing chemotherapy, he knew nothing about it.

DR MARSHALL: My wife was recently diagnosed with Stage III breast cancer, and so we've experienced the fear, the treatment decision-making and the side effects.

She's lost her hair — she looks very cute, but she's lost her hair. She's had mucositis, and we've learned about fatigue. Picking up the kids at school, and all the other things that have to be done, is now a lot more complicated. So I'm living it from that side, and I have to tell you, it's made me a born-again symptom management guy.

John L Marshall, MD

Two months ago, I would have said, "A little bit of mouth sores? It doesn't prevent you from

eating? You're good." I would have let it be, but now I see what it means.

This experience is making me a better doctor and a better dad, and I have also been amazed at the number of people who have come to our aid. Our freezer is full. I have rides for the kids anywhere. The people from work, the people from church and the people from school have all come out to help.

You know the old saying, "It takes a village"? Well, it takes a village to get through something like this, and as oncologists, we're only seeing the two people who show up in the exam room — sometimes the one person — and what we don't realize is the pyramid of infrastructure that it took to get patients through that cycle, get them into the next cycle and get them delivered on time with counts and all of that.

We also don't see the ripple effect of telling people bad news. I'm pretty good at telling people bad news. We all are as oncologists, but if we felt the ripple of every piece of bad news we gave and took it home, we'd go crazy. Particularly right after my wife's diagnosis, every time one of my patients had a bad CT or every time a biopsy was positive, I was feeling the ripple, and it was really striking.

So I'm telling Mrs Jones that she has something going on, and I see in her eyes what I felt in my own heart just a week or two earlier. Before this, I knew what I was doing as an oncologist, but I didn't feel the magnitude of what the dinner table discussion was going to be like that night.

Having lived it now, it's sharpened that feeling. I know I can't maintain that intimacy 20 times a day, but hopefully it will make me even better at being sensitive and making sure that my patients get all the information they need for that dinner table conversation.

DR LOVE: So you're more aware of your importance as a physician?

DR MARSHALL: Yes. Absolutely. Having hung on the words of your colleagues as they talk about side effects, treatment and the like, you realize just how important those words are.

Listening to John's story, I couldn't help but think about the many other families with children who are also affected by this devastating affront to motherhood. This issue of *Breast Cancer Update* carries a strong message to those families and others that the finest minds of this generation of oncology investigators are on the case and are doing their best to move the field forward.

Throughout my career, I have spent considerable time interviewing clinical investigators across many different tumor types, and I have been struck by the disproportionately high fraction of women oncologists that breast cancer has attracted. The five faculty members interviewed for this program and the accompanying gallery of soldiers (page 6-7) are just some of the many who toil day in and day out against the often merciless course of this disease.

It is not difficult to make the argument that a female physician might have an important advantage in understanding and empathizing with female patients. After all, breast cancer affects women almost exclusively and originates in an organ uniquely tied to self-image and femininity.

However, I suspect that women choose breast oncology as a career not because they can provide better medical care but because they understand the destructive impact this illness has on families and are determined to be part of the solution.

In that regard, it is the responsibility of every oncology healthcare professional — both men and women — to provide people facing this disease with the opportunity to join the fight and participate in the clinical research attempting to find the answers needed to keep our families healthy and whole. ■

— Neil Love, MD
NLove@ResearchToPractice.com
May 10, 2007

SELECT PUBLICATIONS

On becoming a breast cancer survivor. Getting through treatment is only the beginning. *Harv Womens Health Watch* 2006;14(2):1-3. No abstract available

Ashing-Giwa KT et al. **Understanding the breast cancer experience of women: A qualitative study of African American, Asian American, Latina and Caucasian cancer survivors.** *Psycho-Oncology* 2004;13(6):408-28. **Abstract**

Baker F et al. **Adult cancer survivors: How are they faring?** *Cancer* 2005;104(11 Suppl):2565-76. **Abstract**

Bouknight RR et al. **Correlates of return to work for breast cancer survivors.** *J Clin Oncol* 2006;24(3):345-53. **Abstract**

Brown RT et al. **Adjustment of children and their mothers with breast cancer.** *J Pediatr Psychol* 2007;32(3):297-308. **Abstract**

Cowden S. **Problems getting back in the swing after breast cancer: Gaps in rehabilitative care.** *Cancer* 2006;107(7):1423-4. **Abstract**

Coyne E, Borbasi S. **Holding it all together: Breast cancer and its impact on life for younger women.** *Contemp Nurse* 2006-2007;23(2):157-69. **Abstract**

Dentschuk A. **The impact of diagnosis and treatment of early breast cancer in young women — My own perspective.** *Breast* 2006;15(Suppl 2):15-6. No abstract available

Drolet M et al. **Not working 3 years after breast cancer: Predictors in a population-based study.** *J Clin Oncol* 2005;23(33):8305-12. **Abstract**

Gilbert M. **A survivor's journey: One woman's experience with cancer-related fatigue.** *Oncologist* 2003;8(Suppl 1):3-4. **Abstract**

Gordon L et al. **Exploring the economic impact of breast cancers during the 18 months following diagnosis.** *Psycho-Oncology* 2007;[Epub ahead of print]. **Abstract**

Grunfeld E et al. **Family caregiver burden: Results of a longitudinal study of breast cancer patients and their principal caregivers.** *CMAJ* 2004;170(12):1795-801. **Abstract**

Gudbergsson SB et al. **A comparative study of living conditions in cancer patients who have returned to work after curative treatment.** *Support Care Cancer* 2006;14(10):1020-9. **Abstract**

Shands ME et al. **Core concerns of couples living with early stage breast cancer.** *Psycho-Oncology* 2006;15(12):1055-64. **Abstract**

Women physician investigators who have participated in Research To Practice breast cancer audio education programs


Kathy Albain, MD


Joanne Blum, MD, PhD


Lisa Carey, MD


Jenny Chang, MD


Melody Cobleigh, MD


Nancy Davidson, MD


Maura Dickler, MD


Sandra Franco, MD


Julie Gralow, MD


Generosa Grana, MD


Frankie Holmes, MD, FACP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Janet Wolter, MD


Denise Yardley, MD

INTERVIEW

Edith A Perez, MD

Dr Perez is Professor of Medicine at Mayo Medical School, Director of the Cancer Clinical Study Unit and Director of the Breast Cancer Program in the Division of Hematology and Oncology at the Mayo Clinic in Jacksonville, Florida.

Tracks 1-18

Select Excerpts from the Interview

Track 1

DR LOVE: Can you discuss what we currently understand about predictive tissue markers of response to aromatase inhibitors?

DR PEREZ: Some important translational data have been released over the past year, and these data have implications for practice. One implication is that there is no point in paying too much attention to progesterone receptor status as it relates to the benefit of aromatase inhibitors. Confusion was raised

when the initial data from ATAC were reported based on local testing for ER and PR. Based on central testing for ER and PR, the trans-ATAC data presented at the 2006 San Antonio meeting demonstrated that patients benefit from anastrozole regardless of whether the PR status is positive or negative (Dowsett 2006). These data are consistent with the data from the other aromatase inhibitor studies (Viale 2005). Those data should help clinicians be confident about using aromatase inhibitors independent of the PR status, as long as the ER status is positive.

Another issue, also related to the testing and use of aromatase inhibitors, is HER2 status. Many people believed that aromatase inhibitors worked only for HER2-positive disease, but now we have data demonstrating that aromatase inhibitors benefit patients with HER2-positive and HER2-negative disease (Dowsett 2006; [1.1]).

1.1

Efficacy of Anastrozole versus Tamoxifen According to HER2 Status: Trans-ATAC Analysis

HER2 status	Patients	Events	HR
HER2-negative	1,526	149	0.66
HER2-positive	190	45	0.92
Combined	1,786	200	0.72

SOURCE: Dowsett M. San Antonio Breast Cancer Symposium 2006;**Abstract 48**.

Track 3

DR LOVE: Can you discuss the study you're conducting that evaluates vinorelbine, capecitabine and trastuzumab?

DR PEREZ: We know both drugs — vinorelbine and capecitabine — show activity in refractory breast cancer as well as up front. Preclinically, both drugs have been shown to work with trastuzumab. Initial data regarding the potential interaction of capecitabine with trastuzumab confused some people (Pegram 2004).

However, elegant data from a group in China showed us nice response rates associated with that combination (Xu 2006). We also know that the combination of capecitabine and vinorelbine can be well tolerated and associated with good responses (Welt 2005). Patients can expect a good quality of life and no alopecia.

Based on this information, we decided to combine all of these data and create a triple-drug regimen comprising capecitabine, vinorelbine and trastuzumab. Patients who received trastuzumab as adjuvant or first-line therapy for metastatic disease are permitted into the study. We did not require prior taxane therapy. We've almost completed accrual to this study, and so far, the tolerability is excellent.

DR LOVE: Do you use the vinorelbine/capecitabine combination for HER2-negative tumors?

DR PEREZ: Sometimes we do because it has good activity and tolerability.

Tracks 6-7

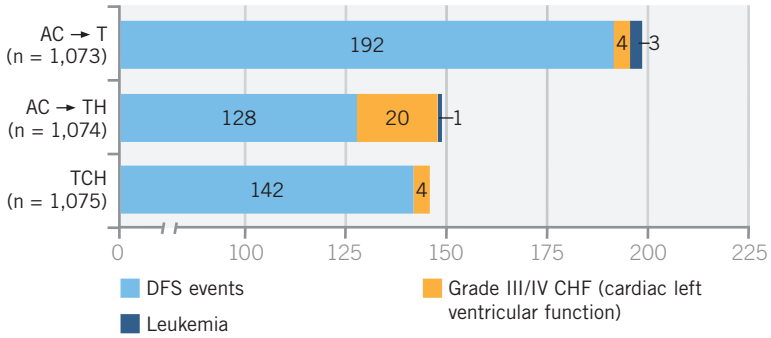
DR LOVE: Can you summarize your thoughts about the BCIRG 006 presentation by Dennis Slamon in San Antonio (1.2)?

DR PEREZ: As a result of these data, the TCH regimen is now an alternative to AC followed by a taxane/trastuzumab (TH). Statistically speaking, no differences exist between AC → TH and the TCH regimen as reported (Slamon 2006).

However, a caveat in the numbers might be of interest. Comparing TCH and AC → TH, the AC → TH group reported 16 additional cases of congestive heart failure, but the TCH group reported 14 additional breast cancer events, including breast cancer relapse and death.

1.2

BCIRG 006: Disease-Free Survival (DFS) Events and Critical Adverse Events at Second Interim Analysis



"Considering the published data just this month from the US Oncology trial that Steve Jones led that showed that docetaxel and cyclophosphamide outperforms significantly Adriamycin and cyclophosphamide for all breast cancers, and now the recent data we have from our update of BCIRG 006, that for HER2-positive malignancies, the difference in disease-free survival events and overall survival events in favor of the AC → TH are now exceeded by critical toxicities with regard to leukemias and congestive heart failure, the question becomes this: What is the role of anthracyclines in the adjuvant treatment of breast cancer?"

— Dennis J Slamon, MD, PhD
San Antonio, December 14, 2006

SOURCE: Slamon D et al. BCIRG 006 Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

DR LOVE: When you see a patient with a HER2-positive, node-positive tumor who is otherwise healthy, what chemotherapy regimen do you generally utilize?

DR PEREZ: We use AC → T (paclitaxel) H as our standard approach — the regimen approved by the FDA. However, we're considering additional steps these days in our practice.

One example is the use of ACE inhibitors to potentially decrease the risk of cardiac toxicity associated with both anthracyclines and, potentially, trastuzumab. As medical oncologists, we haven't been well attuned to the potential value of ACE inhibitors for improving cardiovascular risk in illnesses besides hypertension or those associated with underlying cardiac disease.

These agents might be helpful by reducing the cardiac afterload, which may have clinical implications. We have data indicating that ACE inhibitors may decrease the risk of anthracycline-related cardiac toxicity. We need to address the use of ACE inhibitors in cancer therapy, so we are proposing to conduct a trial. I believe this practice is worthy of investigation, and we will pursue it vigorously during the next few months.

Track 9

DR LOVE: What is your clinical approach for patients with smaller, HER2-positive, node-negative tumors?

DR PEREZ: In the clinical trials, few patients had tumors smaller than one centimeter, so we lack solid data related to the absolute improvement of adding trastuzumab in that setting.

However, two intriguing presentations at the 2006 San Antonio meeting addressed the natural history of small, HER2-positive breast tumors, demonstrating that these patients appeared to have a poor prognosis (Black 2006; Norris 2006; [1.3]).

My interpretation of the data is that HER2 status is the driver of prognosis more than tumor size. So I tend to be more open to discussing the potential of using adjuvant trastuzumab for patients with small breast tumors, although I am clearly pointing out that the eligibility criteria of the studies did not include them.

We're making that recommendation outside of the FDA boundaries because they have only approved adjuvant trastuzumab for patients with node-positive breast cancer. From what I understand, that was based on the data from the joint analysis (NSABP-B-31 and NCCTG-N9831) because only six percent of the patients had node-negative disease.

However, as practicing oncologists, we know data from other studies that enrolled large numbers of patients with node-negative disease demonstrated a benefit in adding trastuzumab (Piccart-Gebhart 2005; Slamon 2006; Smith 2007).

1.3

Ten-Year Breast Cancer-Specific Survival (BCSS) and Relapse-Free Survival (RFS) by HER2 Status: All Cases and the T1pN0 Cohort

	HER2-positive	HER2-negative	*p*-value
BCSS			
All cases (n = 500, 3,336)	58.1%	76.5%	<0.001
All cases, no AST	65.2%	NR	
N0, all cases	75.7%	NR	
N0, no AST	72.8%	NR	
T1pN0, all cases (n = 117, 1,128)	81.3%	90.1%	0.03
T1pN0, no AST	81.0%	NR	
T1cpN0, all cases (n = 96, 823)	79.2%	88.7%	0.033
T1cpN0, no AST	78.1%	89.6%	0.013
T1a-bpN0, all cases (n = 21, 305)	90.2%	93.7%	0.96
RFS			
All cases	49.5%	65.8%	<0.001
T1pN0 cases	71.6%	78.7%	0.20
T1a-bpN0, all cases	75.6%	82.4%	0.66
DRFS			
T1pN0, no AST	77%	86.3%	0.08
T1cpN0, no AST	73.2%	84.8%	0.046

AST = adjuvant systemic therapy; DRFS = distant relapse-free survival; NR = not reported

SOURCE: Norris B et al. San Antonio Breast Cancer Symposium 2006;**Poster 2031**.

So I have zero caveats related to the recommendation of using adjuvant trastuzumab according to nodal status. I prefer to overtreat rather than undertreat because undertreatment may lead to patient death.

DR LOVE: Despite a lack of data, we do have a long history with the concept of relative risk reduction in the adjuvant therapy of breast cancer. It seems as if this can be applied to HER2-positive tumors and trastuzumab.

DR PEREZ: I completely agree. The relative benefits appear to be the same, irrespective of the subgroup analyzed. So the matter at hand will be to understand the natural history of small, HER2-positive breast tumors and whether HER2 testing has been done correctly.

Data from presentations at San Antonio and also from a manuscript published by Steve Chia in the *Journal of Clinical Oncology* (Chia 2004) demonstrate that patients with small tumors — even those smaller than one centimeter — that are Grade III have a 10-year relapse rate that appears to exceed 25 percent.

That is the figure I'm showing to my patients — a relapse rate of about 25 percent at five to 10 years. Based on all the information we have, that kind of relapse risk warrants adjuvant systemic therapy.

Tracks 17-18

DR LOVE: Where do you see *nab* paclitaxel fitting into the treatment of breast cancer?

DR PEREZ: The data with every three-week *nab* paclitaxel versus once every three-week paclitaxel (Gradishar 2005) justify the FDA approval. Data from the randomized Phase II trial, which evaluated *nab* paclitaxel or docetaxel once every three weeks, are tantalizing (Gradishar 2006). I'm happy that there will be a formal, randomized Phase III trial of *nab* paclitaxel weekly versus docetaxel once every three weeks.

DR LOVE: What about the issue of *nab* paclitaxel in combination with trastuzumab for the patient with HER2-positive disease?

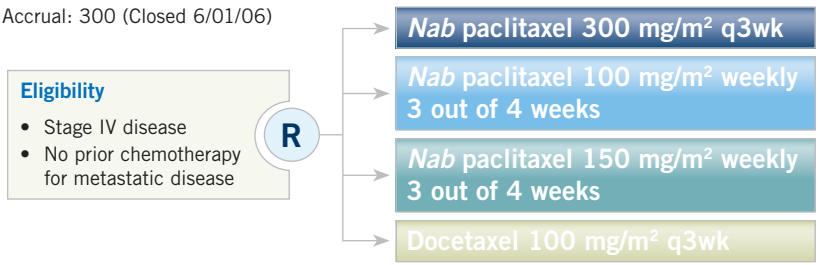
DR PEREZ: The combination clearly shows activity, and an ongoing Phase II study from Memorial is evaluating *nab* paclitaxel/carboplatin and trastuzumab. The benefit of this drug is that it doesn't require premedication. So even if the *nab* paclitaxel were similar in efficacy to paclitaxel, I would still tend to favor it for the potential impact on the quality of life of my patients.

DR LOVE: Can you discuss the study comparing *nab* paclitaxel to docetaxel (Gradishar 2006; [1.4])?

DR PEREZ: This was a 300-patient, randomized Phase II study with four arms. In three of the arms, the patients received *nab* paclitaxel, and the fourth group received docetaxel.

1.4

Randomized Phase II Study of Weekly or Every Three-Week *Nab* Paclitaxel versus Every Three-Week Docetaxel as First-Line Therapy in Patients with Metastatic Breast Cancer



	Nab paclitaxel 300 mg/m² q3wk	*Nab* paclitaxel 100 mg/m² weekly 3 out of 4 weeks	*Nab* paclitaxel 150 mg/m² weekly 3 out of 4 weeks	Docetaxel 100 mg/m² q3wk
Objective response rate	33%	58%*	62%†	36%
Grade III/IV neutropenia	37%	19%	35%	95%
Grade III/IV peripheral neuropathy	14%	7%	12%	5%
Grade III/IV fatigue	4%	0%	3%	15%

* *p*-value = 0.004 versus docetaxel arm; † *p*-value = 0.016 versus docetaxel arm

SOURCE: Gradishar W et al. Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 46**.

The three *nab* paclitaxel arms received 300 mg/m^2 once every three weeks or one of two weekly regimens, either 100 or 150 mg/m^2 three weeks out of four. The docetaxel arm received 100 mg/m^2 of docetaxel once every three weeks.

The response data were fascinating: 33 percent for the once every three-week *nab* paclitaxel and 36 percent for the once every three-week docetaxel (1.4), which is what I would expect from a single-agent taxane in the first-line treatment of metastatic disease. However, the responses for the two weekly *nab* paclitaxel arms were about 58 and 62 percent — beautiful response rates for these weekly regimens. That's why investigators will use 100 mg/m^2 weekly as the appropriate comparator against docetaxel for the Phase III study.

This randomized Phase II study was telling, not only because of the response rate — the progression-free survival rates are still premature, although the numbers are starting to look interesting — but also because the tolerability was good for the weekly *nab* paclitaxel, 100 mg/m^2 three weeks out four. ■

SELECT PUBLICATIONS

Black D et al. **Recurrence risk in T1a-b, node negative, HER2 positive breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 2037**.

Chia SK et al. **Ten-year outcomes in a population-based cohort of node-negative, lymphatic, and vascular invasion-negative early breast cancers without adjuvant systemic therapies.** *J Clin Oncol* 2004;22(9):1630-7. **Abstract**

Dowsett M, on behalf of the TransATAC Investigators. **Relationship between quantitative ER and PgR expression and HER2 status with recurrence in the ATAC trial.** San Antonio Breast Cancer Symposium 2006;**Abstract 48**.

Gradishar W et al. **A randomized phase 2 trial of qw or q3w ABI-007 (ABX) vs q3w solvent-based docetaxel (TXT) as first-line therapy in metastatic breast cancer (MBC).** San Antonio Breast Cancer Symposium 2006;**Abstract 46**.

Gradishar WJ et al. **Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

Norris B et al. **Poor 10 yr breast cancer specific survival (BCSS) and relapse free survival (RFS) for HER2 positive T1pN0 tumors.** San Antonio Breast Cancer Symposium 2006;**Poster 2031**.

Pegram MD et al. **Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer.** *J Natl Cancer Inst* 2004;96(10):739-49. **Abstract**

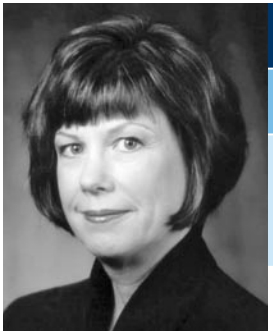
Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. **Abstract**

Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients.** San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

Smith I et al; HERA study team. **2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: A randomised controlled trial.** *Lancet* 2007;369(9555):29-36. **Abstract**

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**.

Xu L et al. **A phase II trial of trastuzumab (H) + capecitabine (X) as first-line treatment in patients (pts) with HER2-positive metastatic breast cancer (MBC).** *Proc ASCO* 2006;**Abstract 10615**.



INTERVIEW

Sandra M Swain, MD

Dr Swain is Medical Director of the Washington Cancer Institute at Washington Hospital Center in Washington, DC.

Tracks 1-16

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: What are your thoughts on the US Oncology trial data comparing adjuvant AC to TC, reported by Steve Jones?

DR SWAIN: I have a lot of confidence in docetaxel. I've used it for a long

time, and my patients have done well. I've used the 100-mg/m^2 dose alone quite often, so I don't have a problem using 75 mg/m^2 with cyclophosphamide.

In addition, the TC regimen brings no cardiac toxicity and probably less risk of leukemia because you don't use an anthracycline or growth factors. I recently read an article in the *Journal of Clinical Oncology* examining the risk of leukemia for patients treated for breast cancer, so that's been on my mind (Le Deley 2007). We probably won't see that with TC, and that's great because we certainly don't want these patients who are at low risk — or any patients, for that matter — developing leukemia.

Track 6

DR LOVE: Can you discuss the design and goals of the NSABP-B-40 neoadjuvant trial?

DR SWAIN: In this study, patients are randomly assigned to receive docetaxel versus docetaxel/capecitabine versus docetaxel/gemcitabine, and all three agents are followed by AC (2.1). In addition, each arm is further randomized to bevacizumab pre- and postoperatively or no bevacizumab.

One of the primary goals of the trial is to evaluate whether a baseline gene or microarray analysis, performed before the patients receive any treatment, will predict which patients will respond. We're moving more into the twenty-first century, trying to tailor treatment and see if we can predict response. In addition, we're evaluating biologic therapy with the bevacizumab randomization.

Track 7

DR LOVE: Can you discuss the paper your group recently published in the *Journal of Clinical Oncology* examining the anti-angiogenic and antitumor effects of bevacizumab in women with inflammatory breast cancer?

DR SWAIN: We conducted a small pilot study in which we administered bevacizumab alone for one cycle, followed by bevacizumab and chemotherapy, to patients with inflammatory breast cancer (Wedam 2006; [2.2]). The goal was to identify molecular markers that would predict response to bevacizumab, so biopsies were performed before and after the bevacizumab monotherapy.

We found a consistent decrease in the activated VEGFR-2 in the tumor cells in patients treated with bevacizumab alone. This is the receptor through which VEGF-A acts to increase angiogenesis. We also found a decrease in vascular permeability and flow by MRI.

Another interesting finding was an increase in apoptosis with bevacizumab alone, similar to that seen by Chang with trastuzumab (Mohsin 2005). We didn't find any correlation to response because it was a small pilot study and almost all the patients responded. That was great for the patients, but we didn't have a large dichotomy to examine.

The next step will be to examine the effects of bevacizumab on the activated receptor and apoptosis in larger studies. Dennis Slamon is conducting a similar kind of study evaluating TAC with or without bevacizumab, and we hope he will examine those issues.

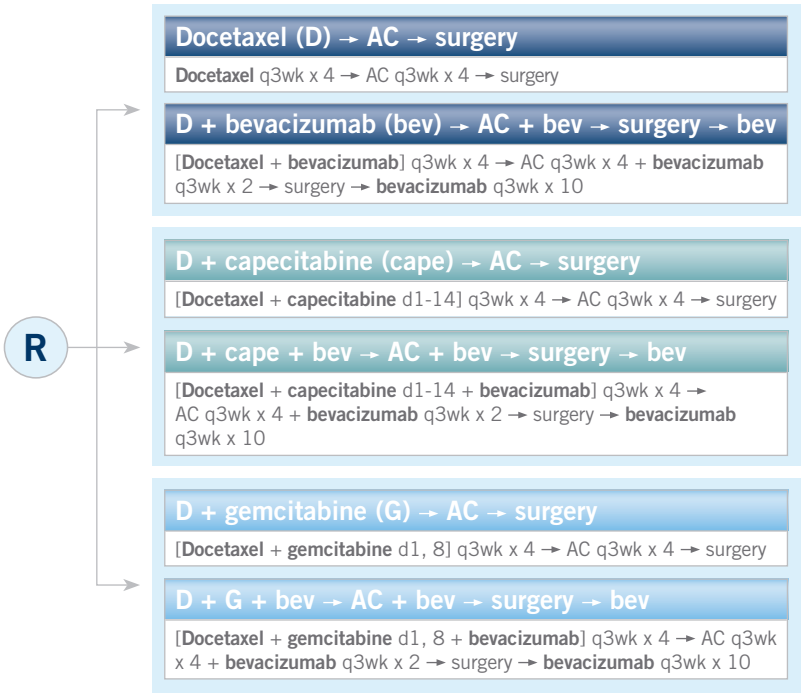
DR LOVE: I was struck by the fact that bevacizumab appears to be working against the tumor cells directly. Did that surprise you?

DR SWAIN: When we designed this study, Ferrara had written reviews and conducted a lot of research geared toward evaluating these receptors and VEGF acting on the endothelial cells (Ferrara 1992, 1997). Although a couple of papers had been published showing that the VEGF receptors were present on tumor cells, it wasn't felt to be a significant mechanism of action.

2.1

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

Protocol ID: NSABP-B-40
Target Accrual: 1,200



Eligibility

- Tumor ≥ 2 cm
- HER2-negative breast cancer

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

SOURCE: NCI Physician Data Query, May 2007.

2.2 **Anti-angiogenic and Antitumor Effects of Bevacizumab**

"We have demonstrated a significant decrease in VEGFR2 activation in tumor cells and increase in tumor apoptosis after one cycle of bevacizumab alone. VEGF released from tumor cells or inflammatory and endothelial cells is known to have multiple paracrine and autocrine effects. These effects have been demonstrated in preclinical settings in prostate cancer, head and neck cancers, acute leukemias, and breast cancer.

Expression of VEGFR2 and p-VEGFR2 have been reported previously in human breast cancer. However, this is the first clinical study to demonstrate that bevacizumab has a direct inhibitory effect on angiogenic parameters in tumor cells, possibly as a result of the disruption of both autocrine and paracrine functions of VEGF. Interestingly, endothelial proliferation was decreased in five of five cases after bevacizumab, which also suggests an inhibitory effect on endothelium....

In this pilot trial, we have demonstrated significant effects of anti-VEGF therapy on VEGFR2 activation, tumor apoptosis, and tumor vascular permeability and flow as measured by DCE-MRI. This study has shed light on the establishment of predictive markers to bevacizumab treatment, although the findings described warrant further investigation in larger cohorts."

[Citations omitted]

SOURCE: Wedam SB et al. *J Clin Oncol* 2006;24(5):769-77. **Abstract**

However, I'm more convinced now that it's really the tumor cells that are important, and I do believe that's the key finding of this study. The stroma is important as well, especially in inflammatory cancer, but that's an aside.

Tracks 10-11

DR LOVE: Where are we with regard to the next generation of adjuvant trials of women with HER2-positive tumors? I understand that the BCIRG and NSABP are considering a study of TCH with or without bevacizumab.

DR SWAIN: We have had many heated discussions about the design of this study, but based on the second interim analysis of the BCIRG 006 trial, which showed TCH was similar in efficacy to AC → TH, people are much more comfortable now with omitting the anthracycline (Slamon 2006). However, some groups in Europe will have an additional arm consisting of AC → TH with or without bevacizumab for those physicians who still feel they need to use an anthracycline.

DR LOVE: In your practice, how do you treat patients with node-positive, HER2-positive disease?

DR SWAIN: Based on the BCIRG 006 data, I feel comfortable using TCH with those patients (Slamon 2006).

DR LOVE: Do you think we'll get to the point that anthracyclines will no longer be used in adjuvant therapy of all breast cancers?

DR SWAIN: I hope that's the case because I believe that anthracycline-associated cardiotoxicity is an important issue, and I believe clinicians will be moving away from anthracyclines in the future.

DR LOVE: What is a patient's risk of developing a serious cardiac problem or leukemia with TCH?

DR SWAIN: The risk of cardiac toxicity is low — almost zero. We don't see cardiac toxicity with trastuzumab monotherapy, and, although some clots and arrhythmias were reported on the TCH arm, the rate of heart failure is just about zero.

As for leukemia, I expect you'll see less on the TCH arm, but the numbers are small at this point.

Track 13

DR LOVE: You recently wrote an editorial in the *JCO* regarding the Onco*type* DX assay and the NSABP-B-20 data (Paik 2006). Can you comment on that (Swain 2006)?

DR SWAIN: In the NSABP-B-20 study, patients with ER-positive, node-negative disease were randomly assigned to tamoxifen with or without chemotherapy.

The trial showed a benefit with the addition of chemotherapy, and when the Onco*type* DX assay was performed, investigators found that patients with a high recurrence score benefited from chemotherapy, whereas those with a low or intermediate recurrence score did not (Paik 2006; [2.3]).

To me, this is an outstanding contribution. I now use Onco*type* DX for all my patients who have ER-positive, HER2-negative, node-negative breast cancer, and I've found it to be helpful.

2.3

Onco*type* DX Recurrence Score (RS) Estimates of Ten-Year Distant Recurrence-Free (DRF) Rate for Patients Treated with Tamoxifen with or without Chemotherapy

	Tamoxifen			Tamoxifen and chemotherapy	
Group	Number of patients	10-year DRF	95% CI	10-year DRF	95% CI
All patients	651	87.8%	83.3% to 92.3%	92.2%	89.4% to 94.9%
Low risk (RS < 18)	353	96.8%	93.7% to 99.9%	95.6%	92.7% to 98.6%
Intermediate risk (RS 18-30)	134	90.9%	82.5% to 99.4%	89.1%	82.4% to 95.9%
High risk (RS ≥ 31)	164	60.5%	46.2% to 74.8%	88.1%	82.0% to 94.2%

SOURCE: Paik S et al. *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

DR LOVE: Do you rely on Onco*type* DX for patients with larger tumors? For example, would you be comfortable omitting chemotherapy for a patient with node-negative disease but a 4-cm tumor if her recurrence score was low?

DR SWAIN: Absolutely. I believe that it's all about the biology and not the size, particularly.

The other important benefit of Onco*type* DX, which was presented at the San Antonio Breast Cancer Symposium, is its reliability in measuring the estrogen receptor (Kim 2006). I believe RT-PCR may be the best way to measure the estrogen receptor. We know immunohistochemistry (IHC) is fraught with problems, and I'm uncomfortable when I receive an estrogen receptor assay result from a small laboratory. ■

SELECT PUBLICATIONS

Albain KS et al. **Global phase III study of gemcitabine plus paclitaxel (GT) vs paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival.** *Proc ASCO* 2004;**Abstract 510**.

Ferrara N, Davis-Smyth T. **The biology of vascular endothelial growth factor.** *Endocr Rev* 1997;18(1):4-25. No abstract available

Ferrara N et al. **Molecular and biological properties of the vascular endothelial growth factor family of proteins.** *Endocr Rev* 1992;13(1):18-32. No abstract available

Goldstein L et al. **E2197: Phase III AT (doxorubicin/docetaxel) vs AC (doxorubicin/cyclophosphamide) in the adjuvant treatment of node positive and high risk node negative breast cancer.** *Proc ASCO* 2005;**Abstract 512**.

Gradishar WJ et al. **Neoadjuvant docetaxel followed by adjuvant doxorubicin and cyclophosphamide in patients with stage III breast cancer.** *Ann Oncol* 2005;16(8):1297-304. **Abstract**

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

Kim C et al. **A comparison of estrogen receptor (ER) measurement by three methods in node negative, estrogen receptor (ER) positive breast cancer: Ligand binding (LB), immunohistochemistry (IHC), and quantitative RT-PC.** San Antonio Breast Cancer Symposium 2006;**Abstract 3116**.

Le Deley MC et al. **Anthracyclines, mitoxantrone, radiotherapy, and granulocyte colony-stimulating factor: Risk factors for leukemia and myelodysplastic syndrome after breast cancer.** *J Clin Oncol* 2007;25(3):292-300. **Abstract**

Mohsin SK et al. **Neoadjuvant trastuzumab induces apoptosis in primary breast cancers.** *J Clin Oncol* 2005;23(11):2460-8. **Abstract**

Paik S et al. **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients.** San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

Swain SM. **A step in the right direction.** *J Clin Oncol* 2006;24(23):3717-8. No abstract available

Wedam SB et al. **Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer.** *J Clin Oncol* 2006;24(5):769-77. **Abstract**

INTERVIEW

Kathleen I Pritchard, MD

Dr Pritchard is Head of Clinical Trials and Epidemiology at Toronto Sunnybrook Regional Cancer Centre, Professor of the Department of Medicine and Faculty of Medicine at the University of Toronto in Toronto, Canada.

Tracks 1-22

Select Excerpts from the Interview

Track 1

DR LOVE: How do you approach endocrine therapy for postmenopausal patients with receptor-positive disease?

DR PRITCHARD: It's clear now that in the adjuvant endocrine setting, every postmenopausal woman should receive an aromatase inhibitor at some point. I tend to start most of my patients on an aromatase inhibitor up front.

It's clear that adding an aromatase inhibitor at the end of five years of tamoxifen, or after two to three years of tamoxifen, is additionally beneficial. In the last few years it's come down the pipeline that every one of the three different aromatase inhibitors seems to be useful in each setting.

We're still awaiting data that might tell us whether it's as good or even better to start with a year or two of tamoxifen — whether there's priming from tamoxifen — and then to switch over to an aromatase inhibitor. Also, what do you do for the patient who has received five years of an aromatase inhibitor? Is that too long, just right or not long enough?

Track 2

DR LOVE: How are you approaching patients who are completing five years of an aromatase inhibitor?

DR PRITCHARD: It's arbitrary that we studied five years of aromatase inhibitors. The data we have from MA17 and other studies have been clear that continuing to administer letrozole brings additional benefit year after year, at least in the post-tamoxifen setting (Ingle 2006).

It seems to be steady up to four years of follow-up, and it may be good administered indefinitely. Right now, we haven't studied more than five years, so I would stop the drug or place patients in a clinical trial at the end of five years of an aromatase inhibitor.

DR LOVE: Do you discuss the option of continuing?

DR PRITCHARD: Yes, and currently in Canada, neither of the trials that will evaluate patients in that setting — NSABP-B-42 or the rerandomization of MA17 — are available.

We should be able to enroll patients on them in the next three to six months. Until then, I've been administering an aromatase inhibitor a little longer and hoping to place these patients on a trial.

NSABP-B-42 will randomly assign women who have undergone any endocrine therapy that adds up to five years and includes an aromatase inhibitor to either five more years of letrozole or not.

The rerandomization of MA17 randomly assigns all women who received five years of tamoxifen and five years of an aromatase inhibitor as part of the MA17 study to receive more letrozole or not.

Now we have an amendment, which will randomly assign anyone who has received five years of an aromatase inhibitor to more aromatase inhibitor or not. So to some degree, it will overlap with NSABP-B-42 but not completely.

Track 4

DR LOVE: What do we know about the etiology and management of the arthralgias that are sometimes seen with the aromatase inhibitors?

DR PRITCHARD: I don't believe we understand it well. Most commonly we see a syndrome of aches and pains. It's an arthralgia/myalgia syndrome but not arthritis. In most of the controlled studies, it's only about five or 10 percent of patients.

I believe it's a real syndrome. I suspect it's similar to the aches and pains some women describe around menopause and that it's an estrogen-deprivation symptom of some type. Some experience it, some don't seem to at all and a few people experience severe symptoms. I try taking them off and switching them to another aromatase inhibitor or switching them back to tamoxifen. In some patients, it seems to dissipate — maybe as a result of the switch.

Track 6

DR LOVE: How do you manage treatment for postmenopausal women who are a few years out after receiving tamoxifen?

DR PRITCHARD: It appears that the risk of relapse for patients with endocrine-responsive breast cancer is steady and goes on for 10 or 15 years. For patients with node-positive disease, it may be as much as four percent a year, and for people with node-negative disease, it may be around two percent a year. When you add that up over five or 10 years, it's substantial.

If I see patients out at that time point, I approach them about receiving an aromatase inhibitor in the postmenopausal setting. The data are good, certainly in MA17 (Ingle 2006). When the study was closed early, women who had been receiving a placebo for three or more years were offered the opportunity to receive letrozole. The women who went on letrozole benefited. It's not a randomized comparison, but it appears as though starting letrozole later still provided benefit.

Track 7

DR LOVE: Where are we in terms of aromatase inhibitors and bone health?

DR PRITCHARD: All of the aromatase inhibitors are associated with osteoporosis and increased fracture rates. So I believe these women should be monitored, have baseline bone mineral density (BMD) recorded, take calcium and vitamin D, exercise and receive bisphosphonates if it's appropriate.

A few trials show that you can prevent most of the osteoporosis and most of the BMD loss with bisphosphonates (Brufsky 2007; Gnant 2007). However, I don't believe that is clear, even in the long-term follow-up of bisphosphonates in healthy women (Bone 2004).

We're also beginning to see some reports of bisphosphonate-associated jaw necrosis. Will that be a long-term side effect that becomes increasingly common over time? I would like to believe that if we treated these patients proactively, we could prevent most of the osteoporosis.

Track 9

DR LOVE: Can you discuss Bill Gradishar's presentation at San Antonio of the EFECT results and your thoughts about those data?

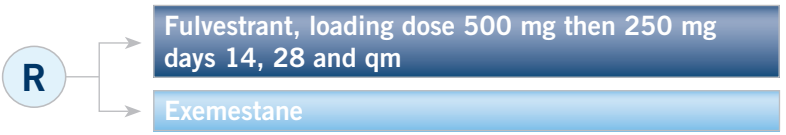
DR PRITCHARD: The EFECT study compared exemestane to fulvestrant for patients whose disease progressed on a nonsteroidal aromatase inhibitor (Gradishar 2006; [3.1]). I would have guessed that fulvestrant would be more active in that setting because it's a drug of a totally different class.

However, lots of data have suggested that exemestane, as a steroidal aromatase inhibitor, provides decent response rates or a decent level of clinical benefit beyond the use of nonsteroidal aromatase inhibitors. So it was perhaps a surprise, and perhaps not, that exemestane and fulvestrant in that setting appear almost identical. In fact, even the side-effect profiles are similar.

DR LOVE: In EFECT, they used a loading dose of fulvestrant, which more people are using now in practice. What are your thoughts on that?

3.1 EFECT: Evaluation of Fulvestrant and Exemestane Clinical Trial

Protocol IDs: EFECT, NCT00065325, 9238IL/0048
Accrual: 693 (Closed)



Eligibility
Postmenopausal, hormone receptor-positive, progression on a nonsteroidal aromatase inhibitor

Efficacy results

	Fulvestrant	Exemestane	*p*-value
OR	7.4%	6.7%	0.7364
CB	32.2%	31.5%	0.8534
TTP	3.7 months	3.7 months	0.6531
DOR	13.5 months	9.8 months	NR
DCB	9.3 months	8.3 months	NR

OR = objective response; CB = clinical benefit; TTP = median time to progression; DOR = median duration of response; DCB = median duration of clinical benefit; NR = not reported

SOURCE: Gradishar W et al. San Antonio Breast Cancer Symposium 2006;**Abstract 12**.

DR PRITCHARD: Good pharmacokinetic data indicate that using no loading dose, it takes three to four months to reach steady-state levels. I believe most of us are using a loading dose, and there doesn't seem to be any real problem with that. A number of trials have been using the loading dose, and no safety problems are apparent.

Track 10

DR LOVE: What's your algorithm for sequential hormonal therapy in the metastatic setting, both for the premenopausal and the postmenopausal patient?

DR PRITCHARD: In the premenopausal setting, I discuss tamoxifen or ovarian ablation. For me, ovarian ablation would involve starting the patient on a luteinizing hormone-releasing hormone analog and then ordering a surgical oophorectomy if she is willing to undergo that. I also usually discuss the option of receiving both ovarian ablation and tamoxifen.

Once the patient has a permanent ovarian ablation, I generally administer an aromatase inhibitor and fulvestrant. Ongoing studies are evaluating fulvestrant in premenopausal patients.

In the postmenopausal setting, I would use an aromatase inhibitor first — unless the disease has progressed on an aromatase inhibitor, which is becoming more common — followed by tamoxifen followed by fulvestrant. We are conducting a study in our center right now evaluating two doses of fulvestrant after progression on an aromatase inhibitor. I believe one could use these hormones in almost any order in the metastatic setting.

Track 19

DR LOVE: Would you discuss the TAnDEM trial data of patients with ER- and HER2-positive, metastatic disease?

DR PRITCHARD: The TAnDEM trial was the first trial to evaluate trastuzumab in combination with an endocrine agent and compared anastrozole/trastuzumab to anastrozole alone (Mackey 2006; [3.2]). The aromatase inhibitor/trastuzumab arm had considerably longer progression-free survival, but the median progression-free survival in both arms was short — between two and three months versus between four and five months.

The stunning aspect is that this is a group of women who don't generally respond well to endocrine therapy, even with the addition of trastuzumab. But within that median progression-free survival, some patients go into long responses or periods of stability with anastrozole and trastuzumab, and there may even be some patients who are able to do that with anastrozole alone.

I believe the reasonable approach for patients like that — if they're relatively asymptomatic and you can monitor them closely — is trying an endocrine

agent with trastuzumab or an endocrine agent alone. If you treat them with an endocrine agent alone and they have visceral disease, you have to watch them closely and monitor liver function, et cetera, to make sure no disease or symptom becomes unmanageable.

You could also make the argument that, on average, this is a group of patients who don't respond well to endocrine treatment with or without trastuzumab, and perhaps you should move ahead to something more energetic, such as a taxane with trastuzumab. ■

3.2

TAnDEM: Randomized Trial Comparing Anastrozole with or without Trastuzumab for Patients with HER2-Positive, Hormone Receptor-Positive, Metastatic Breast Cancer (N = 208*)

Parameter	Anastrozole	Anastrozole + trastuzumab	*p*-value
Median progression-free survival	2.4 months (95% CI: 2.0-4.6)	4.8 months (95% CI: 3.7-7.0)	0.0016
Partial response rate	6.8%	20.3%	0.018
Clinical benefit rate	27.9%	42.7%	0.026
Overall survival	23.9 months (95% CI: 18.2-37.4)	28.5 months (95% CI: 22.8-42.4)	0.325
Overall survival for patients without liver metastasis†	32.1 months (95% CI: 22.0-38.6)	41.9 months (95% CI: 30.3-52.8)	0.0399

* One patient did not receive the study drug and was excluded from analysis.

† Unplanned subgroup analysis

SOURCE: Mackey JR et al. Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

SELECT PUBLICATIONS

Black DM et al; HORIZON Pivotal Fracture Trial. **Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis.** *N Engl J Med* 2007;356(18):1809-22. **Abstract**

Bone HG et al. **Ten years' experience with alendronate for osteoporosis in postmenopausal women.** *N Engl J Med* 2004;350(12):1189-99. **Abstract**

Brufsky A et al. **Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer.** *J Clin Oncol* 2007;25(7):829-36. **Abstract**

Gnant MF et al. **Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: A report from the Austrian Breast and Colorectal Cancer Study Group.** *J Clin Oncol* 2007;25(7):820-8. **Abstract**

Gradishar W et al. **Fulvestrant versus exemestane following prior non-steroidal aromatase inhibitor therapy: First results from EFECT, a randomized, phase III trial in postmenopausal women with advanced breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 12**.

Ingle JN et al. **Duration of letrozole treatment and outcomes in the placebo-controlled NCIC CTG MA.17 extended adjuvant therapy trial.** *Breast Cancer Res Treat* 2006;99(3):295-300. **Abstract**

Mackey JR et al. **Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

INTERVIEW

Martine J Piccart-Gebhart, MD, PhD

Dr Piccart-Gebhart is Head of the Medicine Department in the Breast International Group and is Chair of the Medical Oncology Clinic at the Jules Bordet Institute in Brussels, Belgium.

Tracks 1-17

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Can you review the MINDACT trial?

DR PICCART-GEBHART: This study (BIG 3-04) has a design similar to TAILORx. The 6,000 women enrolled will be assessed by the 70-gene signature MammaPrint assay and Adjuvant! Online (**www.AdjuvantOnline.com**), which we believe is one of the best tools available to predict outcomes for women with breast cancer.

If both tools indicate a high risk of recurrence, the woman will receive adjuvant chemotherapy. If both tools indicate a low risk of recurrence, the patient will not receive chemotherapy. Most of these women will be treated with adjuvant endocrine therapy.

The discordant group, in which the two tools do not provide the same information, is the critical group. These patients will be randomly assigned to either trusting Adjuvant! Online and ignoring the 70-gene signature or trusting the signature and ignoring the clinical and pathological factors integrated in Adjuvant! Online. We want to prove that the 70-gene signature is right. It is interesting that in 80 percent of these discordant cases, the signature indicates that the patient has low-risk disease, whereas Adjuvant! Online tells you she has a high risk of recurrence.

DR LOVE: This assay requires fresh tissue, correct?

DR PICCART-GEBHART: Yes, which is a big challenge.

DR LOVE: Why is it that you decided to pursue this assay in the face of the Onco*type* DX assay, which doesn't require fresh tissue and seems to have more data behind it at the moment?

DR PICCART-GEBHART: You are right — in terms of validation, Onco*type* DX is farther down the road (Paik 2004, 2006), but we believe that in 10 years we will have even better signatures. By using the microarray technology, in fact, we will obtain information on the full genome for all 6,000 women. So we will observe not only the 70 genes but also the entire genome.

That represents a fabulous source of data for translational research because it will allow us to analyze potentially different signatures that will be developed in the next five years — for example, signatures for predicting organ-site metastases.

DR LOVE: Is the MammaPrint assay currently being used in clinical practice?

DR PICCART-GEBHART: No, not that I am aware of. I strongly believe that prospective validation is essential. However, it is FDA approved and commercially available. I suspect some oncologists may want to use it for select cases in which they have doubts and the traditional factors are in the gray area.

Track 5

DR LOVE: Let's talk about adjuvant treatment of patients with HER2-positive tumors. In your own practice outside of a clinical trial setting, how are you approaching patients with node-positive disease?

DR PICCART-GEBHART: I ask myself two questions: Am I worried about an early relapse, and am I worried about the risk of cardiac toxicity?

We conducted an interesting analysis in the HERA study observing the patterns of relapse according to hormone receptor status and nodal status in women on the control arm who did not receive trastuzumab. Women with

four or more positive nodes had a high risk of relapse in the first two years, which indicates that these women are probably better served with a strategy that uses trastuzumab up front.

We also discovered that women with hormone receptor-negative tumors have a higher risk of early relapse compared to those with hormone receptor-positive tumors. Therefore, I use that information to decide between immediate or delayed trastuzumab.

We need to do a lot more work in terms of identifying cardiac risk factors. Some early signals have been provided by the analysis of cardiac toxicity in the NSABP (Tan-Chiu 2005) and HERA studies (Piccart-Gebhart 2005; Smith 2007). In the presence of these risk factors, I will think twice about the use of anthracyclines and perhaps favor a regimen like TCH.

Tracks 6-8

DR LOVE: Would you discuss the ALTTO trial?

DR PICCART-GEBHART: This study will accrue approximately 8,000 women (4.1). We wanted to investigate several possible approaches using chemotherapy and several anti-HER2 treatments, including lapatinib or trastuzumab or the sequence or combination of trastuzumab and lapatinib.

The combination of trastuzumab and lapatinib everyone understands because you can achieve maximal inhibition by attacking the receptors on both sides. That should be the better arm, but the sequential strategy is also important in case the toxicities associated with the combination are problematic.

DR LOVE: The sequential arm will use trastuzumab first followed by a rest period and then lapatinib?

DR PICCART-GEBHART: Yes. We have more data with this type of sequence. For practical reasons, we also felt it would be difficult for the patients to start with an oral drug and then after a few months go back to the hospital to receive an intravenous treatment.

DR LOVE: Which chemotherapy regimens are allowed on the trial?

DR PICCART-GEBHART: This is a worldwide effort, and no standard chemotherapy regimen is accepted throughout the world. Also, we wanted to offer this trial to countries where taxanes are still problematic. So we are not requiring taxanes, but we believe the vast majority of women will receive anthracyclines and taxanes.

At the beginning of the trial, the taxanes will be limited to weekly paclitaxel administered concomitantly with the anti-HER2 treatment for safety reasons. We have safety data for paclitaxel in combination with lapatinib, trastuzumab and the combination. We do not have those data for docetaxel or *nab* paclitaxel, but we hope to obtain the safety data. If these look good, we will amend the protocol and these other taxanes will also be allowed.

The trial will have two strata (4.1). For physicians and patients who choose the strategy of chemotherapy combined with the anti-HER2 therapy, anthracycline-based chemotherapy will be administered first. The selection of a chemotherapy regimen will be open and flexible.

For example, it may be four cycles of AC or three cycles of FEC. That is followed by weekly paclitaxel combined with the anti-HER2 treatment.

In the second group, physicians will be able to choose from a list of candidate regimens. They will have to administer the chemotherapy according to the HERA philosophy, by which the chemotherapy is administered first and then patients are randomly assigned to receive biologic therapy, which is not administered in combination with chemotherapy.

DR LOVE: What are the eligibility criteria for the study?

4.1

Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) Trial: Proposed Design

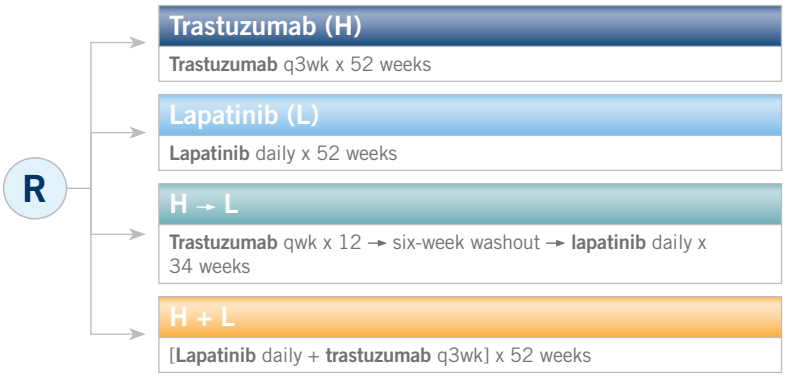
Protocol IDs: BIG 2-06, NCCTG-N063D
Target Accrual: 8,000 (Pending activation)

Eligibility

- HER2-positive breast cancer

In STRATA 1, patients will receive weekly paclitaxel together with the anti-HER2 targeted therapy following anthracycline-based (neo)adjuvant chemotherapy

STRATA 2 will comprise patients who complete all (neo)adjuvant chemotherapy prior to administration of targeted therapy



Study Contacts

Martine J Piccart-Gebhart, MD, PhD
Edith A Perez, MD

SOURCE: *Breast International Group Newsletter* Spring 2007;9(1).

DR PICCART-GEBHART: The trial is for women up to age 70 with a tumor that is one centimeter or greater in size. A difference in comparison to the previous adjuvant trastuzumab trials is that we will define HER2 positivity according to the recently published ASCO guidelines (Wolff 2007). Positivity means IHC staining of 3+, but you now need more than 30 percent of the cells stained for the tumor to be considered 3+. FISH positivity is also defined slightly differently than before in that the FISH ratio has to be greater than 2.2 (Wolff 2007).

Track 9

DR LOVE: How do you approach patients with smaller, HER2-positive, node-negative disease in a clinical setting, particularly those with tumors smaller than one centimeter?

DR PICCART-GEBHART: It's a big dilemma. We don't have a clear answer, and we have to struggle with the decision about whether to use trastuzumab. At my hospital, we have finally decided to use a cutoff of six millimeters. We ignore the possibility of using trastuzumab if the tumor is smaller than that. When the tumor is six millimeters or greater, particularly if the patient is a young woman with an ER-negative tumor, we offer trastuzumab.

Track 15

DR LOVE: What are your thoughts about long-term management of women with ER-positive breast cancer?

DR PICCART-GEBHART: We became aware that hormone receptor-positive breast cancer is a strange disease with a continuous risk of relapse over time. This is bad news because this disease might well be extremely difficult to cure. If that's the case, we need to consider long-term endocrine therapy.

I hope that with pharmacogenomic tools we will be able to identify patients at continued risk of relapse and those who can be cured with a relatively short course of endocrine treatment. I believe the majority will need prolonged endocrine manipulation. We don't know the optimal sequencing for that.

Currently in my practice, I try to use eight years of hormonal therapy. It's not based on solid evidence — rather, it's a compromise drawn from the data with five years of tamoxifen, five years of an aromatase inhibitor, and two to three years of tamoxifen followed by two to three years of an aromatase inhibitor. I try to administer two to three years of tamoxifen and five years of an aromatase inhibitor.

I'm waiting impatiently for the results from BIG 1-98 because one arm involves an aromatase inhibitor followed by tamoxifen. Those results should be available in 2008.

DR LOVE: If a woman has completed five years of an aromatase inhibitor, are there situations in which you'll continue it?

DR PICCART-GEBHART: Yes, if the woman is at particularly high risk with many positive nodes and has been tolerating the therapy well. Of course, I will first do a careful evaluation of the status of her bones, lipids and quality of life. ■

SELECT PUBLICATIONS

Black D et al. **Recurrence risk in T1a-b, node negative, HER2 positive breast cancer**. San Antonio Breast Cancer Symposium 2006;**Abstract 2037**.

Bogaerts J et al. **Gene signature evaluation as a prognostic tool: Challenges in the design of the MINDACT trial.** *Nat Clin Pract Oncol* 2006;3(10):540-51. **Abstract**

Burnell M et al. **A randomized trial of CEF versus dose dense EC followed by paclitaxel versus AC followed by paclitaxel in women with node positive or high risk node negative breast cancer, NCIC CTG MA.21: Results of an interim analysis.** San Antonio Breast Cancer Symposium 2006;**Abstract 53**.

Buyse M et al; TRANSBIG Consortium. **Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer.** *J Natl Cancer Inst* 2006;98(17):1183-92. **Abstract**

Joensuu H et al; FinHer Study Investigators. **Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.** *N Engl J Med* 2006;354(8):809-20. **Abstract**

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

Norris B et al. **Poor 10 yr breast cancer specific survival (BCSS) and relapse free survival (RFS) for HER2 positive T1pN0 tumors.** San Antonio Breast Cancer Symposium 2006;**Poster 2031**.

Paik S. **Molecular profiling of breast cancer.** *Curr Opin Obstet Gynecol* 2006a;18(1):59-63. **Abstract**

Paik S et al. **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *J Clin Oncol* 2006b;24(23):3726-34. **Abstract**

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

Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. **Abstract**

Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients.** San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

Smith I et al; HERA study team. **2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: A randomised controlled trial.** *Lancet* 2007;369(9555):29-36. **Abstract**

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**

Van de Vijver MJ et al. **A gene-expression signature as a predictor of survival in breast cancer.** *N Engl J Med* 2002;347(25):1999-2009. **Abstract**

Van 't Veer LJ et al. **Gene expression profiling predicts clinical outcome of breast cancer.** *Nature* 2002;415(6871):530-6. **Abstract**

Wolff AC et al. **American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer.** *J Clin Oncol* 2007;25(1):118-45. **Abstract**

INTERVIEW

Ruth O'Regan, MD

Dr O'Regan is Director of Clinical and Translational Breast Cancer Research, Director of the Hematology/Oncology Program and Associate Professor of Hematology/Oncology at the Winship Cancer Institute of Emory University in Atlanta, Georgia.

Tracks 1-15

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the US Oncology adjuvant trial comparing TC (docetaxel/cyclophosphamide) to AC chemotherapy?

DR O'REGAN: It is somewhat small for an adjuvant study, but it is useful in that it provides data for both node-positive and node-negative disease (Jones 2006). The data demonstrated that disease-free survival is better with TC.

In my practice, I find the 100-mg/m^2 dose of docetaxel as a single agent difficult to administer, but the 75-mg/m^2 regimen with TC is relatively easy, so it does beg the question of whether you need AC. However, most patients do

well with AC, and it is a tried-and-tested chemotherapy regimen.

DR LOVE: Initially, when Steve Jones presented this at San Antonio (5.1), some people questioned the reported improved tolerability of TC. Do you see this improvement as the result of the lower docetaxel dose?

DR O'REGAN: Yes. Also, patients don't experience nausea with the lower dose, which is nice.

5.1

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

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

Hazard ratios < 1 indicate values in favor of TC.

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

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

SOURCE: Jones SE et al. *J Clin Oncol* 2006;24(34):5381-7. **Abstract**

Tracks 5-7

DR LOVE: What's your take on *nab* paclitaxel and its clinical utility?

DR O'REGAN: I am using *nab* paclitaxel, and I'm surprised that it hasn't been used more extensively, particularly in the first-line setting. Many clinicians are still using it for patients who fail at least one taxane, whereas the first-line data are pretty robust, and *nab* paclitaxel's effectiveness and toxicity profile are better than those of regular paclitaxel. So I am using it in the first-line setting, where I tend to use the every three-week schedule, and perhaps weekly later on.

Although this was a randomized Phase II trial, Bill Gradishar's data demonstrated that the response rate with the weekly schedule of *nab* paclitaxel was double that of docetaxel and it was considerably less toxic (Gradishar 2006).

The weekly schedule of *nab* paclitaxel also appeared to cause less neuropathy. Neuropathy with this agent is an issue, but a lot of patients I've treated have received prior taxanes, so I'm not sure how it will perform in the first-line setting in that regard. In my experience, *nab* paclitaxel is well tolerated.

DR LOVE: Some people also believe that the neuropathy resolves more quickly with *nab* paclitaxel. What's your impression?

DR O'REGAN: I have not been able to "tweak that out" in my own patients. The data are weak because the pivotal trial (Gradishar 2005) included only five patients in the first-line paclitaxel arm.

The *nab* paclitaxel arm in this trial had 24. It is possible because of the way *nab* paclitaxel works that the neuropathy may resolve more quickly, but I'd like to see more data.

DR LOVE: How useful is it clinically to have a shorter infusion time and no need for premedication?

DR O'REGAN: That's a huge advantage, particularly the lack of premedication. Patients complain about having to take the steroids with paclitaxel. In terms of the shorter infusion time, that is a huge benefit in a busy practice.

Track 11

DR LOVE: What are your thoughts about bevacizumab? Are you using it off study?

DR O'REGAN: Yes. When you consider the ECOG-E2100 trial (Miller 2005a), the progression-free survival increase of nearly six months is impressive (5.2). Certainly this benefit may be compared to the combination versus single-agent chemotherapy studies we've conducted before in metastatic breast cancer. In my experience, bevacizumab works well.

Most of the patients I've treated have shown at least some type of a response, although perhaps not as sustained as we would like. I also like bevacizumab because its toxicity doesn't overlap with that of the chemotherapy. Apart from a little hypertension and some headaches, patients tolerate it well.

DR LOVE: When you've used bevacizumab, has it been only in the first-line setting or also in the second line or beyond?

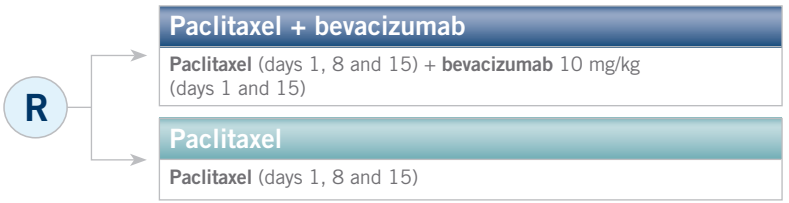
DR O'REGAN: I've used it almost exclusively in the first-line setting with paclitaxel. This is one area in which I believe *nab* paclitaxel is being used in practice. I have seen some patients from the community who've been receiving *nab* paclitaxel and bevacizumab. For a couple of patients, I've used it outside of the first-line setting, but as you would expect, we do not obtain many responses.

I do wonder whether bevacizumab should be considered for other patients in addition to those with metastatic disease, such as those with locally recurrent cancer. It would be interesting to see whether they're more sensitive to the bevacizumab, because some of those patients are difficult to treat.

5.2

ECOG-E2100: Paclitaxel with or without Bevacizumab as First-Line Therapy

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



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

CI = confidence interval

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

Conclusions

"In conclusion, this is a positive study. The addition of bevacizumab to paclitaxel significantly prolongs progression-free survival and more than doubles the objective response rate. Overall survival data are still premature, and longer follow-up will be needed to assess the true impact of this therapy… .

It's now time to move bevacizumab into the adjuvant setting and explore its role there."

SOURCE: Miller KD et al. San Antonio Breast Cancer Symposium 2005a;**Abstract 3**.

DR LOVE: What are your thoughts on using other chemotherapeutic agents, such as capecitabine, with bevacizumab?

DR O'REGAN: It would probably work out fine to administer it with capecitabine. Unfortunately, we have a somewhat negative trial in the second-line setting with bevacizumab and capecitabine, although a response-rate improvement was evident in that trial (Miller 2005b). I believe it's the line of therapy used rather than the agent you use it with that's important.

At San Antonio, an NCCTG trial of docetaxel/capecitabine with bevacizumab was presented (Perez 2006). This regimen showed activity, although it was somewhat toxic. Emerging data suggest that bevacizumab is effective with chemotherapy agents other than paclitaxel, and I have on at least one occasion used capecitabine and bevacizumab for a patient who was not a candidate for paclitaxel in the first-line setting.

DR LOVE: When you use bevacizumab with a chemotherapeutic agent, do you continue the therapy until progression?

DR O'REGAN: If a patient continues to respond, I continue both agents until disease progression, as was done on the trial.

Of course, the big question is whether you could drop the chemotherapy and continue the bevacizumab, but I haven't done that. In some ways, it may make more sense to continue the bevacizumab on its own, but that must be addressed in a trial. ■

SELECT PUBLICATIONS

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

Goldstein L et al. **E2197: Phase III AT (doxorubicin/docetaxel) vs AC (doxorubicin/cyclophosphamide) in the adjuvant treatment of node positive and high risk node negative breast cancer.** *Proc ASCO* 2005;**Abstract 512**.

Gradishar W et al. **A randomized phase 2 trial of qw or q3w ABI-007 (ABX) vs q3w solvent-based docetaxel (TXT) as first-line therapy in metastatic breast cancer (MBC).** San Antonio Breast Cancer Symposium 2006;**Abstract 46**.

Gradishar WJ et al. **Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

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

Jones SE et al. **Three year results of a prospective randomized trial of adjuvant chemotherapy for patients (pts) with stage I-III operable, invasive breast cancer comparing 4 courses of doxorubicin/cyclophosphamide (AC) to 4 courses of docetaxel/cyclophosphamide (TC).** *Proc ASCO* 2003;**Abstract 59**.

Miller K et al. **Capecitabine plus bevacizumab in first line metastatic breast cancer: An interim safety and efficacy report of the first phase of Xeloda plus Avastin 1st line metastatic breast cancer trial.** San Antonio Breast Cancer Symposium 2006;**Abstract 2068**.

Miller KD et al. **A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: A trial coordinated by the Eastern Cooperative Oncology Group (E2100).** San Antonio Breast Cancer Symposium 2005a;**Abstract 3**.

Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005b;23(4):792-9. **Abstract**

Perez EA et al. **North Central cancer treatment group (NCCTG) N0432: Phase II trial of docetaxel with capecitabine and bevacizumab as first line chemotherapy for patients with metastatic breast cancer.** Poster. San Antonio Breast Cancer Symposium 2006;**Abstract 2069**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The trans-ATAC analysis demonstrated that patients with ER-positive, PR-negative breast cancer did not benefit from adjuvant anastrozole.**
   a. True
   b. False
2. **The NCCTG-N0337 trial is evaluating a "nonalopecia regimen," which consists of capecitabine, vinorelbine and trastuzumab.**
   a. True
   b. False
3. **The second interim analysis of BCIRG 006 demonstrated that AC → TH was superior to TCH with regard to _____.**
   a. Disease-free survival
   b. Overall survival
   c. Both a and b
   d. None of the above
4. **Which of the following is not being evaluated in the ALTTO trial?**
   a. Trastuzumab alone
   b. Lapatinib alone
   c. Trastuzumab followed by lapatinib
   d. Trastuzumab and lapatinib
   e. Lapatinib followed by trastuzumab
5. **In the US Oncology adjuvant trial, docetaxel/cyclophosphamide (TC) resulted in a _____ percent relative improvement in five-year disease-free survival compared to AC chemotherapy.**
   a. Six
   b. 10
   c. 33
   d. 50
6. **A pilot study conducted by Swain and colleagues demonstrated that one cycle of bevacizumab monotherapy significantly decreased VEGFR-2 activation in tumor cells and increased tumor apoptosis.**
   a. True
   b. False
7. **NSABP-B-40 will incorporate which of the following biologic agents in the neoadjuvant treatment of HER2-negative breast cancer?**
   a. Trastuzumab
   b. Lapatinib
   c. Bevacizumab
   d. Erlotinib
   e. Cetuximab
8. **In the EFECT study, exemestane resulted in a superior time to progression compared to fulvestrant among women with metastatic breast cancer who were previously treated with a nonsteroidal aromatase inhibitor.**
   a. True
   b. False
9. **In EFECT, fulvestrant was administered with a 500 mg loading dose on day 0, then 250 mg on days 14 and 28 followed by 250 mg monthly.**
   a. True
   b. False
10. **NSABP-B-42 will evaluate _____ in women who previously received five years of adjuvant aromatase inhibitor therapy.**
    a. Tamoxifen
    b. Fulvestrant
    c. Continued therapy with an aromatase inhibitor
11. **According to ECOG-E2100, paclitaxel and bevacizumab significantly prolong disease-free survival compared to _____ as initial chemotherapy for patients with metastatic breast cancer.**
    a. Paclitaxel alone
    b. Paclitaxel and capecitabine
    c. *Nab* paclitaxel and bevacizumab
12. **Compared to the standard formulation of paclitaxel, *nab* paclitaxel requires _____.**
    a. No premedication with steroids
    b. Shorter infusion time
    c. Both a and b

Post-test answer key: 1b, 2a, 3d, 4e, 5c, 6a, 7c, 8b, 9a, 10c, 11a, 12c

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

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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Sandra M Swain, MD	5 4 3 2 1	5 4 3 2 1
Kathleen I Pritchard, MD	5 4 3 2 1	5 4 3 2 1
Martine J Piccart-Gebhart, MD, PhD	5 4 3 2 1	5 4 3 2 1
Ruth O'Regan, MD	5 4 3 2 1	5 4 3 2 1

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Objectives were related to overall purpose/goal(s) of activity. . . . . 5 4 3 2 1 N/A
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