Breast Cancer®

UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

SPECIAL ISSUE

Proceedings from a Clinical Investigator "Think Tank"

EDITOR

Neil Love, MD

PANEL MEMBERS

Harold J Burstein, MD, PhD
Aman U Buzdar, MD
Daniel F Hayes, MD
Clifford Hudis, MD
Kathy D Miller, MD
C Kent Osborne, MD
Mark D Pegram, MD
Peter M Ravdin, MD, PhD
Professor John F R Robertson, MB, ChB, BSc, MD
George W Sledge Jr, MD
Charles L Vogel, MD
Eric P Winer, MD

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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 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.
- 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 this special edition of *Breast Cancer Update* is to support these global objectives by offering the perspectives of breast cancer investigators present at a Think Tank meeting on the integration of emerging clinical research data into the management of breast cancer.

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EDITOR'S NOTE

Neil Love MD

If these people can't agree on how to manage breast cancer, what are the rest of us supposed to do?

The enclosed audio program provides highlights of a daylong roundtable meeting with a dozen prominent breast cancer clinical investigators examining a number of the most challenging and controversial questions in current breast cancer management.

During the event, we asked the faculty to discuss four major treatment areas:

1. Adjuvant therapy for patients with HER2-positive tumors
2. Adjuvant chemotherapy
3. Adjuvant endocrine therapy for patients with ER-positive tumors
4. Systemic management of metastatic disease

Considering the crucial practical issues that these topics represent, it is noteworthy that these investigators generally disagreed with each other on many important facets of these topics, specifically related to what constitutes a reasonable approach to clinical care.

We were actually able to quantify the disparity in the perceptions of these mavens because immediately prior to the think tank, we asked each roundtable participant to complete a survey asking whether he or she "agreed," "disagreed" or was "in between" with regard to a series of 27 clinical practice questions. The results of this fascinating exercise are reproduced in the accompanying monograph. What is particularly interesting is that in only about one third of these cases did a majority of the participants reach a consensus. My favorite questions were the ones that split the faculty in neat thirds, four for each answer.

The disagreement we observed is relevant to one of the most common comments we receive about our audio programs, namely that doctors in practice feel a sense of reassurance when they hear the "experts" struggle with the interpretation of research data and treatment decision-making.

An example of how this controversy plays out in clinical decision-making is the choice of chemotherapy regimen in a patient with ER-positive, HER2-negative, node-positive disease. During the Think Tank, Chuck Vogel identified four anthracycline/taxane regimens with "Level 1" supportive evidence on this question (Figure 1). However, our CME group's national Patterns of Care surveys of US-based medical oncologists and breast cancer clinical inves-

tigators demonstrates that, although about two thirds of these docs usually turn to dose-dense AC → paclitaxel or TAC, a substantial minority rely on other regimens.

1

Clinical Trials of Adjuvant Chemotherapy

Trial	Chemotherapy regimens	DFS	*p*-value	OS	*p*-value
Hudis 2005	AC/paclitaxel q3wk AC/paclitaxel q2wk	71.6% 76.7%	0.012	79.5% 83%	0.049
Martin 2005a	FAC TAC	68% 75%	0.001	81% 87%	NR
Roche 2004	FEC100 x 6 FEC100 x 6 → docetaxel x 3	73.2% 78.3%	0.014	86.7% 90.7%	0.017
Martin 2005b	$FE_{90}C$ x 6 $FE_{90}C$ x 4 → paclitaxel qwk x 8	79.2% 86.9%	0.0009	94.5% 91.8%	0.1375

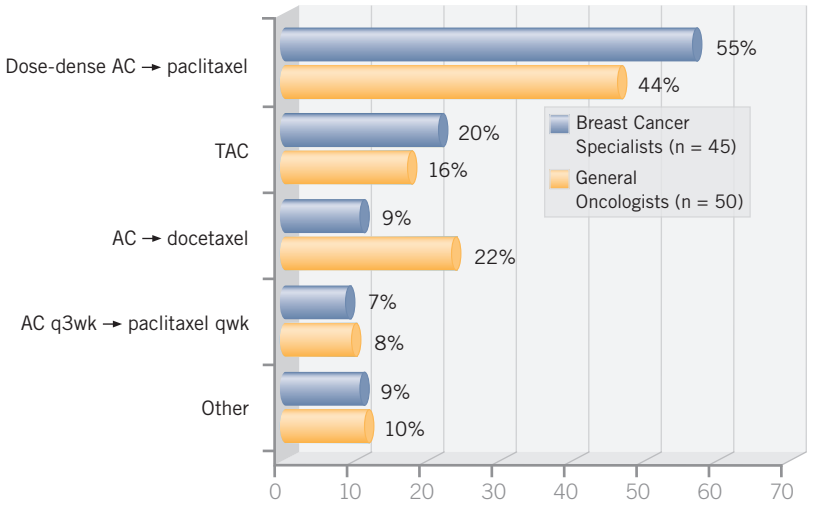
NR = not reported

SOURCES: Hudis C et al. San Antonio Breast Cancer Symposium 2005;**Abstract 41**; Martin M et al. *N Engl J Med* 2005a;352(22):2302-13. **Abstract**; Roche H et al. San Antonio Breast Cancer Symposium 2004;**Abstract 27**; Martin M et al. San Antonio Breast Cancer Symposium 2005b;**Abstract 39**.

2

Patterns of Care Survey of Medical Oncologists: Adjuvant Chemotherapy for Patients with ER-Positive, Node-Positive Disease

Which chemotherapy regimen would you most likely recommend for a 55-year-old woman with a 1.2-cm, Grade II, ER/PR-positive, HER2-negative tumor and three positive lymph nodes?



SOURCE: 2005 *Breast Cancer Update* Patterns of Care Survey of Medical Oncologists.

Clearly, the available research evidence on this question and many others in contemporary oncology leaves a great deal of room for research to practice applications, as demonstrated by the furious debate of these elite investigators on a variety of topics.

Our CME group found this day of repartee highly informative and entertaining, and to further explore the debate, we will assemble a similar group for another Think Tank event early this summer. Given the timing (soon after ASCO), this meeting will undoubtedly shed more light on the important research to practice issues that are vexing to us all. ■

— Neil Love, MD
NLove@ResearchToPractice.net

SELECT PUBLICATIONS

Berry DA et al. **Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer.** *JAMA* 2006;295(14):1658-67. **Abstract**

Bria E et al. **Benefit of taxanes as adjuvant chemotherapy for early breast cancer: Pooled analysis of 15,500 patients.** *Cancer* 2006;[Epub ahead of print]. **Abstract**

Cianfrocca M, Gradishar WJ. **Controversies in the therapy of early stage breast cancer.** *Oncologis*t 2005;10(10):766-79. **Abstract**

Crown J et al. **Docetaxel (T) given either concurrently or sequentially to anthracycline-based (A) adjuvant therapy (adjRx) for patients (pts) with node-positive (N+) breast cancer (BrCa). Comparison with non-taxane combination chemotherapy. First results of the BIG 2-98 Trial at 5 years median follow-up.** *Proc ASCO* 2006;**Abstract LBA519**.

Harlan LC et al. **Community-based use of chemotherapy and hormonal therapy for early-stage breast cancer: 1987-2000.** *J Clin Oncol* 2006;24(6):872-7. **Abstract**

Hudis C et al. **Five year follow-up of INT C9741: Dose-dense (DD) chemotherapy (CRx) is safe and effective.** San Antonio Breast Cancer Symposium 2005;**Abstract 41**.

Knoop A et al. ***TOP2A* aberrations as predictive and prognostic marker in high-risk breast cancer patients. A randomized DBCG Trial (DBCG89D).** *Proc ASCO* 2006;**Abstract 532**.

Kummel S et al. **Randomised trial: Survival benefit and safety of adjuvant dose-dense chemotherapy for node-positive breast cancer.** *Br J Cancer* 2006;94(9):1237-44. **Abstract**

Mamounas EP et al. **Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28.** *J Clin Oncol* 2005;23(16):3686-96. **Abstract**

Martin M et al; Breast Cancer International Research Group 001 Investigators. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13. **Abstract**

Martin M et al. **Multicenter, randomized phase III study of adjuvant chemotherapy for node positive breast cancer comparing 6 cycles of $FE_{90}C$ versus 4 cycles of $FE_{90}C$ followed by 8 weekly paclitaxel administrations: Interim efficacy analysis of GEICAM 9906 Trial.** San Antonio Breast Cancer Symposium 2005;**Abstract 39**.

Muss HB et al; Cancer and Leukemia Group B. **Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer.** *JAMA* 2005;293(9):1073-81. **Abstract**

Roche H et al. **Five years analysis of the PACS 01 trial: 6 cycles of FEC100 vs 3 cycles of FEC100 followed by 3 cycles of docetaxel (D) for the adjuvant treatment of node positive breast cancer.** San Antonio Breast Cancer Symposium 2004;**Abstract 27**.

Trudeau M et al. **Selection of adjuvant chemotherapy for treatment of node-positive breast cancer.** *Lancet Oncol* 2005;6(11):886-98. **Abstract**

SECTION 1

ADJUVANT THERAPY FOR PATIENTS WITH HER2-POSITIVE TUMORS

Tracks 1-17

Select Excerpts from the Discussion

Tracks 4-7

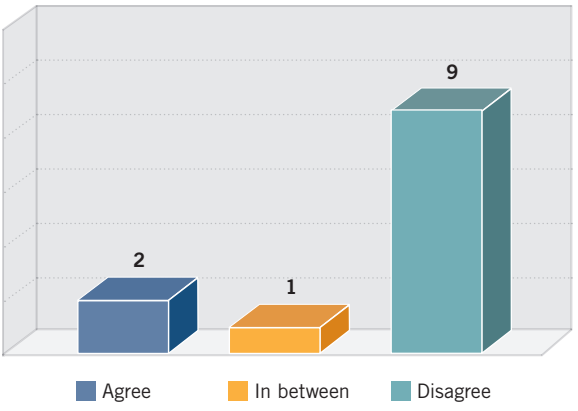
DR LOVE: Mark, what's your reaction to the TOPO II data that were presented as a part of the BCIRG 006 analysis?

DR PEGRAM: The TOPO II data from BCIRG 006 are retrospective and are the result of a subset analysis of an interim analysis of the efficacy data; ergo, all of the data should be considered exploratory in nature and hypothesis generating (Press 2005; Slamon 2005). In terms of clinical practice, you have to understand the caveats and limitations of the data set before you make any decisions about its applicability to clinical practice.

The topoisomerase story began with Hy Muss's publication in the mid-

FACULTY POLL QUESTION 1

Breast cancers that are HER2-positive should be subjected to assays of TOPO II, which should be used to select chemotherapy regimens to combine with trastuzumab, specifically whether to include an anthracycline.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

1990s of a CALGB trial looking at different doses of doxorubicin-containing adjuvant chemotherapy (Muss 1994). Among patients with elevated HER2 expression, a dose effect of the different doses of doxorubicin was seen, whereas in the non-HER2-expressing subset no such effect was evident, suggesting that patients with HER2-positive disease uniquely benefit from adjuvant anthracyclines.

This is what really started the whole dogma in clinical practice that patients with HER2-positive disease uniquely benefit from anthracyclines and why clinicians began using HER2 as a marker to predict responsiveness to doxorubicin. However, the question from a research point of view is whether it's really HER2 that's driving this phenotype or something else.

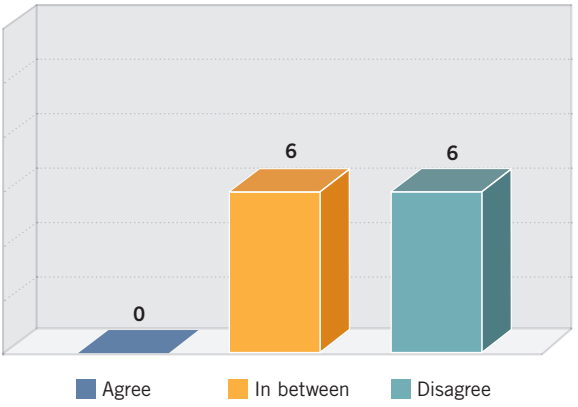
We talked to Giovanni Pauletti at UCLA, who was then mapping the HER2 amplicon, and he, as well as others, pointed out that the TOPO II gene is in close physical proximity to the HER2 gene on the long arm of chromosome 17 and that, on occasion, it is coamplified with the HER2 gene.

Inasmuch as TOPO II alpha is the target for the anthracyclines, perhaps this is what's driving the sensitivity phenotype to doxorubicin rather than HER2 itself.

A number of groups have tested this hypothesis in clinical trials, particularly in neoadjuvant clinical trials. We knew that we'd have an opportunity to test

FACULTY POLL QUESTION 2

Patients with HER2-positive, node-negative breast cancers that are less than 1 cm should generally receive adjuvant trastuzumab/chemotherapy as part of their treatment plan.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

this hypothesis in the BCIRG trial because we had both an anthracycline- and a nonanthracycline-containing trastuzumab arm in this three-arm trial, and amplification of HER2 was an eligibility criterion.

Mike Press has completed the TOPO II analysis for 2,120 of the 3,200 patients in the BCIRG 006 trial. In this cohort, he found that approximately 35 percent of the patients had coamplification of TOPO II and that this coamplification seemed to confer a therapeutic advantage to anthracycline-based trastuzumab regimens.

Patients with HER2-positive breast cancer that was not coamplified for TOPO II, who constituted two thirds of the patients, did not appear to have the same benefit and therefore may be ideal candidates for efficacious nonanthracycline-based trastuzumab regimens, thus avoiding potential cardiac toxicity.

Analysis of Coamplification of TOPO II in BCIRG Adjuvant Trial 0006

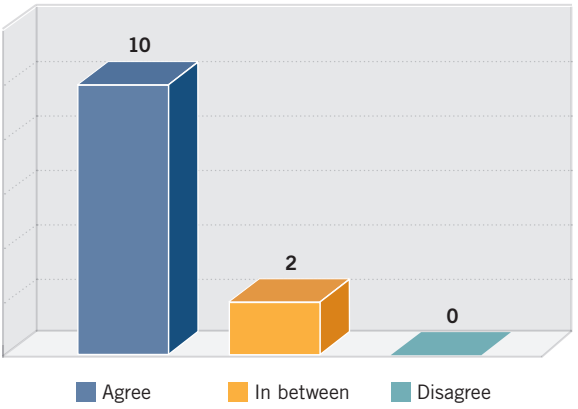
"Coamplification of the TOPO II gene with HER2 may identify a subset of the HER2 amplified that might benefit from an anthracycline, making it worth taking the risk of the cardiac dysfunction. Conversely, for 65 percent of the patients, there is no TOPO II amplification and these patients may be ideal candidates for an efficacious nonanthracycline-containing regimen."

SOURCE: Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2005. **Abstract 1**

DR LOVE: Dan, you chaired

FACULTY POLL QUESTION 3

Patients with HER2-positive, node-negative breast cancers that are 1-2 cm should generally receive adjuvant trastuzumab/chemotherapy as part of their treatment plan.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

the San Antonio session where Dr Slamon presented these data, and following the talk you made the comment that the TOPO II data were not ready for clinical practice. Could you explain?

DR HAYES: There could be a number of reasons for this to be a false-positive result, and there are a lot of reasons why it could be real. We need longer follow-up and we need other groups to evaluate this in their own trials.

DR PEGRAM: With the complete data set from the BCIRG 006 trial of all 3,200 patients and longer follow-up, the statistical power will be ever increasing, and it may yield a significant result in the end.

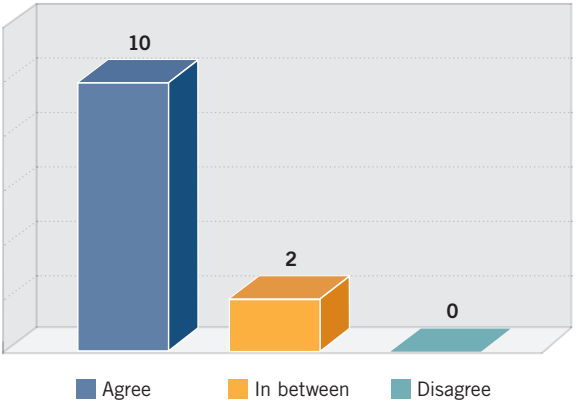
Tracks 8-10

DR LOVE: Dr Burstein, could you summarize the issue of concurrent versus sequential trastuzumab with chemotherapy?

DR BURSTEIN: We have a wealth of data from more than 10,000 patients assigned to randomized trials of chemotherapy with or without the addition of trastuzumab, all reported in 2005 and most now in publication (HERA Study Team 2005; Piccart-Gebhart 2005a, 2005b; Romond 2005a, 2005b). All of these trials had remarkably consistent results in terms of the improvement in hazard ratios with the addition of trastuzumab.

FACULTY POLL QUESTION 4

Adjuvant trastuzumab should generally be started concurrently with chemotherapy rather than sequentially.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

The interesting question has been whether it is better to give adjuvant trastuzumab concurrently with chemotherapy or sequentially. In the North American Intergroup trial, NCCTG-N9831, in arm A patients received chemotherapy alone, in arm B they received AC followed by paclitaxel followed by trastuzumab, and in arm C the patients received AC followed by concurrent paclitaxel/trastuzumab and then ongoing trastuzumab.

The analysis comparing arms A and B showed no significant difference in event-free survival, whereas the preliminary comparison of arms B and C — concurrent versus sequential therapy — suggested roughly a 40 percent reduction in the risk of recurrence with concurrent therapy, which was statistically significant (Perez 2005).

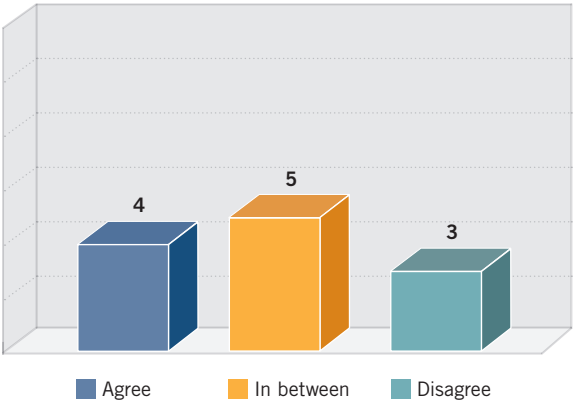
In the HERA trial, the patients were randomly assigned to zero, one or two years of trastuzumab, and all trastuzumab was given sequentially to chemotherapy. In contrast to the Intergroup findings, this trial showed roughly a 50 percent reduction in the risk of recurrence with sequential trastuzumab, as measured by disease-free survival (Piccart-Gebhart 2005).

DR LOVE: How does one reconcile the N9831 and the HERA data?

DR BURSTEIN: My own hypotheses are, first, that N9831 remains somewhat underpowered because of the lack of events. Therefore, it's possible, if not probable, that an ongoing analysis of arms A and B — that is, no trastuzumab

FACULTY POLL QUESTION 5

Adjuvant trastuzumab as monotherapy is a reasonable nonprotocol option in patients who are unfit to receive chemotherapy.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

versus sequential trastuzumab — might have shown more of an advantage.

Also, all the patients in the N9831 trial received anthracycline- and taxane-based therapy, whereas the HERA trial did not specify the adjuvant chemotherapy to be used.

Whereas the vast majority of patients in HERA received anthracycline-based regimens, only one quarter received a taxane, and those patients who received an anthracycline and a taxane received the least benefit from trastuzumab.

My interpretation of the N9831 and HERA trials is that concurrent therapy might be clinically more efficacious overall than sequential therapy, and sequential therapy is only modestly better than no

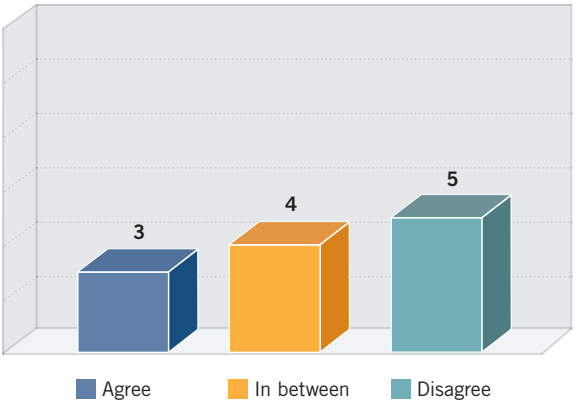
Concurrent versus Sequential Chemotherapy and Trastuzumab in the NSABP/NCCTG Joint Analysis

"Though early, the comparison suggested delayed administration of trastuzumab may be less effective than concurrent administration. Recent data from the Herceptin Adjuvant (HERA) trial showed that treatment with trastuzumab begun after the completion of chemotherapy substantially reduced the rate of recurrence relative to the rate associated with chemotherapy alone. Since only 26 percent of patients received taxanes in the HERA trial, comparison of those results with ours may be problematic."

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

FACULTY POLL QUESTION 6

Delayed adjuvant trastuzumab as monotherapy is a reasonable nonprotocol option in patients diagnosed up to three years previously.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

therapy in patients receiving anthracycline- and taxane-based treatment.

The BCIRG 006 trial also looked at concurrent trastuzumab, and those data suggest that trastuzumab concurrent with chemotherapy is beneficial (Slamon 2005).

DR LOVE: Do you feel single-agent trastuzumab is a reasonable option in the delayed adjuvant setting for patients who did not receive it previously?

DR BURSTEIN: For patients who completed anthracycline- and taxane-based chemotherapy six or 12 months previously and did not receive trastuzumab, few data suggest that the subsequent addition of trastuzumab will significantly lengthen their disease-free survival.

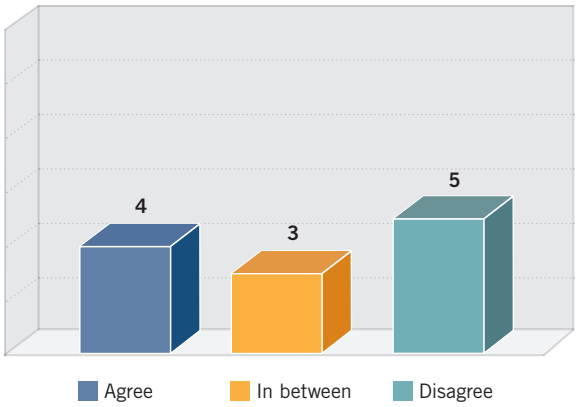
Track 11

DR LOVE: What about using a chemotherapy/trastuzumab combination without a taxane?

DR WINER: I'm not sure that absolutely every patient with HER2-positive breast cancer needs to receive AC followed by paclitaxel, particularly patients who don't want to receive a taxane or those with a lower risk of recurrence. Based on the HERA data, I believe it's reasonable to give four cycles of AC

FACULTY POLL QUESTION 7

Dose-dense AC → paclitaxel/trastuzumab is a reasonable nonprotocol adjuvant option for patients with HER2-positive disease.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

followed by a year of trastuzumab. The risk reduction is every bit as large as in the US trials.

DR LOVE: Can anyone identify a patient for whom you would consider adjuvant trastuzumab without chemotherapy?

DR VOGEL: I just had a patient with high-risk, node-negative breast cancer and a concomitant Epstein-Barr virus infection and hepatitis C. She is very well informed and deathly afraid of immunosuppression secondary to chemotherapy, and no one could convince her to receive chemotherapy.

For this patient, even in the absence of data, I thought it was better to administer trastuzumab monotherapy than not to give her trastuzumab.

DR LOVE: What about patients for whom you previously wouldn't have administered adjuvant chemotherapy because of age or comorbidities?

DR VOGEL: I would consider trastuzumab alone.

DR OSBORNE: I have not given single-agent trastuzumab in the adjuvant setting in practice, but I'm a believer in targeted therapy.

I believe tumors are driven by certain pathways and that, if you block that pathway, you will kill the tumor. We've seen that now with hormonal therapy.

For patients with ER/PR-positive tumors, except for those tumors that

are resistant, endocrine therapy is very good and chemotherapy doesn't add anything or it adds, at most, only a tiny benefit. I believe we will find that in the future, for patients with HER2-positive disease, HER2-targeted therapy without chemotherapy will be all we need. ■

SELECT PUBLICATIONS

Chang JC et al. **Induction of apoptosis without change in cell proliferation in primary breast cancers with neoadjuvant trastuzumab.** San Antonio Breast Cancer Symposium 2003;**Abstract 24**.

Geyer CE Jr. et al. **Cardiac safety analysis of the first stage of NSABP B-31, a randomized trial comparing the safety and efficacy of Adriamycin and cyclophosphamide (AC) followed by Taxol to that of AC followed by Taxol plus Herceptin in patients (Pts) with operable, node-positive (N+), HER-2 overexpressing breast cancer (HER2+BC).** San Antonio Breast Cancer Symposium 2003;**Abstract 23**.

HERA Study Team. **Trastuzumab (H: Herceptin) following adjuvant chemotherapy (CT) significantly improves disease-free survival (DFS) in early breast cancer (BC) with HER2 overexpression: The HERA Trial.** San Antonio Breast Cancer Symposium 2005;**Abstract 11**.

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**

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Press MF et al. **Topoisomerase II-alpha gene amplification as a predictor of responsiveness to anthracycline containing chemotherapy in the Cancer International Research Group 006 clinical trial of trastuzumab (Herceptin) in the adjuvant setting.** San Antonio Breast Cancer Symposium 2005;**Abstract 1045**.

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

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

Slamon D et al. **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 HER2 positive early breast cancer patients: BCIRG 006 study.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

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SECTION 2

ADJUVANT CHEMOTHERAPY

Tracks 1-12

Select Excerpts from the Discussion

Tracks 1-2

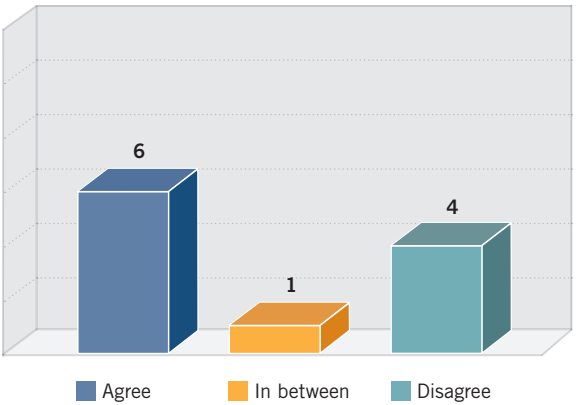
DR LOVE: Chuck, can you summarize your data with regard to the use of growth factor support during the administration of adjuvant chemotherapy?

DR VOGEL: In our study, docetaxel was chosen as a representative regimen that could cause somewhere around a 20 percent risk of febrile neutropenia at 100 mg/m^2. All three endpoints — febrile neutropenia, febrile neutropenia-related hospitalization and use of anti-infectives — showed dramatic improvement with the addition of pegfilgrastim (Vogel 2005).

Most people would agree with the new NCCN guidelines (Lyman 2005) stating that prophylactic growth factors should be used for patients with greater than 20 percent risk of febrile neutropenia. The use of prophylactic growth factors should also be considered in the intermediate-risk group, 10

FACULTY POLL QUESTION 8

Patients receiving regimens with intermediate risk (10%-20%) for febrile neutropenia should be treated with preemptive myeloid growth factors if they have significant comorbidities.



Note: One participant failed to respond to this question (n = 11).

SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

to 20 percent. Patients at low risk should not receive growth factors.

AC followed by docetaxel, AT and TAC (Martin 2005) all have very high febrile neutropenia rates, and prophylactic growth factors should be strongly considered with these regimens. AC is considered an intermediate-risk regimen, as is docetaxel/capecitabine.

FAC, FEC and TC are regimens associated with borderline to low febrile neutropenia rates. Certainly, dose densification of any of these would be a reason to use prophylactic pegfilgrastim, as would the avoid-

First and Subsequent Cycle Use of Pegfilgrastim

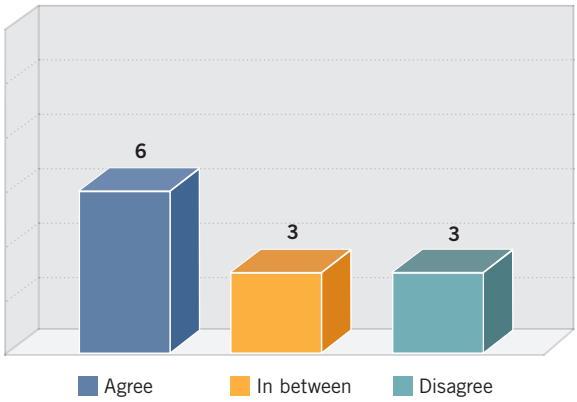
"Patients receiving pegfilgrastim, compared with patients receiving placebo, had a lower incidence of febrile neutropenia (1% v 17%, respectively; P < .001), febrile neutropenia–related hospitalization (1% v 14%, respectively; P < .001) and use of IV anti-infectives (2% v 10%, respectively; P < .001)... .

Early intervention with pegfilgrastim prevents febrile neutropenia by 94% and further prevents hospitalizations and use of IV anti-infectives by 80%. The use of pegfilgrastim with chemotherapy regimens with a moderate rate of febrile neutropenia, such as standard-dose docetaxel and combination docetaxel, doxorubicin, and cyclophosphamide chemotherapy, is warranted."

SOURCE: Vogel CL et al. *J Clin Oncol* 2005;23(6):1178-84. **Abstract**

FACULTY POLL QUESTION 9

When an oncologist elects to use adjuvant AC → docetaxel, the dose of docetaxel should be 100 mg/m², and pre-emptive myeloid growth factors should be utilized.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

ance of dose reductions and delays.

A third reason to consider it would be the risk factors that may cause patients to be at risk for febrile neutropenia.

DR BURSTEIN: I believe most of us would have a hard time consenting to a regimen associated with a one in five chance of a patient being hospitalized with febrile neutropenia compared to one that wasn't, simply for the administration of prophylaxis. So I don't find a problem with the recommendation for prophylactic treatment at 15 to 20 percent risk.

The problem is that we as a community haven't defined an acceptable level of febrile neutropenia. For instance, with nausea and vomiting, we all agree the desired goal is zero, so we liberally use prophylaxis.

For cancer pain, the goal is zero, so we liberally use pain medicine. We haven't said what we're willing to tolerate in the way of febrile neutropenia risk.

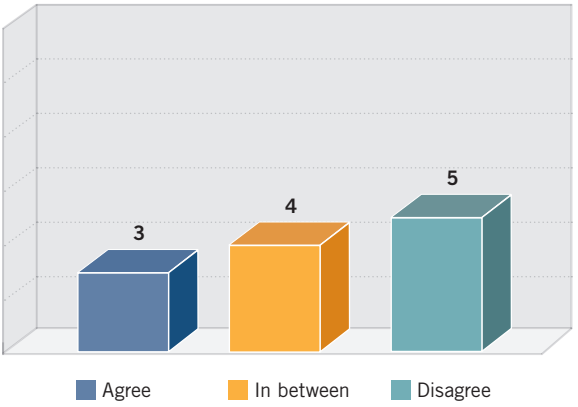
The only other anecdote I can offer is that as I administer AC every three weeks for patients destined to receive adjuvant trastuzumab, I'm struck by how many patients end up having dose delays and tweaks.

It's clearly more toxic than using dose-dense AC followed by paclitaxel with growth factor support.

This hasn't caused me to use G-CSF prophylactically in these settings, but it

FACULTY POLL QUESTION 10

Docetaxel/cyclophosphamide (TC) is generally a preferable regimen to AC.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

is impressive how predictable and clockwork-like every two-week AC with growth factor support is compared to other treatments.

I believe if you asked patients whether they would take a growth factor for a four percent decrease in their chance of febrile neutropenia, they'd all say yes. Whether that is cost effective is a totally different question.

Track 4

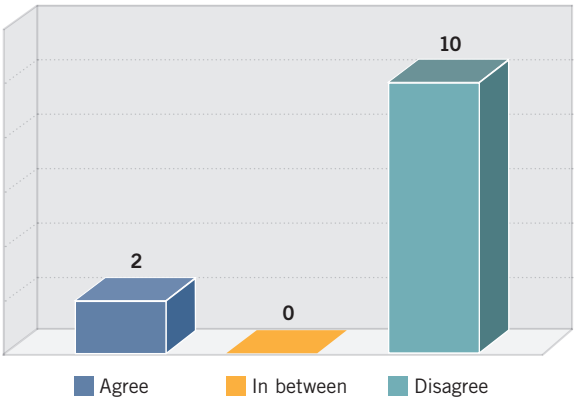
DR LOVE: Cliff, what's your take on the adjuvant trial data that Steve Jones presented at San Antonio comparing docetaxel/cyclophosphamide to AC?

DR HUDIS: We vary in our acceptance of new regimens based on the clinical endpoint bar they cross. Sometimes disease-free survival is absolutely fine. In other settings, people go ballistic if you don't have overall survival data as well. Here is a setting in which, at the second analysis, we have an improvement in disease-free survival and we still don't have an overall survival advantage.

I recall that when these data were presented for the first time at ASCO a couple of years ago, with widely separated curves, we were told that the trial would never be statistically significant because it was underpowered. So this

FACULTY POLL QUESTION 11

Docetaxel and docetaxel-based adjuvant regimens are generally about as safe and tolerable as paclitaxel and paclitaxel-based adjuvant regimens.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

result came as a bit of a surprise at San Antonio.

Having said all that, I have a bias. If I were a user of AC, I'd have a hard time not justifying TC. If nothing else, it's no more acutely toxic, by the randomized comparison, and it certainly should eliminate the small but meaningful long-term risk of cardiac toxicity. It will be interesting to see the long-term leukemia risk without the anthracycline.

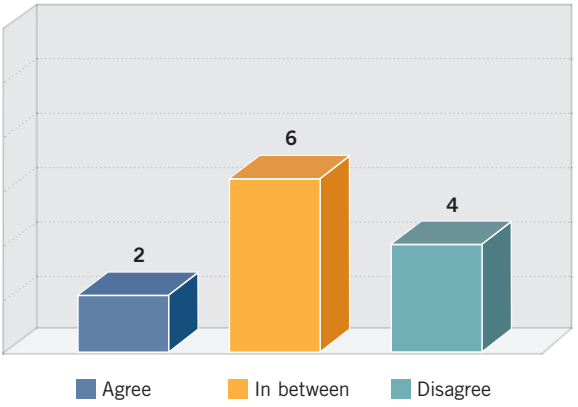
DR RAVDIN: The hazard ratio for recurrence shows a 24 percent proportional advantage in survival for docetaxel/cyclophosphamide, which is as big a step as we usually take in our clinical trials, and it shows a 36 percent improvement in disease-free survival. I believe the improvement in overall survival is real, and the correct interpretation isn't that it doesn't show a survival advantage but that it's underpowered to show a 24 percent advantage.

DR WINER: It's one study, not multiple studies, and it comes on the heels of the negative ECOG trial of AC versus AT (Goldstein 2005). I have a difficult time reconciling those two trials. If, in fact, the substitution of docetaxel for cyclophosphamide wasn't better, I find it certainly not inconceivable but a little funny that it's better than an anthracycline.

TC is a fine regimen to use, but I don't believe that it has to be the standard regimen to replace AC at the moment. I haven't chosen to use it as a standard regimen other than for patients for whom I don't want to administer an

FACULTY POLL QUESTION 12

In patients with ER-positive, HER2-negative, node-negative tumors under 1 cm, the Oncotype DX assay should be offered, and patients with high recurrence scores should be offered chemotherapy plus endocrine therapy.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

anthracycline.

DR HUDIS: This makes a point that there's no evidence that TC is inferior to AC, and it may well be safer in the long term. So I would feel little risk in substituting docetaxel for doxorubicin. I never use AC alone, so it's easy for me to say that. In my hands, everybody who receives AC also receives paclitaxel.

DR HAYES: If someone called me and said, "I'm going to use TC instead of AC," I would say, "I believe that's a perfectly fine regimen."

Tracks 5-6

DR LOVE: Cliff, ER status and response to chemotherapy have become a controversial issue. What's your viewpoint?

DR HUDIS: Don Berry started the discussion of the impact of ER status on chemotherapy outcomes in the modern era by performing an unplanned retrospective analysis of CALGB trials on the basis of ER status (Berry 2006).

He initially presented his three-study analysis at San Antonio in 2004, and compared the high-dose every four-week CAF regimen to the standard AC arm of CALGB-9344. He then studied the AC → paclitaxel arm of 9344

against the standard arm of the dose-dense 9741 trial.

For patients with ER-negative disease, the hazard for disease-free survival was significantly improved with each one of these steps — better CAF, addition of paclitaxel, dose-dense scheduling. Adding up the overall impact for ER-negative breast cancer, we see a profound chemotherapy effect.

In the subset of patients with ER-positive disease, the difference in each one of these steps was not statistically significant, but they were always favorable.

Five-Year Follow-Up of Intergroup Adjuvant Dose-Dense Trial C9741

"Long-term follow-up of CALGB 9741 reveals no change in the initial conclusions. Efficacy, disease-free and overall survival is the same with sequential versus concurrent doxorubicin and cyclophosphamide, but superior for dose-dense administration of these agents with paclitaxel. There is no change in the initial conclusions regarding toxicity. Q2week therapy is tolerable and, it's worth mentioning, faster by a third, and there is no evidence of any increase in long-term toxicity.

An unplanned retrospective subset analysis does clearly suggest a larger absolute benefit in ER-negative disease, but it is important to emphasize that it does not exclude a long-term benefit in those with ER-positive disease."

SOURCE: Jones SE et al. Presentation. San Antonio Breast Cancer Symposium 2005. **Abstract 40**

The point estimate for benefit is half the size for the patients with ER-positive disease compared to those with ER-negative disease. It is likely that it is still favorable, although the confidence interval does not exclude the possibility of no benefit at all.

To some degree, this has been wildly overinterpreted as suggesting that chemotherapy doesn't work in patients with ER-positive disease.

It simply doesn't say that. It says that the magnitude of the benefit is likely to be much smaller than for those with ER-poor disease.

The important point is that when people say that the addition of dose-dense scheduling in 9741 doesn't yield much among patients with ER-positive disease, they're really not comparing apples to apples when they then look at the TAC-FAC data (Martin 2005).

The TAC-FAC trial demonstrated hazard rates for risk reductions, which looked about the same in the ER-positives and the ER-negatives. The FAC control arm, of course, includes no paclitaxel or docetaxel.

You can't say that each individual step is or is not significant vis-à-vis another separate randomized trial. You can't compare these regimens head to head.

If you were to argue that you know to utilize TAC instead of dose-dense AC → paclitaxel in a patient with ER-positive, node-positive disease, then you're presuming to know the results of NSABP-B-38.

I would argue that there is equipoise on this question and that either regimen

is entirely appropriate for patients with ER-positive disease.

Tracks 9, 11-12

DR LOVE: Eric, what are your thoughts about the influence of ER status on the effects of chemotherapy, particularly with the newer adjuvant regimens?

DR WINER: It's very hard for me to get more excited about TAC as opposed to dose-dense AC followed by paclitaxel. I believe the bottom line is that if you take all patients with ER-positive breast cancer, the benefits of chemotherapy are dramatically less than in patients with ER-negative disease.

Estrogen Receptor Status and Outcomes of Modern Chemotherapy Among Patients with Node-Positive Breast Cancer

"Our study has … substantive clinical implications. First, although patients with ER-positive breast tumors may reasonably opt for chemotherapy, they should recognize that the benefits are not great as compared with those for patients with ER-negative disease. The benefits of intensive and extensive chemotherapy for unselected patients who have ER-positive disease treated with tamoxifen are modest at best. Whether such patients should opt for chemotherapy will depend on their attitudes toward the associated negative sequelae."

SOURCE: Berry DA et al. *JAMA* 2006;295(14):1658-67. **Abstract**

Almost certainly, some groups of women with ER-positive breast cancer derive no benefit and others probably derive every bit as much benefit as the ER-negative group. It's not going to be chemotherapy agent specific, particularly when we get down to the level of taxanes.

DR OSBORNE: This is such an important question because 60 percent of all patients have ER-positive/PR-positive disease. Will anyone conduct a randomized trial of chemotherapy versus no chemotherapy or endocrine therapy alone versus the addition of chemotherapy in that subgroup?

DR HAYES: The patients with node-negative, ER-positive disease in the TAILORx, or ECOG-PACCT-1, study will all be profiled by the Onco*type* DX assay. Those patients with a good recurrence score of 11 or lower will receive hormone therapy only.

Those with a high recurrence score of 25 and higher will all receive hormone therapy and chemotherapy of "dealer's choice." Those in the intermediate group will be randomly assigned to receive chemotherapy or not (investigator's choice). They then will all receive hormone therapy, also at the investigator's choice.

DR SLEDGE: One of the practical implications of this discussion is that it is almost impossible to sort all this out in any clinically reasonable time frame during a patient encounter. It would be wonderful to have strategies to facilitate this because there's no way that anybody in the community has enough

time for these kinds of conversations with the average patient. ■

SELECT PUBLICATIONS

Berry DA et al. **Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer.** *JAMA* 2006;295(14):1658-67. **Abstract**

Bria E et al. **Benefit of taxanes as adjuvant chemotherapy for early breast cancer: Pooled analysis of 15,500 patients.** *Cancer* 2006;106(11):2337-44. **Abstract**

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

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

Duric VM et al. **Patients' preferences for adjuvant chemotherapy in early breast cancer: What makes AC and CMF worthwhile now?** *Ann Oncol* 2005;16(11):1786-94. **Abstract**

Eiermann W et al. **Phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus doxorubicin and cyclophosphamide followed by docetaxel (AC → T) in Her-2/neu negative early breast cancer patients with positive axillary lymph nodes: Interim analysis of the BCIRG 005 study.** San Antonio Breast Cancer Symposium 2005;**Abstract 1069**.

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**.

Harlan LC et al. **Community-based use of chemotherapy and hormonal therapy for early-stage breast cancer: 1987-2000.** *J Clin Oncol* 2006;24(6):872-7. **Abstract**

Hudis C et al. **Five year follow-up of INT C9741: Dose-dense (DD) chemotherapy (CRx) is safe and effective.** San Antonio Breast Cancer Symposium 2005;**Abstract 41**.

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**.

Kummel S et al. **Randomised trial: Survival benefit and safety of adjuvant dose-dense chemotherapy for node-positive breast cancer.** *Br J Cancer* 2006;94(9):1237-44. **Abstract**

Kuru B et al. **A comparison of the outcomes of non-randomised chemotherapy regimens in node positive breast cancer.** *J Exp Clin Cancer Res* 2005;24(3):363-72. **Abstract**

Lyman GH. **Guidelines of the National Comprehensive Cancer Network on the use of myeloid growth factors with cancer chemotherapy: A review of the evidence.** *J Natl Compr Canc Netw* 2005;3(4):557-71. **Abstract**

Martin M et al; Breast Cancer International Research Group 001 Investigators. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13. **Abstract**

Martin M et al. **Multicenter, randomized phase III study of adjuvant chemotherapy for node positive breast cancer comparing 6 cycles of $FE_{90}C$ versus 4 cycles of $FE_{90}C$ followed by 8 weekly paclitaxel administrations: Interim efficacy analysis of GEICAM 9906 Trial.** San Antonio Breast Cancer Symposium 2005b;**Abstract 39**.

Roche H et al. **Five years analysis of the PACS 01 trial: 6 cycles of FEC100 vs 3 cycles of FEC100 followed by 3 cycles of docetaxel (D) for the adjuvant treatment of node positive breast cancer.** San Antonio Breast Cancer Symposium 2004;**Abstract 27**.

Vogel CL et al. **First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study.** *J Clin Oncol* 2005;23(6):1178-84. **Abstract**

SECTION 3

ADJUVANT ENDOCRINE THERAPY FOR PATIENTS WITH ER-POSITIVE TUMORS

Tracks 1-21

Select Excerpts from the Discussion

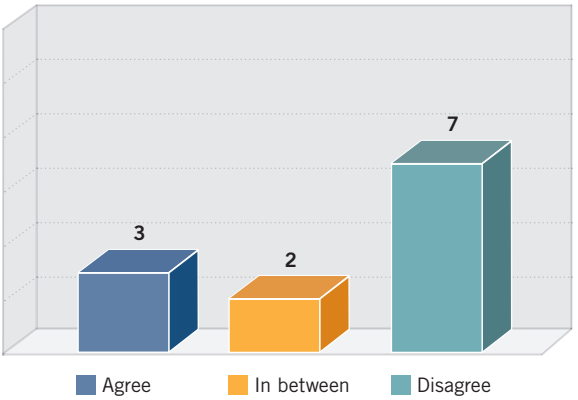
Tracks 1, 3

DR LOVE: Aman, what do you consider the optimal adjuvant endocrine approach for postmenopausal patients with ER/PR-positive disease?

DR BUZDAR: I believe the most effective therapy for patients with newly

FACULTY POLL QUESTION 13

Postmenopausal patients with strongly ER/PR-positive, node-negative tumors between 1-2 cm are optimally treated with tamoxifen for 2-3 years, followed by an aromatase inhibitor.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

diagnosed breast cancer should be offered up front. We are now looking at more than 30,000 patients who have been randomly assigned in the aromatase inhibitor trials, which clearly demonstrate that it doesn't matter where we put the aromatase inhibitors, they have better efficacy, a reduced risk of recurrence and a better safety profile. The most effective therapy should be offered up front to these patients.

If we look at the ATAC trial, which has the longest follow-up — and all of the other studies show the same thing — among patients with receptor-positive disease, initial endocrine therapy with an aromatase inhibitor reduces the risk of recurrence by 26 percent. The absolute number, at six years, is about 3.7 percent more women

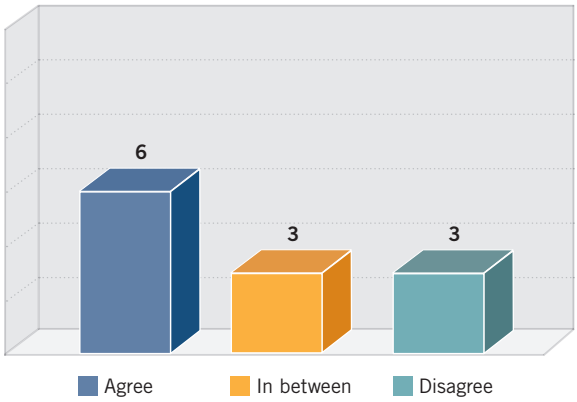
Clinical Implications of the ATAC Trial Results

"The present data suggest that it is not appropriate to wait 5 years to start an aromatase inhibitor. Furthermore, the higher rates of recurrence (especially in years 1–3), and the increased numbers of adverse events and treatment withdrawals associated with tamoxifen, lend support to the approach of offering the most effective and well tolerated therapy at the earliest opportunity. 5 years of anastrozole should now be considered as the preferred initial adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localised breast cancer."

SOURCE: Howell A et al. *Lancet* 2005;365(9453):60-2. **Abstract**

FACULTY POLL QUESTION 14

HER2 and PR status should not currently be used to select adjuvant endocrine therapy.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

alive and free of disease if we start with an aromatase inhibitor (Howell 2005). BIG 1-98 shows a similar type of benefit (Thürlimann 2005).

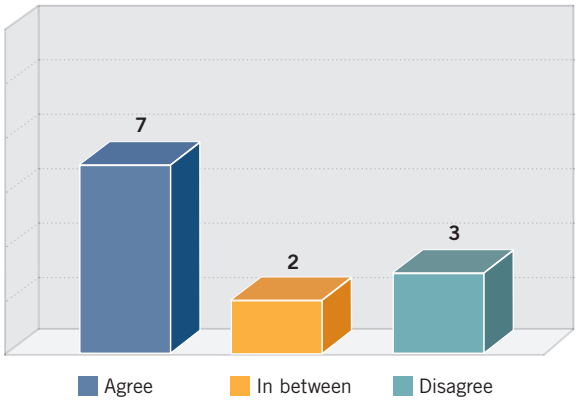
At times, physicians become confused when they see the proportional reductions in the studies that were initiated after two to three years or after the completion of five years of adjuvant tamoxifen therapy. You are comparing apples to oranges. You cannot take that type of data and compare it to the up-front data because in those types of studies, the patient population is different because the patients at high risk have relapsed.

We can also reduce the risk of recurrence if we start an aromatase inhibitor after two to three years of tamoxifen. This is a proportional reduction because the continuation of tamoxifen therapy is inferior to switching the patient to an aromatase inhibitor (Boccardo 2005; Coombes 2004; Jakesz 2005). The ATAC data show about 40 additional events in the first 2.5 years, which include distant and local recurrences (Baum 2003). I am not aware of any way to select those patients to whom we can safely offer tamoxifen therapy.

DR RAVDIN: Disease-free survival is always better on the aromatase inhibitor arm in all these trials, and the number of deaths is small and not statistically significant. When you have a disease-free survival advantage, that means overall you have more patients surviving. Irrespective of whether some of those patients drop off because of toxicity, patients on average are doing better at later time points.

FACULTY POLL QUESTION 15

Over the first two years after diagnosis, patients with both HER2-positive and HER2-negative, ER-positive tumors experience clinically significantly fewer relapses when treated with an AI compared to tamoxifen.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

Tracks 4-5, 7

DR LOVE: What about survival in trials of aromatase inhibitors compared to tamoxifen?

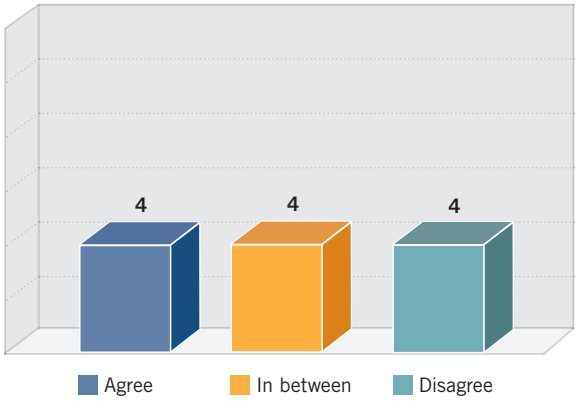
DR BUZDAR: Richard Gray took the published events in the adjuvant aromatase inhibitor trials — he did not have access to individual data points or the patients' information — and assessed disease-free survival and recurrences. Then he assessed deaths from cancer and noncompeting causes. Twenty percent fewer breast cancer deaths occurred among the patients treated with the aromatase inhibitors compared to the patients who were on tamoxifen or placebo, and the confidence interval did not include one.

Also, without question, every study shows a disease-free survival advantage with the aromatase inhibitors compared to tamoxifen, and the side effects are predictable compared to the unpredictable side effects that cannot be prevented with tamoxifen.

DR OSBORNE: I don't think we can be so dogmatic about this issue. We have 25 million patient-years of exposure to tamoxifen. I don't know how many we have for an aromatase inhibitor, but it's probably a twentieth. We don't know what's going to happen after five years with an aromatase inhibitor. You can

FACULTY POLL QUESTION 16

Over the first five years after diagnosis, patients with both HER2-positive and HER2-negative, ER-positive tumors experience clinically significantly fewer relapses with five years of an AI than with five years of tamoxifen or two to three years of tamoxifen followed by an AI.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

guess that there won't be any more long-term side effects, but we don't know.

We can't make dogmatic statements about which sequence is best in the absence of any information on toxicity or benefit. Given the information from the ATAC trial with hormone receptor analyses and the models suggesting the possibility of a huge benefit for tamoxifen followed by an aromatase inhibitor, depending on what happens after five years, I think we have to be open to the idea that either of these strategies might, in the end, be worthwhile.

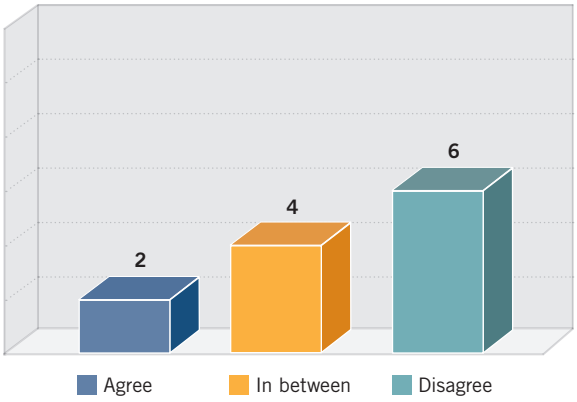
DR BURSTEIN: I continue to find MA17 to be the most intellectually fascinating of the adjuvant endocrine trials because it has shown us two things. First, it has shown that treatment beyond five years changes the natural history of the disease (Goss 2005a). That's been a very powerful finding. Second, the more recent data suggest that even gaps in the treatment can be followed up by late interventions (Goss 2005b). This is forcing us to realize that we're talking about a disease in which the outcomes matter over years five, 10 and 15, something that the most recent overview also suggested.

Tracks 10-11

DR LOVE: With regard to the duration of adjuvant therapy with an aromatase inhibitor, I assume people who start aromatase inhibitors up front are stopping after five years. Cliff, could you comment on this issue?

FACULTY POLL QUESTION 17

Adjuvant AIs should generally be continued beyond five years of treatment.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

DR HUDIS: The interesting thing about MA17 (Goss 2005a) and now MA17R (Goss 2005b) is the notion that you can reduce that hazard rate at almost any time in those first 10 years and maybe longer. This is motivation for chronic suppressive therapy. I have a bias toward leaving patients on a therapy that they're tolerating.

Clinical Implications of the Post Unblinding Results from MA17

"The principle that's enunciated by these data may be true not just for women post-tamoxifen, but for all women with hormone-dependent breast cancer. There are two points that I think are highlighted. The first is the chronic relapsing and ongoing risk of recurrence for hormone-dependent breast cancer patients. The second thing is that the introduction of effective endocrine therapy probably at any stage in the pathway of these women will result in benefit."

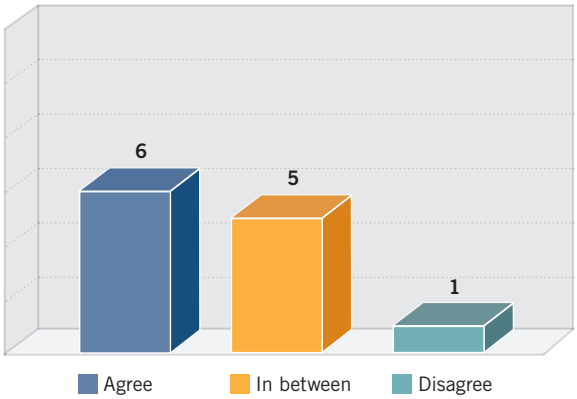
SOURCE: Goss PE et al. Presentation. San Antonio Breast Cancer Symposium 2005. **Abstract 16**

We stop tamoxifen for two reasons. One, we had clear evidence of accumulating toxicity, which we have yet to garner with the aromatase inhibitors, but it could be there. Two, we had one randomized trial that failed to demonstrate benefit (Fisher 2001).

DR RAVDIN: I believe it's analogous to the situation with five years of tamoxifen. Patients were reluctant to stop tamoxifen when we didn't have any

FACULTY POLL QUESTION 18

Premenopausal patients age 40 to 45 with ER-positive, node-positive tumors who cease menstruation with chemotherapy should be treated with tamoxifen for two years and then, if still amenorrheic and chemically postmenopausal, should be switched to an AI.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

data, and many elected to stay on the therapy. In this situation, we do have randomized trials that are addressing this question. I trust that the Data and Safety Monitoring Committees will stop those trials, the way they stopped the tamoxifen trials, if evidence appears of bad effects.

DR BURSTEIN: We've created a very awkward situation. If a woman begins an aromatase inhibitor up front, she receives five years of adjuvant endocrine therapy. If she were to come to you having started on tamoxifen, then after five years of treatment she would receive 10 years of adjuvant endocrine therapy. If she switched somewhere in between, she would receive either five or 10 years, depending on how you look at the literature. That seems somehow inconsistent.

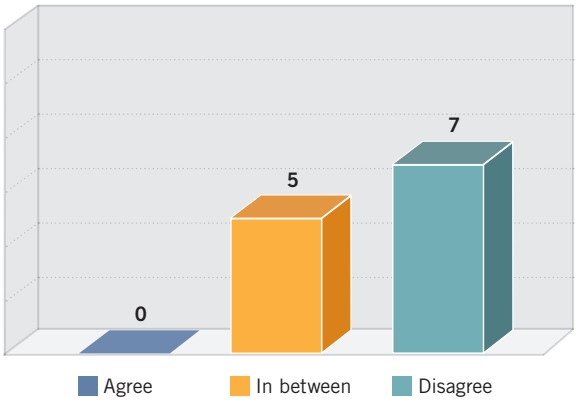
Tracks 12-14

DR LOVE: Kent, can you summarize what we know about predictors of response to hormonal therapy?

DR OSBORNE: One important issue is whether HER2 overexpression and PR loss predict for less benefit from tamoxifen than from an aromatase inhibitor. To me, the data are overwhelming that PR status predicts for response to tamoxifen.

FACULTY POLL QUESTION 19

Premenopausal patients with ER-positive, node-positive tumors who continue menstruation after chemotherapy should be offered (in addition to other options) ovarian suppression/ablation with an AI.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

In a prospectively designed SWOG trial published by Peter, patients with metastatic disease were treated with tamoxifen. The trial was designed to address the value of PR status. On multivariate analysis, PR status was found to be an independent predictor (Ravdin 1992).

That was the first prospective trial following another five or 10 studies published in the early 1980s and late 1970s suggesting that patients with PR-negative disease responded less well to tamoxifen.

What about HER2 overexpression and tamoxifen? Most, but not all, studies show less benefit if HER2 is overexpressed. Preclinical studies strongly support the clinical data. So I tend to believe the majority of the clinical data, along with the biology, that HER2 does predict for less responsiveness to tamoxifen.

We have very little data with the aromatase inhibitors. We have three separate neoadjuvant trials (Ellis 2001; Smith 2005; Zhu 2004) and a fourth (Dixon 2004) from Mike Dixon's group in Edinburgh that show very similar results. Whether it is letrozole or anastrozole, the responses are really quite good for patients with HER2-positive disease.

DR SLEDGE: I find the ER-PR data interesting biologically. Having said that, I don't know how much real-world relevance it has because I can't pick out any population of patients in whom tamoxifen does better than an aroma-

tase inhibitor. Because of that, my default — unless it's going to be the oddball patient who can't tolerate an aromatase inhibitor for some reason — will be to use an aromatase inhibitor.

Tracks 19-20

DR LOVE: Eric, can you comment on our current investigational strategies for premenopausal patients with ER-positive disease?

DR WINER: The issue of ovarian suppression with an aromatase inhibitor is being addressed in the SOFT and TEXT trials. At least some reason exists to be concerned that this could possibly be an inferior strategy.

In a woman who has a high level of estrogen in the premenopausal state, the estrogen levels go down after she receives ovarian suppression. Then adding an aromatase inhibitor and taking a woman down to extremely low levels of estrogen may add benefit. It's also possible that taking those two steps down is, in fact, no better than a single step.

Of course, from a toxicity standpoint — as I think we're learning from both TEXT and SOFT — that deep plunge into not only menopause but menopause and an aromatase inhibitor is a pretty tough maneuver for most of these patients. So for premenopausal women, I would strongly argue against using ovarian suppression and an aromatase inhibitor as an up-front strategy outside of a clinical trial.

What about the use of an aromatase inhibitor for a woman who is premenopausal at diagnosis, stops cycling soon after diagnosis and is now on tamoxifen for two years? This situation is much more analogous to the postmenopausal woman. She has now been without premenopausal levels of estrogen for two years.

It is more likely that substituting an aromatase inhibitor for tamoxifen after two years could be of additional benefit. We don't know that from any of the clinical trials that have been performed, but it seems more rational.

However, we've all seen in practice — and Hal actually has a whole series of these women — patients who have been without menstrual cycles for a couple of years go off tamoxifen and start cycling again.

DR HUDIS: I believe we're wrong to treat patients with aromatase inhibitors who are in their midforties and had no periods while on tamoxifen. The random sampling of their estradiol and FSH does nothing to change that.

DR OSBORNE: We've started measuring them, and I'm totally flabbergasted by the number of patients who are amenorrheic, even in their late forties, early fifties, who still have premenopausal levels of estrogen.

DR BURSTEIN: The point is that amenorrhea is menopause, but that's not a

very good definition for treating patients with aromatase inhibitors. We began to notice some patients — all of whom were women in their forties who had chemotherapy-induced amenorrhea — who were thought biochemically or on strong clinical grounds to be truly menopausal and were put on an aromatase inhibitor.

Usually, within six to 18 months they began to have menstruation again or had biochemical evidence of residual ovarian function, suggesting that they were not obtaining a therapeutic gain from an aromatase inhibitor. ■

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

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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 MA.17.** Presentation. San Antonio Breast Cancer Symposium 2005. **Abstract 17**

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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.** Presentation. San Antonio Breast Cancer Symposium 2005. **Abstract 44**

SECTION 4

SYSTEMIC MANAGEMENT OF METASTATIC DISEASE

Tracks 1-22

Select Excerpts from the Discussion

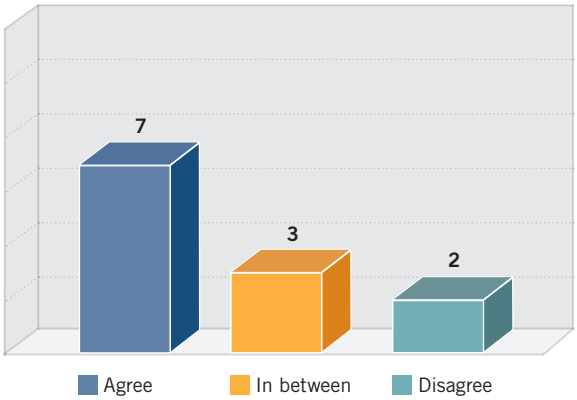
Tracks 1-2

DR LOVE: Dr Miller, would you comment on ECOG-E2100 and the treatment of patients who previously received an adjuvant taxane?

DR MILLER: This trial (Miller 2005a) specifically allowed patients who had had an adjuvant taxane as long as their disease-free interval was greater than 12 months. Approximately 18 percent of the patients were in this situation,

FACULTY POLL QUESTION 20

An effective treatment option for patients who develop cancer relapse after having received a taxane-containing adjuvant chemotherapy regimen is a taxane plus bevacizumab.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

and they were nicely matched between the two treatment groups.

The overall result in these patients was essentially a doubling of objective response rates, which translated into a highly significant, more than five-month improvement in progression-free survival. It's certainly fair to wonder if those results held up in the patients who received taxane-containing adjuvant therapy.

We have evaluated a variety of subsets, including the subset that received previous taxane-based therapy. Their hazard ratio was 0.38, compared to 0.51 for the overall group. This translated into an improvement in their progression-free survival from four months to 12.4 months. So, if you've had an adjuvant taxane, you do gain substantial benefit from a taxane plus bevacizumab.

Toxicity in this trial was

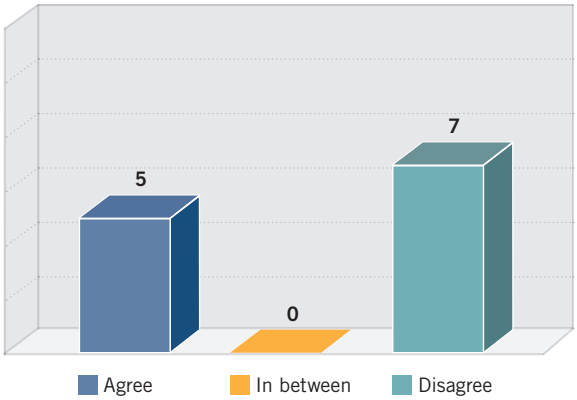
ECOG-E2100: Effect of Paclitaxel/ Bevacizumab in Patients Previously Treated with a Taxane

"Of note, patients who received previous adjuvant taxane therapy had the most striking improvement in their progression-free survival. This hazard ratio of 0.38 translates to an improvement in progression-free survival from just over four months to 12.4 months. The overall survival data for E2100 remained premature, with only 275 events reported."

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

FACULTY POLL QUESTION 21

Patients with ER/PR/HER2-negative tumors should be offered bevacizumab plus chemotherapy in the first-line setting. One acceptable treatment option is capecitabine/bevacizumab.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

also favorable, with 15 to 16 percent of patients developing hypertension that needed therapy and no major differences in the chemotherapy-related toxicities. There were slight increases in fatigue and neuropathy, likely because patients were responding for longer durations, so they received more exposure to chemotherapy.

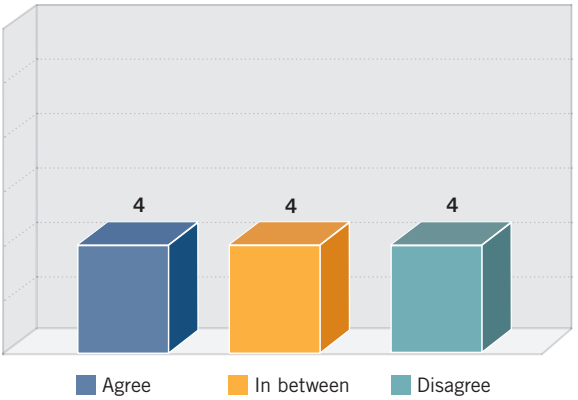
In whom would I not consider this combination? One obvious group is patients who were not eligible for the E2100 trial, who received an adjuvant taxane and relapsed in fewer than 12 months. Those patients actually were allowed to enroll in the previous randomized trial of capecitabine with or without bevacizumab as their first therapy (Miller 2005b).

This previous trial also found increases in response rate by adding bevacizumab to capecitabine but no difference in progression-free survival. There were, however, huge differences in the patient populations, particularly in the extent of previous chemotherapy. About a third of patients in E2100 were completely chemotherapy-naïve, including no adjuvant chemotherapy and much less exposure to previous taxanes.

I believe the biggest difference between the trials is a matter of timing — as breast cancers progress, they express a greater number and have greater redundancy in the proangiogenic pathways. This explanation fits the E2100 data nicely and is why, for this patient, I would strongly recommend a taxane and bevacizumab-containing regimen rather than some other chemotherapy

FACULTY POLL QUESTION 22

Patients with ER/PR/HER2-negative tumors should be offered bevacizumab plus chemotherapy in the first-line setting. One acceptable treatment option is combination carboplatin/paclitaxel/bevacizumab.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

combination and holding bevacizumab in reserve until further progression.

Tracks 3-5

DR LOVE: Many oncologists tell us they're confused about where bevacizumab fits into the management of metastatic breast cancer. Does that surprise you, Kathy?

DR MILLER: It has surprised me from the day I presented these results. No other trial in first-line treatment for metastatic breast cancer has found this degree of improvement in outcome with this minimal toxicity (Miller 2005a). The only study that has come close is the original trastuzumab randomized trial (Slamon 2001), and that was hampered by a significant rate of congestive heart failure in one of the two

ECOG-E2100: Conclusions

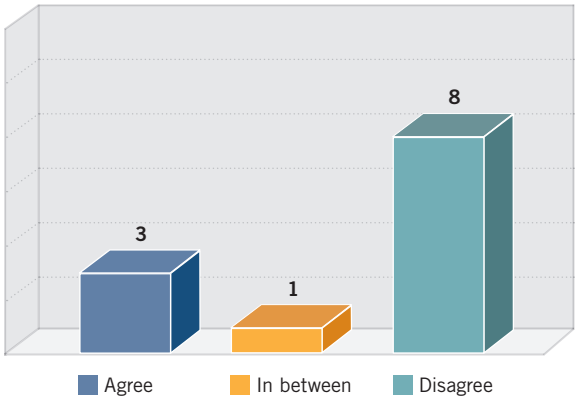
"In conclusion, this is a positive study. The addition of bevacizumab to paclitaxel significantly prolongs progression-free survival and more than doubles the objective response rate. Overall survival data are still premature, and longer follow-up will be needed to assess the true impact of this therapy...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

It's now time to move bevacizumab into the adjuvant setting and explore its role there. We'll also need to continue to develop methods to identify those patients who are most likely to benefit from VEGF targeted therapies."

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

FACULTY POLL QUESTION 23

Patients with ER/PR/HER2-negative tumors should be offered bevacizumab plus chemotherapy in the first-line setting. One acceptable treatment option is combination capecitabine/paclitaxel/bevacizumab.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

arms.

I don't recall anyone looking at those results and saying, "It's only five months and we just don't know where this fits in. We have so many other things to give patients."

No other drugs were approved for breast cancer between then and the E2100 data. And this trial applies to a much larger subset of our patients. I quite honestly don't understand the reluctance.

DR BURSTEIN: I like the E2100 study, and it's an exciting proof of principle. I would use the regimen for treatment of the patient who had received an adjuvant taxane, but let me ask you

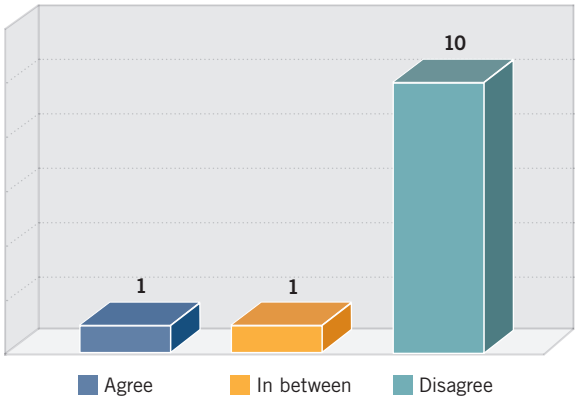
ECOG-E2100: Safety and Tolerability of Paclitaxel/Bevacizumab

"The addition of bevacizumab to paclitaxel had the expected toxicities. Approximately 15 percent of patients developed hypertension requiring therapy, and in our patient population the rates of significant thromboembolic events, serious bleeding, or Grade three and four proteinuria were extremely rare. Bevacizumab did also not meaningfully influence the chemotherapy-associated toxicities. There was a small nonsignificant increase in the rates of Grade three neuropathy, and a significant though relatively low increase in the rates of fatigue. There was no influence in myelosuppression, and no apparent effect on cardiac function."

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

FACULTY POLL QUESTION 24

Patients with metastatic disease experiencing prolonged useful responses to bevacizumab plus chemotherapy should be presented with the option of continuing bevacizumab and switching to another chemotherapy.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

to play it out a little more. For instance, we have trials of combination versus sequential chemotherapy with a statistically significant survival advantage. I have, in general, resisted those, believing that we should treat sequentially.

One of the challenges your two trials pose for me is that they suggest a relatively specific window during which bevacizumab is effective. Conceptually, I find it hard to imagine that the drug works in the first-line setting but not elsewhere.

DR MILLER: It may be hard to explain, but these are the data we have, and it does fit the biology. We also have data suggesting that increases in proangiogenic peptide expression result in a relative resistance to chemotherapy. These become more numerous as patients progress, and this makes inhibiting any single factor inherently less effective, which is different from the chemotherapy trials.

The other difference is that the chemotherapy trials usually have only found a progression-free survival improvement of two to three months at the cost of substantial increases in toxicity. I suspect we will have an overall survival improvement; it's just too early to know yet.

This should not be taken as an assumption that no survival advantage exists, merely that it's an effective therapy. We have to wait longer to get those results.

DR WINER: I, too, am enthusiastic about bevacizumab, but three issues have led people to be less enthusiastic. One is that this applies to a large subset of patients. I believe people would be happier if this could be targeted to a specific group. People are also less enthusiastic because of not knowing quite what to do with the results of the capecitabine trial. The third and very real issue is the cost.

DR HUDIS: Unfortunately, the cost got in everyone's way. This is the first drug that forced a change in dispensing practices for our whole institution. We can't write for it without pre-approval from the insurance company, and we've never had that for any agent in our setting.

The second issue, which we don't talk much about, is that although the toxicities are manageable and those of us who used the drug got used to it, it represents a little bit of a change in practice patterns for oncologists. They're suddenly paying attention to proteinuria and hypertension.

DR MILLER: I don't deny that the cost is an issue. But the cost is not markedly different from the cost of trastuzumab when it was first available, and I don't recall reluctance with that agent.

When I've heard people talk about their reluctance, they haven't said, "If cost were not an issue, I would use it in a heartbeat." So I think cost is one component of the reluctance but certainly not the only one.

DR SLEDGE: Physicians like to be able to say, "This drug will improve your survival by X months." I think part of the problem with this drug is that we don't have those survival data yet.

From a quality-of-life standpoint, those of us who have used it have found it to be an incredibly easy drug for patients, with truly trivial toxicity compared to every single chemotherapeutic agent in the therapeutic armamentarium. It also more than doubles the response rate.

DR OSBORNE: I believe the cost of this drug has perhaps crossed the line in the eyes of private practitioners. We're beginning to realize there's a limit.

Track 5

DR LOVE: Kathy, what has been your reaction to the discussions regarding the cost of bevacizumab?

DR MILLER: I am frustrated by the inconsistency in how we view costs of therapies. In many settings we routinely use growth factors and expensive supportive care agents for regimens that have a low risk, when the guidelines wouldn't suggest it, and people order lots of horrendously expensive combined PET/CT scans, which don't add to treatment.

So I have a problem hearing about the cost of one specific drug that had a

huge benefit in this trial. I'm not arguing that we shouldn't consider the costs. Of course, they're important for all of our practices, our individual patients and our society. But to consider the costs in a vacuum only as they apply to one drug is a mistake.

Tracks 6-7

DR LOVE: Cliff, are you using capecitabine combined with bevacizumab?

DR HUDIS: Absolutely. The data are not really negative (Miller 2005b). The response rate is higher. A principle has been clearly established, in my mind, that bevacizumab adds to chemotherapy in a cohort of patients.

DR BURSTEIN: We should be in dialogue about where and how best to use these therapies, and I take Kathy's point that the expense is not unique to this drug. There is a compelling reason to think we often overtreat in the way of PET scans, stereotactic radiosurgery the third or fourth time around for brain metastases, or unbelievable efforts at other supportive care, which have a relatively modest cost-effective gain. I believe we should engage in a serious dialogue about these issues.

Tracks 11-12

DR LOVE: George, what efforts are being made to determine the role of bevacizumab with other agents in the first- and second-line settings?

DR SLEDGE: The XCaliBr trial uses front-line capecitabine with bevacizumab for patients who have received basically any adjuvant chemotherapy.

This trial has recently been expanded to approximately 112 patients, and it should have decent confidence intervals for response rate and progression-free survival.

This trial also recommends that patients cross over to a second-line chemotherapy, either vinorelbine or paclitaxel, at the investigator and patient's choice, with bevacizumab.

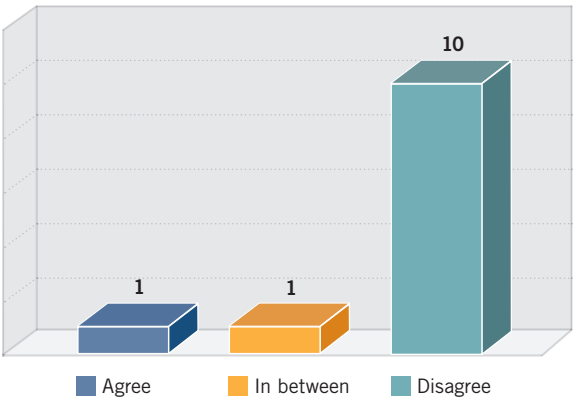
So we will obtain data from this trial in terms of second-line responses to either vinorelbine or paclitaxel with bevacizumab. The data should be available to us some time next year.

Resistance remains a big issue for anti-angiogenic therapy in just about every disease that we've evaluated it in to date, and it's certainly not surprising that it will continue to be a problem.

Therefore, it's not surprising that crossing over to another chemotherapy agent with bevacizumab is unlikely to make much difference.

FACULTY POLL QUESTION 25

One acceptable nonprotocol option for patients with ER-positive tumors who develop progressive metastatic disease on an AI is to continue the AI and add in fulvestrant.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

Track 16

DR LOVE: John, do we have any information about combination hormonal therapy with fulvestrant and an aromatase inhibitor in the metastatic setting?

DR ROBERTSON: This is being evaluated in the ongoing SoFEA trial, in which the aromatase inhibitor is continued and fulvestrant is added on in the hope that by keeping down the estradiol level, more fulvestrant will compete with the receptor and perhaps give a better initial response or even longer-term control. But I'm not sure that we're going to see the result of this study in our lifetime.

Theoretically, fulvestrant with an aromatase inhibitor is as good as any other option. The problem with this combined approach is that we have no human data for any combination. We have nothing to suggest that this combination will be better.

Track 18

DR LOVE: What's the evidence supporting a loading dose of fulvestrant?

DR ROBERTSON: First, tamoxifen reaches a steady state at two weeks, whereas fulvestrant can take up to four or five months to reach a steady state.

Another issue, which I believe makes people slightly uncomfortable, is that in the second-line study, fulvestrant was just as good as anastrozole after tamoxifen (Howell 2002; Osborne 2002).

The first-line study, however, had two problems. Although it was a randomized study, 10 percent more people were assigned to fulvestrant versus tamoxifen.

In addition, in the intention-to-treat population, the time-to-progression curve for the initial fulvestrant arm drops down much more quickly than the curve for tamoxifen, and then, after the first six months, it runs parallel to tamoxifen. It makes one think that perhaps the drug is not on board in that first six months.

The question is: why would you see this in the first-line and not the second-line setting? You could argue that some of those patients in the second-line setting may be having a tamoxifen withdrawal effect while the fulvestrant levels are going up.

DR HAYES: I would argue that this drug clearly has a dose-response curve. Kent's trials demonstrated that the lower dose had to be dropped because it was ineffective (Osborne 2002).

In addition, I don't know any drug we use for which we don't want to use the right dose. It's clear from the pharmacokinetics of this drug that if you use the loading dose, you reach what should be acceptable levels faster. We don't use a loading dose for tamoxifen because patients take it every day.

Track 21

DR LOVE: Hal, what investigational strategies are being pursued with fulvestrant?

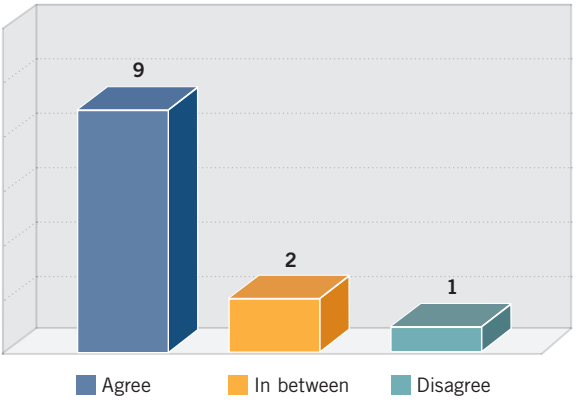
DR BURSTEIN: We have a wealth of endocrine options coming forward. How to integrate fulvestrant is one of them. Many of us are starting to think about it in the adjuvant setting.

What's disappointing is that we don't really have a surrogate, short of a large, randomized, prospective study that will take a decade to finish, to tell us what to do with this drug.

It's at the fundamental level of failure of what our laboratory correlative studies have allowed us to do so far because we're still left having to resort to tremendously large studies to answer these questions. It's a real barrier for more rapid integration.

FACULTY POLL QUESTION 26

In a nonprotocol setting, a loading dose of fulvestrant should generally be utilized.



SOURCE: Survey of Think Tank Participants, February 25, 2006, Miami, Florida.

The question is: fulvestrant with or without an aromatase inhibitor or fulvestrant after an aromatase inhibitor in the adjuvant setting or combinations thereof?

Track 22

DR LOVE: Eric, can you talk about the delayed fulvestrant trial?

DR WINER: This is not fully hashed out by any means.

We've prepared a concept of a trial looking at fulvestrant in the extended adjuvant setting for women who have received five years of an aromatase inhibitor or who have received tamoxifen followed by some amount of an aromatase inhibitor.

The concept would be to compare fulvestrant with either no therapy or a placebo in those women and potentially allow women to start on the therapy even after a break of a year or two or three years, with the idea that whenever a woman with ER-positive breast cancer starts a new endocrine therapy, a benefit and a decrease in events may occur. ■

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

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the BCIRG 006 trial, amplification of the topoisomerase II-alpha gene was significantly correlated with responsiveness to _____-containing chemotherapy.**
   a. Doxorubicin
   b. Paclitaxel
   c. Docetaxel
   d. Cyclophosphamide

2. **The most recent NCCN guidelines state that prophylactic growth factor support should be initiated for patients receiving adjuvant chemotherapy regimens with greater than a 20 percent risk of febrile neutropenia.**
   a. True
   b. False

3. **Dr Don Berry recently published in *JAMA* an unplanned retrospective analysis of three studies, which evaluated the benefits of adjuvant chemotherapy according to ER status.**
   a. True
   b. False

4. **At the 2005 San Antonio meeting, Stephen Jones reported a 36 percent improvement in disease-free survival for adjuvant docetaxel/cyclophosphamide versus AC.**
   a. True
   b. False

5. **The ECOG-PACCT-1 trial will evaluate hormonal therapy versus chemotherapy for patients with node-negative, ER-positive disease who have Onco*type* DX recurrence scores in the intermediate range.**
   a. True
   b. False

6. **In the ATAC trial, anastrozole was found to reduce the time to recurrence by 26 percent compared to _____ in postmenopausal women with hormone receptor-positive disease.**
   a. Placebo
   b. Letrozole
   c. Tamoxifen
   d. Exemestane
   e. None of the above

7. **MA17 evaluated the role of letrozole after _____ years of adjuvant tamoxifen.**
   a. Two
   b. Three
   c. Five
   d. 10
   e. None of the above

8. **ECOG trial E2100 evaluated paclitaxel with or without bevacizumab as _____.**
   a. Adjuvant therapy
   b. First-line therapy of metastatic disease
   c. Second-line therapy of metastatic disease

9. **The addition of bevacizumab to paclitaxel resulted in a doubling of response rate compared to paclitaxel alone.**
   a. True
   b. False

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

EVALUATION FORM

Breast Cancer Update — Think Tank Issue 1, 2006

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

Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of switching to or sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment 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
- 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

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

EFFECTIVENESS OF THE SPECIFIC SEGMENTS OF THIS PROGRAM

Which of the following modules did you find particularly relevant to your practice?

- ☐ Adjuvant Therapy for Patients with HER2-Positive Tumors
- ☐ Adjuvant Chemotherapy
- ☐ Adjuvant Endocrine Therapy for Patients with ER-Positive Tumors
- ☐ Systemic Management of Metastatic Disease

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

☐ Audio CDs ☐ Audio tapes ☐ Downloaded MP3s from website

EVALUATION FORM

Breast Cancer Update — Think Tank Issue 1, 2006

REQUEST FOR CREDIT — please print clearly

Name:..... Specialty:.....

Degree:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ BS ☐ RN ☐ PA ☐ Other.....

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

Street Address:..... Box/Suite:.....

City, State, Zip:.....

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

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

Signature: ..... Date:.....

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

☐ Yes ☐ No

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

.....

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

.....

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

.....

Additional comments about this activity:

.....

FOLLOW-UP

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

☐ Yes, I am willing to participate in a follow-up survey.

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

BCUTT0106

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

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Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@ResearchToPractice.net
For CME Information	Email: CME@ResearchToPractice.net

This program is supported by education grants from Amgen Inc, AstraZeneca Pharmaceuticals LP and Genentech BioOncology.

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Last review date: May 2006
Release date: May 2006
Expiration date: May 2007
Estimated time to complete: 4.25 hours