Breast Cancer® UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

SPECIAL ISSUE

Proceedings from a Clinical Investigator "Think Tank"

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STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. To bridge the gap between research and patient care, *Breast Cancer Update* utilizes a moderated forum 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 Drs Buzdar, Chlebowski, Dickler, Ellis, Goss, Jahanzeb, Leyland-Jones, Mackey, Pegram, Pritchard, Sparano and Winer on the integration of emerging clinical research data into the management of breast cancer.

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This program is supported by education grants from Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Genentech BioOncology and Sanofi-Aventis.

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SECTION 1

Adjuvant Endocrine Therapy

Tracks 1-10

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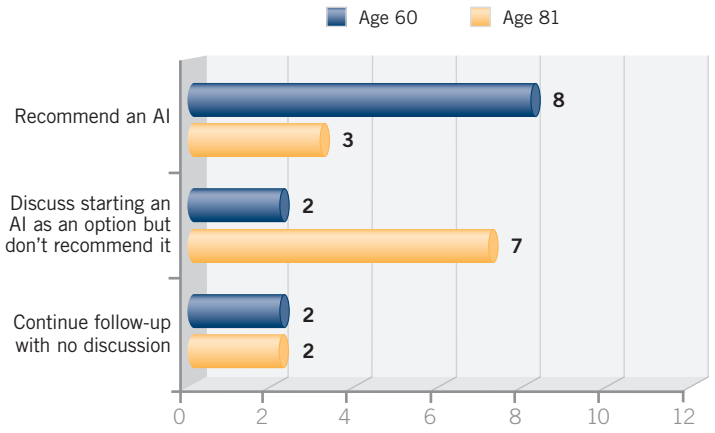
FACULTY POLL QUESTIONS 1 AND 2

A patient treated eight years ago for an ER-positive, PR-positive, HER2-negative tumor with four positive nodes received chemotherapy followed by tamoxifen for five years and now presents for routine follow-up, doing well off tamoxifen for three years. You would:



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

Select Excerpts from the Discussion

Track 1

DR LOVE: Kathy, would you recommend delayed endocrine therapy in this situation?

DR PRITCHARD: For reasons I don't understand, data from MA17 are now showing that the women who were initially on placebo and crossed over to letrozole after the trial stopped have actually done better than the women who were originally assigned to placebo. That's not a randomized comparison, but I believe it gives us a clear signal that starting an aromatase inhibitor even one, two or three years after finishing tamoxifen still has an effect.

I believe using an aromatase inhibitor for either of these patients is logical, and I probably would recommend one in both cases. The question with the older patient is, how long does the average 81-year-old live? Still, she's at high risk and Muss's paper suggests that older women don't experience many quality-of-life problems on aromatase inhibitors, at least in the short term (Muss 2006).

DR GOSS: I feel strongly that we have a large, prevalent pool of women in the world with hormone receptor-positive breast cancer and that many of them have been incompletely treated. We're seeing a benefit across a huge spectrum of time for the application of endocrine therapy, and I believe clinicians should ask, "Why shouldn't I use it?" rather than, "Why should I use it?"

I see patients being excluded unnecessarily based on age, preexisting osteoarthritis and other trivial reasons. Clinicians are dismissing the application of a treatment that's highly effective, and I believe this problem must be addressed by the oncology community worldwide.

DR LOVE: Is there an upper limit, in terms of the number of years since completing tamoxifen, at which you feel it's been too long to consider additional adjuvant endocrine therapy?

DR GOSS: The data are confined to a range of one to seven years, from our postunblinding analysis. It was previously shown, biologically, that if you initiate tamoxifen at any time in the pathway of this follow-up, you can effect benefit, and I believe that's true here.

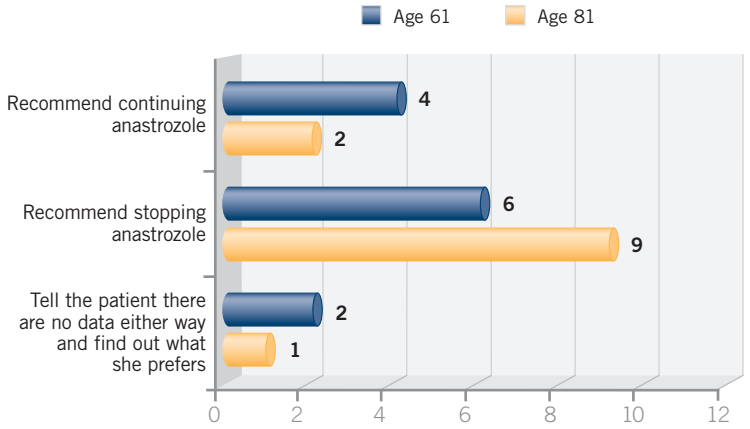
Tracks 2, 5

DR LOVE: Matt, when you see a postmenopausal patient who was diagnosed 10 or 15 years ago and never received adjuvant endocrine therapy, do you consider therapy now?

DR ELLIS: That presents a conundrum. I'm certain Paul would agree that a point exists at which offering endocrine therapy is inappropriate. One would imagine that it could be as far out as 15 to 20 years. Certainly the idea that

FACULTY POLL QUESTIONS 3 AND 4

A patient was treated five years ago for an ER-positive, PR-positive, HER2-negative tumor with four positive nodes. She received chemotherapy followed by anastrozole for five years and has tolerated therapy without major difficulties. You would:



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

patients with ER-positive disease have a poorer prognosis beyond five years underscores the fact that intervention could be beneficial.

DR WINER: I don't object to administering an aromatase inhibitor to the elderly woman eight years after tamoxifen, and I would agree that her median survival is probably in the range of six to seven years.

However, it's extremely unlikely that a modeling approach or clinical trial would demonstrate a survival advantage here. I expect the disease-free survival advantage will be modest for an 81-year-old patient, depending on her competing morbidities, so I'm not going to push her to receive an aromatase inhibitor at this point.

DR LOVE: Aman, how much of a delay are you comfortable with?

DR BUZDAR: I'm comfortable within the MA17 period, which was approximately six months. Although our gut reaction is that we should be prescribing endocrine therapy to these patients, currently we don't have strong evidence to support that, except for the MA17 data, which came after code breaking and the patients were given a choice — they were not randomly assigned.

I believe we need to wait until we have prospectively randomized studies before we offer all patients delayed therapy.

DR GOSS: Although I agree that a randomized trial would be preferable, it'll be many years before we have such data, and it's difficult to imagine that with the strong biological effect we're seeing in MA17 — albeit not Level 1 evidence — there's no likelihood of affecting events for patients with hormone receptor-positive disease in follow-up.

Tracks 6-7

DR LOVE: In the clinical setting, how do you approach the patient who has completed five years of an adjuvant aromatase inhibitor?

DR SPARANO: I try to clarify for the patient which of the recommendations that we are making are data driven, with unequivocal proof that this is the appropriate choice, and which of our recommendations are not supported by clear data but are based on our intuition, and then work with the patient to devise a plan that best suits the situation.

For a patient who's completed five years of up-front aromatase inhibitor therapy, we don't have the data, so my approach is to consider the patient's risk of recurrence as it was estimated at baseline and take into account how well the patient tolerated the aromatase inhibitor, her age, comorbidities, et cetera.

DR MACKEY: In the clinical setting, I believe the continuation of an aromatase inhibitor beyond five years is purely speculative. We have a good grasp regarding the toxicities with five years of an aromatase inhibitor — some of the best data come from the ATAC trial — but some of the side effects could be cumulative over time (ATAC Trialists' Group 2006).

For example, we probably expect higher degrees of bone toxicity with extended aromatase inhibitor therapy, but I believe one of the biggest worries would be neuropsychiatric complications of long-term estrogen deprivation. A lot of data from epidemiologic studies show that lower serum estrogens are associated with a higher risk of dementia.

In my practice, I don't continue patients beyond five years of an aromatase inhibitor because of the lack of data and the potential for long-term effects.

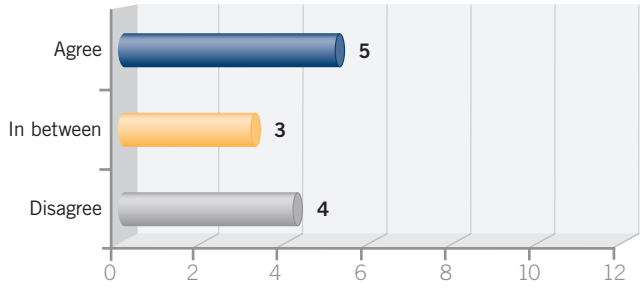
DR LOVE: Rowan, could you address this issue of cognitive functioning?

DR CHLEBOWSKI: Evidence from a number of preclinical, observational studies suggested that estrogen, especially exogenous estrogen, was associated with favorable effects on cognition. Then the data from the Women's Health Initiative (WHI) randomized trial, with more than 16,000 otherwise healthy postmenopausal women, demonstrated an increase in strokes associated with estrogen use, and among women 65 years of age or older, dementia was increased (Chlebowski 2006).

Therefore, we have to worry that anything that increases arterial vascular events will have an unfavorable effect on cognition, and in the ATAC trial,

FACULTY POLL QUESTION 5

I don't consider either PgR or HER2 when deciding on the choice of adjuvant endocrine therapy for postmenopausal women.



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

we see that anastrozole carries a significantly reduced risk of arterial vascular effects compared to tamoxifen (ATAC Trialists' Group 2006).

Thus, I'm less concerned about this issue. We don't know what the effect of aromatase inhibitors is on cognition, but I would need a new signal to become concerned about that side effect with the long-term use of aromatase inhibitors.

DR LOVE: MJ, one of the major options for patients completing five years of an AI is participation in NSABP-B-42, which is evaluating an additional five years of AI therapy. However, in a nonprotocol setting, how do you approach women who are reaching five years on an aromatase inhibitor in your practice?

DR JAHANZEB: I tell patients that emerging evidence shows that their risk of recurrence persists and we don't know whether it's more beneficial to continue or stop the aromatase inhibitor. Then, if they choose to continue, it's informed consent, and I find that approximately a third of my patients continue the aromatase inhibitor, whereas the other two thirds don't.

Tracks 8-9

DR LOVE: Mark, do you consider the tumor's PR or HER2 status when selecting adjuvant endocrine therapy?

DR PEGRAM: At UCLA, we feel strongly that HER2 is a broad marker for endocrine resistance independent of the type of antiestrogen therapy used, and that's what the data are bearing out, so I don't see how that could be useful in

decision-making. Also, the data indicate benefit from an aromatase inhibitor in HER2-positive and in HER2-negative disease, and it appears that aromatase inhibitors, as a class, are generally more active than tamoxifen regardless of HER2 status.

DR GOSS: I believe the data are showing that although HER2 positivity is a relative endocrine-resistance marker, both tamoxifen and aromatase inhibitors are effective — it's just that aromatase inhibitors, as in every other clinical setting, are more effective. In my opinion, a higher relapse risk, such as a HER2-positive or PR-negative tumor, more strongly justifies the use of an up-front aromatase inhibitor over tamoxifen.

DR LOVE: Eric, how do you view the value of PR and HER2 in selecting an adjuvant endocrine agent?

DR WINER: I believe that both PR and HER2 are perhaps not predictive factors but prognostic factors, and for a patient at higher risk of relapse in the first few years, I am more inclined to use the aromatase inhibitor up front.

DR BUZDAR: If you examine BIG 1-98 or Dowsett's data, on patients with PR-negative and HER2-positive tumors, the benefit of aromatase inhibitors over tamoxifen is modest, but it is still in the same direction (BIG 1-98 Collaborative Group 2005; Dowsett 2005). ■

SELECT PUBLICATIONS

The Arimidex, Tamoxifen, Alone or in Combination Trialists' Group. **Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: Long-term safety analysis of the ATAC trial.** *Lancet Oncol* 2006;7(8):633-43. **Abstract**

Breast International Group (BIG) 1-98 Collaborative Group. **A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer.** *N Engl J Med* 2005;353(26):2747-57. **Abstract**

Chlebowski RT et al. **Coronary heart disease and stroke with aromatase inhibitor, tamoxifen, and menopausal hormone therapy use.** *Clin Breast Cancer* 2006;6(Suppl 2):58-64. **Abstract**

Coates AS et al. **Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: Update of study BIG 1-98.** *J Clin Oncol* 2007;25(5):486-92. **Abstract**

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

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** San Antonio Breast Cancer Symposium 2003;4. No abstract available

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

Muss HB et al. **The benefits of letrozole in postmenopausal women with early stage breast cancer who have had five years of tamoxifen are independent of age.** San Antonio Breast Cancer Symposium 2006;**Abstract 102**.

Tracks 1-20

Select Excerpts from the Discussion

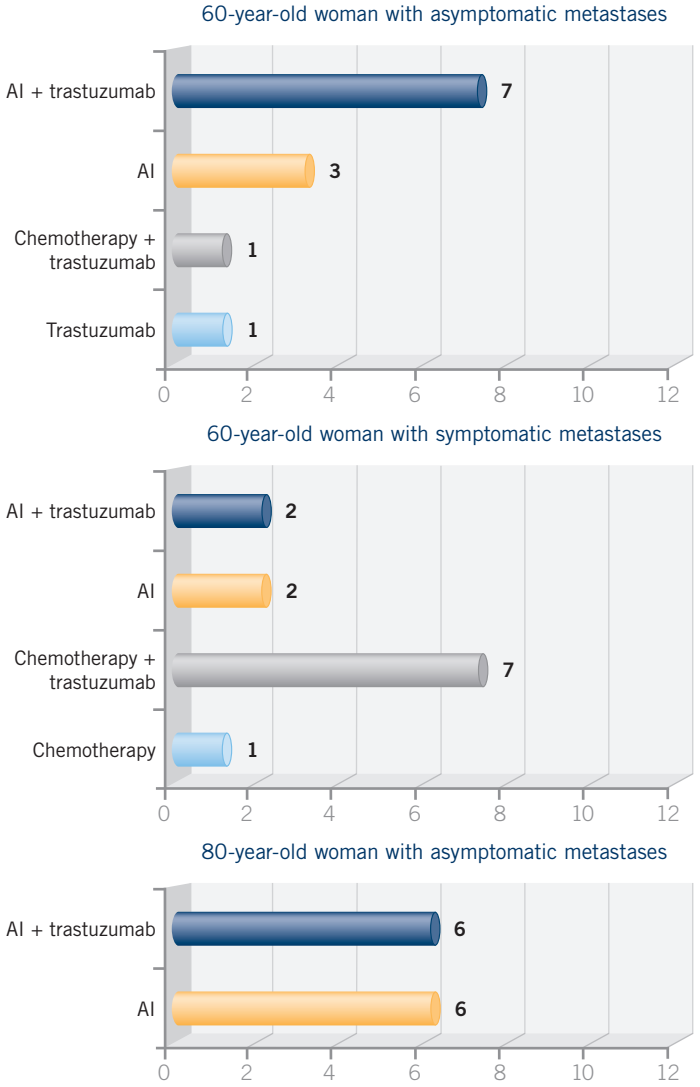
Tracks 1-2

DR LOVE: John, how do you think through these three challenging clinical cases, starting with the asymptomatic 60-year-old?

DR MACKEY: I believe the standard approach is that with which the overall

FACULTY POLL QUESTION 6

Patient presents with de novo bone and liver mets and a breast mass, which on biopsy proves to be an ER-positive, PR-positive, HER2-positive cancer.



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

survival advantage has been demonstrated, which is with combination chemotherapy and trastuzumab (Slamon 2001).

The TAnDEM data didn't change my approach for the average woman who

comes in at age 60 with visceral metastases, particularly since we performed an unplanned subgroup analysis of the women with liver metastases and they did not appear to benefit from the addition of trastuzumab to anastrozole in terms of overall survival. It was the women without liver metastases who might have had a survival advantage associated with the addition of trastuzumab (Mackey 2006). If she were not willing to go through chemotherapy, I would talk to her about the TAnDEM trial and trastuzumab with an aromatase inhibitor.

DR GOSS: I want to remind people that in the population with HER2-negative disease, one of the most elegantly demonstrated points in the up-front aromatase inhibitor trials was that visceral metastases respond extremely well. I only make this point because I'm aware that in clinical practice, many people still revert to chemotherapy when a patient has two or three asymptomatic liver metastases.

DR SPARANO: I agree with Paul entirely that endocrine therapy would be the default position to take for patients with asymptomatic metastatic disease. With regard to HER2-positive disease, I would favor saving trastuzumab for a time when I needed to use chemotherapy because of the clear benefit when it is added to chemotherapy in terms of objective response, time to progression and overall survival.

I would not use it when I'm administering endocrine therapy, when I believe it brings less potential for benefit and I also have to tie the patient to receiving parenteral therapy in addition to an oral therapy that's well tolerated.

DR PEGRAM: I believe that if you follow your patients closely, endocrine therapy should be up for discussion with the patient, particularly in light of its convenience. But we have to recognize from the TAnDEM trial that the expectation from an aromatase inhibitor alone is modest, and the time of benefit is short for the majority of patients (Mackey 2006).

As long as you capture those early progressions in a timely fashion and treat them with trastuzumab-based therapy, which is arguably the most important of the targeted therapies that you're going to use for these patients, then that's fine. Close clinical follow-up is the key to the management of these cases if you're not going to start with a trastuzumab-based regimen.

Outside of that caveat, my preference would be to use a trastuzumab-based regimen up front. I would probably start with an aromatase inhibitor in this particular case because of the lack of side effects compared to cytotoxic therapy.

DR DICKLER: I agree. In the TAnDEM trial, the median progression-free survival went from 2.4 to 4.8 months with the addition of trastuzumab to anastrozole (Mackey 2006; [1.1]). Some patients derive most of that benefit, and others don't derive any.

Without being able to select those patients, I will probably use the combination of trastuzumab and an aromatase inhibitor up front because some people will derive a great benefit. Until I know who those patients are and I can

1.1

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. San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

select them when I'm starting therapy, I will administer the combination initially.

I also feel that using hormonal therapy is important. I've had patients in my practice with metastatic disease for eight to 10 years. It's important to be able to delay the onset of chemotherapy because it has a big impact on quality of life.

DR WINER: I didn't find the TAnDEM trial to be practice changing to any significant degree. Prior to TAnDEM, I would selectively use an aromatase inhibitor for some patients and trastuzumab monotherapy for some patients. Most patients with HER2-positive disease in my clinical practice receive some form of chemotherapy with trastuzumab, and I will continue that practice.

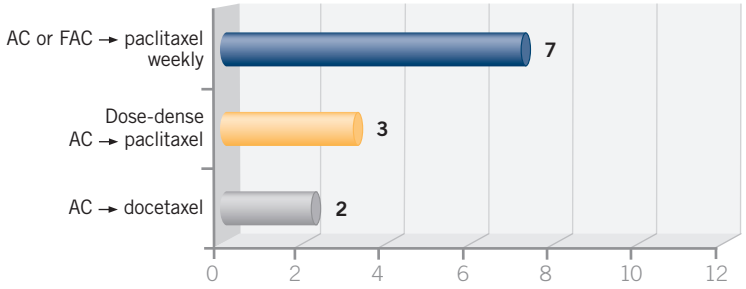
Track 5

DR LOVE: Let's talk about adjuvant therapy of HER2-positive disease. Eric, what chemotherapy regimen were you combining with trastuzumab before the results of BCIRG 006 were reported at the 2006 San Antonio Breast Cancer Symposium, and what are you using now?

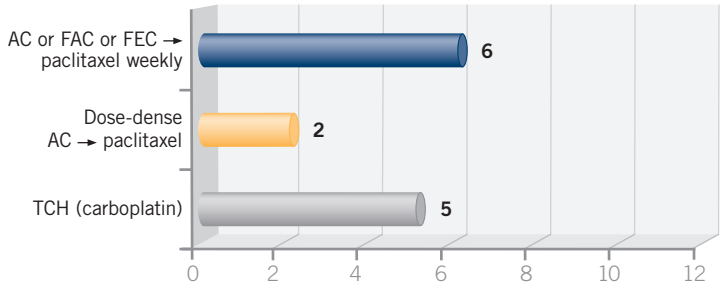
DR WINER: Prior to the San Antonio meeting, for most patients I used AC followed by TH (paclitaxel/trastuzumab), the Intergroup regimen, and I still do, although my comfort level has increased in terms of using TCH (docetaxel/carboplatin/trastuzumab) for the patient who has me worried about cardiac toxicity.

FACULTY POLL QUESTIONS 7 AND 8

Prior to the 2006 San Antonio meeting, my usual chemotherapy with trastuzumab was:



Currently, my usual chemotherapy with trastuzumab is:



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

We have years and thousands of patients of experience using anthracyclines in this setting of HER2-positive disease. I'm not ready to shift everyone, but it's interesting.

So my questions are: Do you believe carboplatin makes any difference? In an ideal world, wouldn't you like to suddenly find 10,000 patients to ask whether you can use even kinder and gentler chemotherapy with trastuzumab?

My guess is that trastuzumab in the end is the great equalizer and that the chemotherapy doesn't make a difference as long as you use some.

DR LOVE: Mark, do we need the carboplatin in TCH?

DR PEGRAM: The docetaxel/trastuzumab (TH) versus TCH question has been addressed in a randomized trial for patients with metastatic breast cancer. It is not kinder and gentler because in that trial the dose of docetaxel was 100 mg/m^2 in the TH arm and 75 mg/m^2 in the TCH arm (Forbes 2006).

1.2

Potential Treatment Regimens for Patients with Smaller HER2-Positive Tumors

"For an otherwise healthy woman with a smaller HER2-positive tumor, you can go with either of the BCIRG 006 trastuzumab regimens, and patients should be aware of the differences in efficacy and toxicity between the regimens.

In addition, although we don't have data, I believe docetaxel/cyclophosphamide, the regimen Steve Jones evaluated (Jones 2006), would be equally efficacious because the taxane is the same and cyclophosphamide has additive and synergistic interactions with trastuzumab.

My sense is that the chemotherapy platform you build trastuzumab on is much less important than using trastuzumab and using it for an optimum period of time, which is yet to be determined. For a HER2-driven tumor, that is the critical factor."

SOURCE: Slamon D. *Cardiologic Issues in Breast Cancer Management* 2007;1(1).

The toxicity was arguably higher in the TH arm compared to the TCH arm, and the efficacy was equivalent in both arms (Forbes 2006). In terms of the therapeutic index, you could argue, based on that study, that TCH would still come out the winner.

DR LOVE: Mark, for a 62-year-old woman with HER2-positive disease with two positive nodes who is otherwise healthy, what are you likely to recommend as adjuvant therapy outside of a study?

DR PEGRAM: I will definitely discuss both treatment options with the patient — TCH or an anthracycline/taxane/trastuzumab regimen — and I would point out the various toxicity profiles and ascertain the patient's impression of what she would like to choose. I would not say that the patient must receive TCH, but I believe it's reasonable to offer it as a treatment option.

I agree that it's reasonable to be conservative with regard to changing clinical practice based on an abstract presentation of an interim analysis (Slamon 2006). As a general rule, those are rarely practice-changing presentations, but this does bring up the issue of a nonanthracycline-based chemotherapy regimen to integrate with trastuzumab in the adjuvant setting.

It puts the option on the table, and it's a reasonable treatment option. I agree with Eric that trastuzumab probably is the great equalizer and the chemotherapy base will perhaps become a secondary issue.

DR LOVE: What about using TCH with the "C" being cyclophosphamide (1.2)?

DR PEGRAM: The US Oncology network is exploring that combination in ongoing trials. The hypothesis behind the synergy of trastuzumab and cytotoxic agents extends equally to the alkylating agents, as it did for the platinum salts. I believe that's a reasonable substitution, and I will be interested

to follow the data as they emerge.

DR LOVE: Matt, how are you approaching treatment for these patients right now?

DR ELLIS: Before the BCIRG 006 data were reported at the 2006 San Antonio meeting, I carefully evaluated the patient's baseline ejection fraction and age. This was because of the analysis conducted in NSABP-B-31 showing that the older the patient and the lower the baseline ejection fraction, the more likely a patient was to develop congestive heart failure with trastuzumab (Tan-Chiu 2005).

If the patient appeared to be in a higher-risk group — older or with a lower baseline ejection fraction — I would use TCH. Now I'm even less likely to use AC → T, driven by the safety data.

DR LOVE: Again, a 62-year-old, healthy woman with a normal ejection fraction: What are you likely to recommend?

DR ELLIS: I agree with Mark. You have to work through the issues, and I'd emphasize that I'd like to see five-year data. But at this point, I would tend more towards TCH.

Track 7

DR LOVE: Joe, what is your take on the BCIRG 006 presentation?

DR SPARANO: BCIRG 006 was an important trial for two reasons. First, when the data were initially presented, it was the third trial clearly showing a dramatic improvement in outcome with adjuvant trastuzumab (Slamon 2005).

Second, it put the TCH regimen on the table as an alternative, notwithstanding the limitations due to the fact that the trial was not designed to compare the two trastuzumab-containing regimens with regard to efficacy. It was designed to compare the two experimental trastuzumab regimens to the standard regimen without trastuzumab.

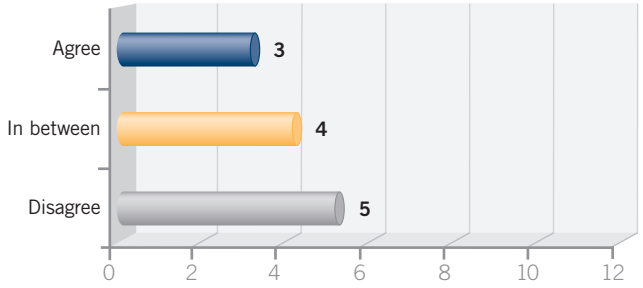
Nevertheless, it still puts that regimen on the table. Has it changed my practice? Not necessarily. I still feel more comfortable with the totality of evidence from all the studies using doxorubicin-based therapy.

Also, I find that when I meet with a patient, there's so much information to review, and she is often overwhelmed by all the components of therapy we need to discuss. Therefore, I generally choose not to put this on the table unless I believe it should be there because of my concerns related to cardiac toxicity.

More relapses do appear to occur with TCH thus far. On the other hand, it is associated with less cardiac toxicity. I'm not sure yet about leukemia — it's four cases for the anthracycline-based regimens versus zero cases for TCH. We

FACULTY POLL QUESTION 9

Patients with HER2-positive, node-negative, invasive tumors of essentially any size should receive adjuvant trastuzumab.



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

need more time before we have an answer to that (Slamon 2006).

DR LOVE: John, do you agree that more relapses occurred with TCH?

DR MACKEY: Statistically, no. The trial was designed — if both arms outperformed the control — to provide a protocol-specified comparison of the two arms. That protocol-specified comparison produces a *p*-value that is not even close to a trend and, in fact, is heading in the direction of no difference between the two arms (Slamon 2006). All I can say is that the efficacy data indicate that they're indistinguishable and the safety data, I believe, favor TCH.

Tracks 9-10

DR LOVE: Eric, can you comment on your decision-making process for patients with ER-negative, HER2-positive tumors smaller than five millimeters (T1a) and those with ER-negative, HER2-positive tumors between five and 10 millimeters (T1b)?

DR WINER: The difference is pretty big in terms of the volume of those tumors. I'll draw a line in the sand at T1a. The woman with a T1b tumor I will treat with trastuzumab and chemotherapy. I am not at the point where I'm willing to do that for a patient with a T1aN0 tumor.

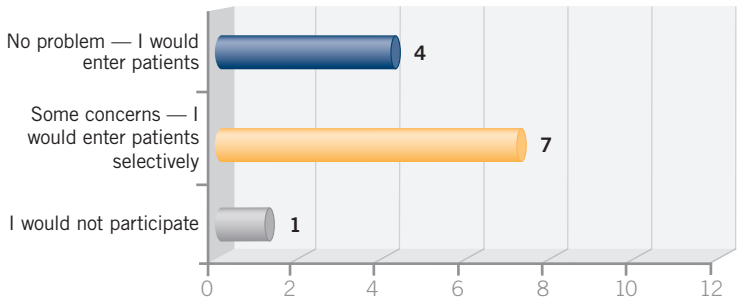
DR LOVE: What about an 8-mm tumor that is ER-positive and HER2-positive?

DR WINER: I'm more on the fence.

DR PEGRAM: The bottom line is that trastuzumab, not the endocrine therapy,

FACULTY POLL QUESTION 10

How would you feel in general about recommending participation in a randomized trial of TCH alone or with bevacizumab?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

will do the lion's share of the work in terms of clinical benefit in these patients with HER2-positive tumors. So trastuzumab must be considered the base from which you formulate further combinations. If the patient had ER-positive disease, it would be reasonable to add endocrine therapy.

Although HER2 is a marker for relative endocrine resistance, it doesn't mean patients don't obtain a benefit from endocrine therapy — they just derive less benefit. So for a patient with a smaller ER-positive, HER2-positive tumor, I believe it would be reasonable to consider an endocrine and HER2-directed combination in the absence of chemotherapy.

DR LOVE: Joe, in your practice, how do you approach patients with HER2-positive tumors that are smaller than one centimeter?

DR SPARANO: If the patient has a HER2-positive tumor, she derives relatively greater benefit from chemotherapy. Without question, she would also derive benefit from trastuzumab. The critical question is, at what level of risk do you pull the trigger? And when you pull the trigger, do you pull it once or twice?

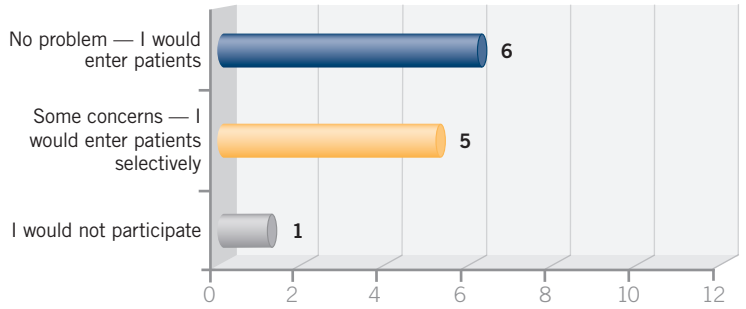
If we pull the trigger, I feel obligated to use chemotherapy with trastuzumab. I have used trastuzumab with endocrine therapy alone in certain circumstances, and they tend to be older patients with high-risk disease, not patients with smaller tumors.

DR LOVE: Are you generally treating patients with a HER2-positive tumor that is smaller than one centimeter?

DR SPARANO: Yes. Absolutely, because they do have a higher risk of recurrence, as we know from the Onco*type* DX™ recurrence score. I fall in Eric's

FACULTY POLL QUESTION 11

How would you feel in general about recommending participation in a randomized adjuvant trial of chemotherapy with trastuzumab versus chemotherapy with trastuzumab/lapatinib versus chemotherapy with lapatinib?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

camp, and I draw a line in the sand for patients with tumors that are T1a or less, at which I say, "We don't need to use chemotherapy or trastuzumab in that setting."

DR LOVE: Kathy, how do you approach these patients?

DR PRITCHARD: This decision is easy for me in Ontario because I am not reimbursed for trastuzumab if the patient has a tumor that is smaller than one centimeter. I also can't use trastuzumab unless I also use chemotherapy.

Left to my own devices, I would use trastuzumab for some patients with tumors that are smaller than one centimeter, and I would use trastuzumab alone for some patients who are elderly or frail.

Tracks 13-14

DR LOVE: What are your thoughts on the results from the poll questions regarding participation in trials with lapatinib or bevacizumab for patients with HER2-positive disease?

DR MACKEY: I'm encouraged by this type of reaction because the BCIRG 006 data we're talking about are six weeks old, and we are already shifting the majority of the poll participants to considering these novel trial designs.

We've struggled for 25 years to prove that anthracyclines matter. We finally achieved a four percent disease-free survival advantage (EBCTCG 2005). We have to admit that there may be more important issues to address, such as the

biological questions, rather than being stuck on what is an old, toxic treatment.

I believe we will see a great deal of interest in these new trials, in which the biology drives the question (1.3). Also, we will find increasingly that we're willing to pursue regimens that require, in a sense, a withdrawal of some of the accepted past treatments because we can't simply keep adding to the toxicities by adding yet another agent.

1.3 Proposed HER2 Adjuvant Trials

Study	Randomization
NSABP/BCIRG	TCH ± bevacizumab
ALTTO	P x 12wk + H x 1y versus P x 12wk + L x 1y versus (P + H) x 12wk → washout → L x 34wk versus (P + H + L) x 12wk → L+ H x 34wk

T = docetaxel; C = carboplatin; H = trastuzumab; L = lapatinib; P = paclitaxel

SOURCE: NCI Physician Data Query, April 2007.

DR PRITCHARD: It would be nice to see the TCH data published in a peer-reviewed setting before we gallop off in any direction.

Having said that, I believe logic and momentum are behind this as a concept. That's why you're seeing people considering it fairly quickly. This would be a reasonable trial with a reasonable control arm.

DR LOVE: Would you be comfortable with the ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) trial, which includes a treatment arm without trastuzumab?

DR PRITCHARD: I'm comfortable with both trials.

DR LOVE: Aman, for a patient with multiple positive nodes, how comfortable are you with the ALTTO trial, in which she might not receive trastuzumab?

DR BUZDAR: If the trial had a lapatinib arm, I would not have any reservations because I believe lapatinib, at least in the setting for which we have information, shows substantial antitumor activity, even in patients with trastuzumab-resistant disease.

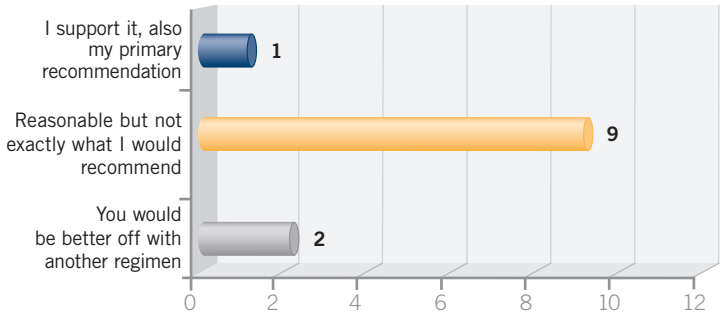
DR GOSS: I'm extremely pleased that Aman gave that answer because it reminds me of the ATAC trial, when it was designed and initiated. At that time, no patient with metastatic disease had ever been treated with anastrozole as first-line therapy.

Second, no human being had ever been treated with the combination of anastrozole and tamoxifen. A 9,000-patient trial was initiated in 1997 in which the standard practice was abandoned in favor of a novel therapy, based on a class effect.

That's what the ALTTO trial is doing with lapatinib, which is another anti-HER2 therapy. I believe this is correct. If you try to reinvent the wheel for

FACULTY POLL QUESTION 12

A 60-year-old patient with a node-positive, HER2-positive tumor comes to you for a second opinion after having dose-dense AC → paclitaxel/trastuzumab recommended. The patient asks you about that recommendation, and you say:



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

each and every scenario with novel agents in a class, you're going to slow down the rate of discovery. So I concur with Aman's answer exactly.

DR LEYLAND-JONES: I have no problems with the ALTTO trial. In fact, I was one of those who argued in favor of the lapatinib-alone arm.

The only concern I have with the trial of TCH with or without bevacizumab is the fact that we currently have only 40 patients evaluated for cardiac risk with the combination. So my concerns are the potential cardiac risk and the fact that the database on the safety of the two drugs is so small.

Track 16

DR WINER: Evidently we've all convinced ourselves that we're okay with the ALTTO trial. However, I don't believe there's a single person around the table who wouldn't like more data with lapatinib — something that would round out what we know.

I expect it's likely we will have that over the course of the next six or 12 months. Of course, if we don't have the data we need or if the data from the ongoing studies cause concern, the ALTTO study will be adjusted as necessary.

The issues with the bevacizumab trial are somewhat different. I'm not bothered by TCH being the control arm. I believe that's an acceptable control. Given concern about cardiac toxicity, it is, in fact, probably the best control arm.

If I were faced with a woman who had a small node-negative, HER2-positive

tumor, I'm not sure I would want her to be randomly assigned to six cycles of docetaxel/carboplatin and trastuzumab and bevacizumab. It's potentially a lot of therapy for that patient with relatively low-risk disease. In clinical trials, we all make decisions about patients with which we have less equipoise.

Track 20

DR LOVE: John, what are your thoughts about using dose-dense AC → paclitaxel/trastuzumab?

DR MACKEY: When you have a number of good choices, why would you fly by the seat of your pants with a regimen from a 70-patient study in a preselected population? Because we have other good options, I wouldn't go there. I wouldn't say that it's wrong — it's a reasonable recommendation — but it wouldn't be what I would recommend.

DR LOVE: Maura, can you comment on why so many people at Memorial Sloan-Kettering are using this approach now?

DR DICKLER: The chemotherapy is well tolerated, and you move through it quickly. I believe it is the ease of administration and the fact that dose-dense AC → T doesn't increase cardiac events (Hudis 2005). ■

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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**

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**.

Burstein HJ et al. **Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: A pilot study.** *J Clin Oncol* 2003;21(1):46-53. **Abstract**

Burstein HJ et al. **Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2001;19(10):2722-30. **Abstract**

Buzdar AU et al. **Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: An update of the initial randomized study population and data of additional patients treated with the same regimen.** *Clin Cancer Res* 2007;13(1):228-33. **Abstract**

Buzdar AU et al. **Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer.** *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

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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**.

Hurley J et al. **Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer.** *J Clin Oncol* 2006;24(12):1831-8. **Abstract**

Joensuu H et al, on behalf of the 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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Pegram M et al. **Phase II combined biological therapy targeting the HER2 proto-oncogene and the vascular endothelial growth factor using trastuzumab (T) and bevacizumab (B) as first line treatment of HER2-amplified breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 301**.

Perez EA et al. **HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 Intergroup adjuvant trial.** *J Clin Oncol* 2006;24(19):3032-8. **Abstract**

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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**.

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.** San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

Slamon DJ et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344(11):783-92. **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**

SECTION 3

Adjuvant Chemotherapy

Tracks 1-22

Select Excerpts from the Discussion

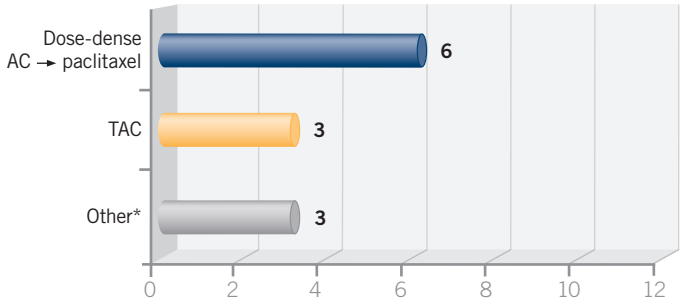
Tracks 1, 3-5

DR LOVE: Can you comment on the adjuvant chemotherapy regimen you use for patients with node-positive, HER2-negative disease?

DR MACKEY: At our center, we would use TAC. Dose-dense AC → paclitaxel is also a good and reasonable option.

FACULTY POLL QUESTION 13

In general, what adjuvant chemotherapy regimen would you likely recommend for a 60-year-old healthy woman with a triple-negative tumor and four positive nodes?



* FAC → paclitaxel; CEF or DD EC → T; DD AC → paclitaxel or TAC

SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

DR JAHANZEB: We use TAC most often at our institution. The use of dose-dense chemotherapy is notably regional. We are far enough away from New York that we don't use it.

DR DICKLER: Do you use prophylactic antibiotics and growth factors?

DR JAHANZEB: Yes, as a rule, because a febrile neutropenia rate of 24 percent is well above the NCCN guideline's threshold above which they would be routinely used.

DR LOVE: Joe, you're in the New York area. What do you do?

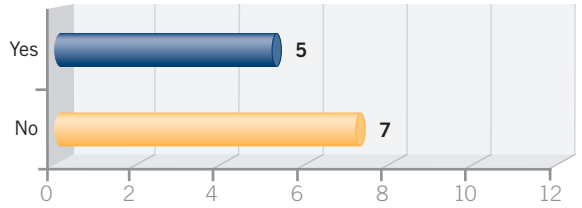
DR SPARANO: My preference for the dose-dense regimen is due to the fact that even if it's not more effective than using the same drugs every three weeks, it is completed in one third of the time. It is also associated with less toxicity. I, and many people, have concerns about the toxicity associated with TAC.

DR LOVE: What are your thoughts about using dose-dense AC without a taxane?

DR SPARANO: I was the one person who said, "Yes, commonly." The reason for that is twofold. First, I was strongly reassured by the long-term safety data with dose-dense therapy from CALGB-9741 with regard to cardiac toxicity and secondary leukemia (Hudis 2005). Second, the Canadian trial (MA21) demonstrated that some treatment effect might be achieved by shortening the interval for only the anthracycline component of therapy (Burnell 2006).

FACULTY POLL QUESTION 14

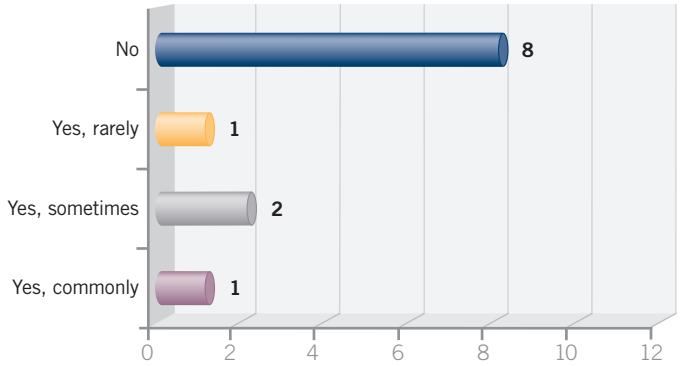
Do you consider dose-dense AC (without a taxane) a reasonable and acceptable nonprotocol option as adjuvant therapy?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

FACULTY POLL QUESTION 15

Have you prescribed dose-dense AC (without a taxane)?



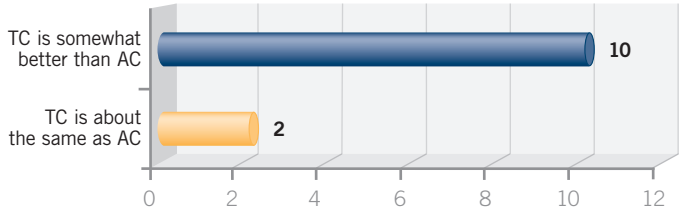
SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

DR WINER: I said, "Yes, sometimes." I would be a "No" if it weren't for the fact that we have an ongoing CALGB study of dose-dense AC and colleagues at my institution occasionally use this regimen.

I take the position that if you're going to use AC, use it the way it's been used before. I worry that there might be a duration of therapy that's too short and that six weeks from beginning to end may be a problem. That said, I can't jump up and down and say it's a crazy thing to do.

FACULTY POLL QUESTION 16

How would you compare the antitumor efficacy of TC versus AC?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

Tracks 11-15

DR LOVE: Rowan, are you using the docetaxel/cyclophosphamide (TC) regimen in your clinical practice?

DR CHLEBOWSKI: Yes. I like this combination, and we've adopted it as our low-risk regimen. The TC regimen is easy to administer, and patients don't experience nausea and vomiting as they do with AC. With regard to long-term risk, I would be willing to swap docetaxel for an anthracycline. Although we have only one trial, it demonstrated a nice difference (Jones 2005).

DR LOVE: Joe, how do you feel about the data Jones reported?

DR SPARANO: This is an important study. It's clearly positive and took many of us by surprise. It goes against our biases as medical oncologists in terms of our belief that doxorubicin is an effective drug and that, rather than replacing it, we should substitute the cyclophosphamide with docetaxel. That's what we did in ECOG trial E2197, which compared doxorubicin/docetaxel to doxorubicin/cyclophosphamide, and that resulted in a negative study (Goldstein 2005).

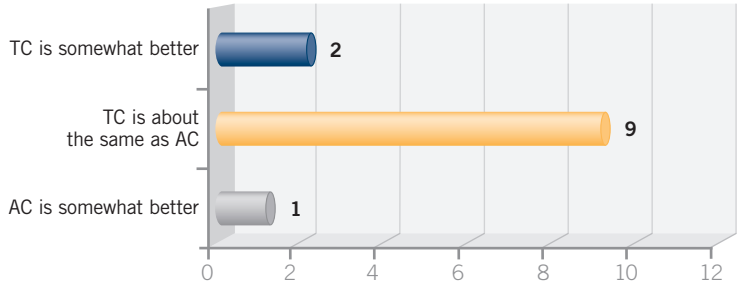
What's nice about the Jones data is that the treatment effect is nearly identical to that seen in the paclitaxel arm of CALGB-9344, the Phase III study of adjuvant cyclophosphamide/doxorubicin with or without paclitaxel, but without the duration issue (Henderson 2003). It also removes from the regimen a drug — doxorubicin — that we're all concerned about with regard to long-term toxicity.

DR LOVE: What about tolerance of AC versus TC?

DR SPARANO: My experience is anecdotal, but the data speak for themselves. It is a tradeoff in terms of certain toxicities. One of the problems is that when

FACULTY POLL QUESTION 17

How would you compare the short-term tolerability of TC versus AC?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

we consider docetaxel, we generally think of TAC, which is clearly more toxic than some of the other regimens. I believe that as clinicians use TC, they'll become more comfortable with it and we will see greater use of it.

DR PEGRAM: I've used TC a lot since the data were first presented (Jones 2005). It is our standard treatment for patients at high risk with node-negative disease for whom we are not considering longer-duration or more intense combinations.

A certain tradeoff is evident in terms of neutropenia, but it's relatively low risk and manageable. Clearly the TC regimen has less potential for upper gastrointestinal toxicity, and it avoids the issue of cardiotoxicity altogether.

DR GOSS: Does anyone here use four cycles of AC anymore?

DR PEGRAM: Not alone.

DR PRITCHARD: Does anyone still use CMF? It's definitely not cardiotoxic, it doesn't cause leukemia and it's as effective as AC.

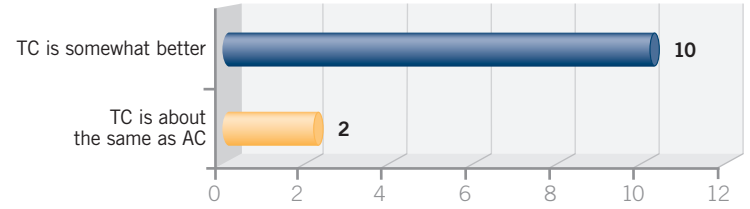
DR PEGRAM: Yes.

DR ELLIS: I would like to comment on that. What the TC data have done for me is put to rest my 10-year struggle with CMF. I agree with Kathy that CMF has been a reasonable regimen to consider for many patients, particularly patients with ER-positive, HER2-negative disease.

The conundrum with CMF has always been oral versus IV cyclophosphamide. In the classic NSABP-B-15 comparison of AC to CMF, oral cyclophosphamide was used, and that is a difficult regimen to administer (Fisher 1990). Now I can administer TC and forget CMF, which for me is a huge relief. I'm

FACULTY POLL QUESTION 18

How would you compare the short- and long-term risks of serious complications with TC versus AC?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

no longer torturing myself over administering IV CMF and then worrying that I'm undertreating patients.

DR DICKLER: Although alopecia does occur with the TC regimen, and women hate to lose their hair.

DR PEGRAM: Yes, but it's only 12 weeks versus six months of therapy.

DR ELLIS: If you discuss it with your patients, I believe most women will trade some hair loss for finishing up treatment more quickly.

DR CHLEBOWSKI: Another option is capecitabine. At the San Antonio meeting, data were presented from a randomized, 300-patient comparison of two schedules of capecitabine versus CMF in advanced disease, and a survival advantage and less toxicity were seen with capecitabine (Stockler 2006). I'm not using CMF in the adjuvant setting, but given these data, I wonder why anybody would want to use CMF in any breast cancer treatment setting.

DR WINER: I don't have trouble administering TC, and I agree that it's probably less toxic. However, doesn't it bother anyone that the well-executed Intergroup trial, ECOG-E2197, which compared doxorubicin/docetaxel to doxorubicin/cyclophosphamide, showed no benefit and yet the Jones data suggest that docetaxel is better (Goldstein 2005; Jones 2005)?

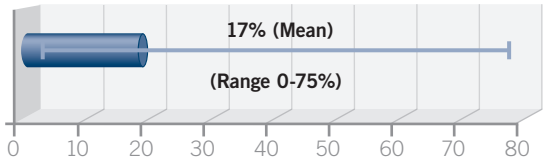
If anything, I would have expected that substituting docetaxel for cyclophosphamide would provide a bigger hit. I find it troublesome.

DR LOVE: Do you have any explanation?

DR WINER: I don't have an explanation, and it's why, based on this one study, I would conclude that TC is about the same as AC. I'm not ready to say it's better based on one study of 1,000 patients, given that the other study has a result that causes concern.

FACULTY POLL QUESTION 19

For approximately what percentage of patients whom you consider for adjuvant therapy for ER-positive, node-negative tumors do you obtain an Onco*type* DX assay?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

DR LOVE: Joe, how many patients were in the E2197 trial?

DR SPARANO: Approximately 2,900 patients were enrolled, and although the four-year disease-free survival was projected to be about 78 percent in the AC arm, it was actually 87 percent in both arms (Goldstein 2005).

DR BUZDAR: I agree with Eric. The E2197 trial did not show any subset of patients who derived an advantage, or a hint of an advantage, when docetaxel replaced cyclophosphamide.

A consistent, slightly inferior outcome was evident from combining docetaxel with an anthracycline, so I would be cautious when interpreting the study comparing AC to TC with a smaller sample size. I believe it should be confirmed before we jump on the bandwagon.

DR WINER: Don't get me wrong. I'm pondering whether I should go back to my practice and consider using TC more often — I'm just not ready to tell patients that I know it's a better regimen.

DR DICKLER: I believe that it can be equal, but potentially less toxic, with the doxorubicin eliminated.

DR WINER: Absolutely.

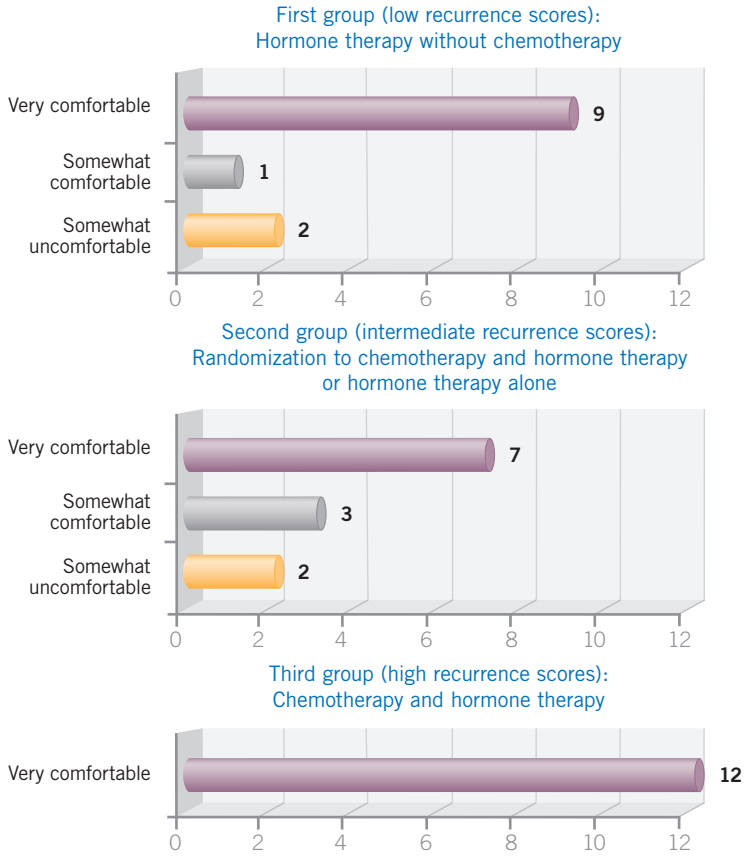
Tracks 17-22

DR LOVE: Joe, how do you feel the Onco*type* DX assay compares to other assays?

DR SPARANO: The key difference with Onco*type* DX is that it gives you three categories as opposed to two. With most other genomic studies, you have a good group and a bad group, but this study also indicates a midrange group. For the patients whose recurrence score is very high or very low, you obtain a definitively informative result. In practice, what's happening is that more

FACULTY POLL QUESTION 20

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



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

patients are falling into the midrange group, and that result doesn't help you make a clinical decision.

DR LOVE: Aman, what's your take on this?

DR BUZDAR: The problem with the Onco*type* DX data is that they are retrospective. TAILORx is an important trial because it will determine whether this assay is of value in identifying subsets of patients prospectively.

DR WINER: I believe Onco*type* DX is built on solid ground, albeit retrospective in a prospectively defined cohort. I do use the Onco*type* DX assay in

practice, but not for all patients because I question how much value we can obtain from chemotherapy for many patients with ER-positive, node-negative breast cancer. While it doesn't help me in every case, in some it does help push me in one direction or another.

DR DICKLER: When we read a pathology report and consider the size, grade and estrogen receptor status of the tumor, we're putting patients on curves using historical data. To me, Onco*type* DX and Adjuvant! Online perform the same function but in a different manner, and I believe it is the way of the future.

I do use Onco*type* DX, and although I don't use it all the time, for patients with ER-positive disease, who I suspect gain little from chemotherapy, I feel it helps me better stratify their risk.

DR LEYLAND-JONES: Let me be provocative. If we can use the "poor man's" equivalent of the Onco*type* DX assay and examine the tumor's ER status, PR status, grade and Ki67, then how do we justify the Onco*type* DX?

DR SPARANO: I couldn't agree more that you could possibly obtain the same results by reliably examining ER, PR, grade and maybe Ki67, but the operative word is "*reliably*." All of these assays are notoriously difficult, and we see great variation, perhaps less for ER and PR, but certainly for grade and Ki67.

DR GOSS: My understanding is that grade is incorporated in the signature, but an intraobserver variation appeared in the original assessment of grade when the score was developed. In some published data, you can see pathologists calling it Grade I versus Grade III, and vice versa. It's not a lot of cases, but it's enough to influence the scoring system.

In our institution, investigators and pathologists continue to argue that the Onco*type* DX assay is a test to eliminate sloppy pathology reporting in community oncology settings, whereas in a high-quality pathology setting, the score doesn't add that much value to the parameters we've been discussing.

DR LOVE: Joe, do you think that's the case?

DR SPARANO: That may be true, and the TAILORx trial may provide the opportunity to test that hypothesis by evaluating the local versus central determination of some of those factors in academic versus community centers.

DR PEGRAM: The promise that Onco*type* DX brings to the field is the application of the multiplex PCR technology. It's just a first step. It's simply a 21-gene set. It happens to be the proof-of-principle gene set for the technology, and in the future this will probably be the least important gene set to examine in breast cancer.

For example, a 186-gene set that's a marker of stem cell populations was recently published in *The New England Journal of Medicine*, with a discussion of its impact on prognosis (Liu 2007). Suites of genes will likely emerge that are predictive for response to individual targeted or cytotoxic agents and that will

trump anything we gain from the current generation of multiplex PCR assays. I believe that's the direction in which the field needs to move.

DR SPARANO: That's exactly the point, and that's why a coprimary objective of the TAILORx trial is to collect these tissues and peripheral blood specimens that we can use to evaluate other diagnostic tests as the technology emerges in the next five to 10 years.

DR ELLIS: I believe all those who think that a "poor man's" Onco*type* DX assay is out there are deluding themselves. I was in the room when the PACCT-1 trial was being designed and, thinking we could perhaps randomly assign the intermediate group based on several risk strata, we reviewed all the literature on Ki67, grading, ploidy and all the other factors that have been examined, and it was clear that precision in those assays was totally inadequate for designing a prospective trial.

Fifteen years of attempts to create a Ki67 assay have failed, and this continues to be a big problem. I use that assay in my lab, but only with regard to biological endpoints for research. As a clinical assay, it's a nightmare.

What quantitative PCR brought to the table was precision. The patient in front of you has a binary outcome — either she will relapse or she won't — and we're trying to predict that outcome. That individual doesn't have a gray zone of risk. So, if you consider that risk score, I believe you can identify patients — who are actually at the lowest-risk end — whom you can tell with about 95 percent confidence, "You're not going to relapse from your breast cancer." I believe that's a powerful statement.

My point is that the TAILORx trial includes an observational cohort, which is the low-risk group, for whom we will confirm prospectively that they're truly at low risk. For me, to be able to define that group is comforting and a big step forward.

DR WINER: The TAILORx trial will generate a rich data set. I don't believe anyone is suggesting that Onco*type* DX is the be-all and end-all and that something better won't emerge. I would tend to agree that in expert centers where the pathology is particularly good and testing for ER, PR and HER2 is particularly reliable, tests like this are less useful.

However, Paul and I live in the same town, and if we have our expert breast pathologists examine the same specimen, most of the time they agree but not all the time. In addition, not all of our breast specimens are read at either center by the expert breast pathologists, and once you move outside of that select group, you hear a fair amount of disagreement about grade.

DR SPARANO: I have one final comment about the midrange score for the listening clinicians. If you examine the risk of distant recurrence for patients with a midrange recurrence score, you see that the 10-year distant relapse-free interval was 95 percent for patients treated with tamoxifen and 94 percent for those treated with tamoxifen and chemotherapy (Paik 2006; Sparano 2006).

For those who are concerned about randomly assigning patients with a score in that range, those data should help them feel more comfortable. ■

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Berry DA et al. **Effects of improvements in chemotherapy on disease-free and overall survival of estrogen-receptor negative, node-positive breast cancer: 20-year experience of the CALGB & US Breast Intergroup.** *Breast Cancer Res Treat* 2004;88(Suppl 1):A-29. **Abstract**

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Fisher B et al. **Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial.** *J Natl Cancer Inst* 2001;93(9):684-90. **Abstract**

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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**

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Liu R et al. **The prognostic role of a gene signature from tumorigenic breast-cancer cells.** *New Engl J Med* 2007;356(3):217-26. **Abstract**

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Paik S et al. **HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15.** *J Natl Cancer Inst* 2000;92(24):1991-8. **Abstract**

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Tracks 1-10

Track 1	Clinical implications of ECOG-E2100 and treatment with bevacizumab beyond the first-line setting
Track 2	Flexibility in expanding the scope of bevacizumab beyond use with paclitaxel in the first-line setting
Track 3	Side effects and tolerability of bevacizumab
Track 4	Long-term responders to capecitabine/bevacizumab in the metastatic setting
Track 5	Value of bevacizumab for patients with asymptomatic metastatic disease in the absence of a survival advantage
Track 6	Expected benefit from the incorporation of bevacizumab into the adjuvant setting
Track 7	Advantage of shorter infusion time and lack of premedication with nanoparticle albumin-bound (*nab*) paclitaxel
Track 8	Need for head-to-head clinical trials comparing *nab* paclitaxel with standard taxane dose and schedules
Track 9	Evaluation of *nab* paclitaxel in the adjuvant setting
Track 10	NSABP Phase II trial of neoadjuvant chemotherapy with sequential weekly *nab* paclitaxel followed by FEC

Select Excerpts from the Discussion

Tracks 1-3, 6

DR LOVE: Mark, can you comment on the use of bevacizumab for patients with HER2-negative metastatic disease?

DR PEGRAM: I was impressed by the ECOG-E2100 data (Miller 2005a). The hazard ratio is reminiscent of our experience in the pivotal trial of trastuzumab as first-line therapy for HER2-positive metastatic disease (Slamon 2001). Moreover, if you look at the one-year survival outcome differences, you see that they also fall right on top of the one-year survival differences that were recorded early on in the trastuzumab pivotal trial.

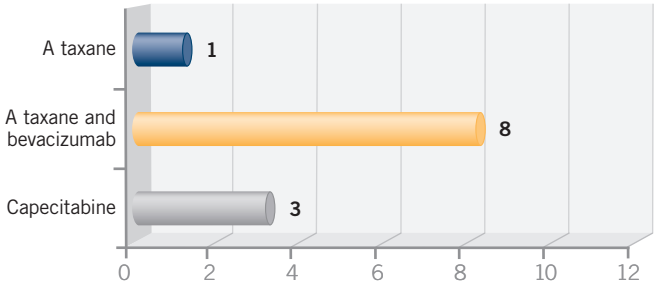
Clearly we have demonstration of efficacy in terms of improved time to tumor progression. The overall survival data are not yet mature for that data set, but I would expect they should be this year. The last time Kathy Miller updated that data set, I believe only about 30 percent of the final number of survival events had occurred (Miller 2005a). So we'll have to wait for the final analysis.

DR LOVE: What about the use of bevacizumab as second-line therapy?

FACULTY POLL QUESTION 21

A 60-year-old woman received AC for a triple-negative tumor. One year later, she is diagnosed with asymptomatic bone metastases and two small pulmonary nodules.

Cost and reimbursement issues aside, which therapy is likely to provide the best therapeutic ratio?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

DR PEGRAM: That question is being addressed in the ongoing RIBBON 2 study. Patients on that study are able to select from a menu of different chemotherapy options at the investigator's discretion, and then they are randomly assigned to bevacizumab or placebo in the second-line setting. Short of any data from such a trial, I probably would not routinely recommend bevacizumab in a second-line setting because we have literally no data to support it at this time.

DR LEYLAND-JONES: In terms of activity in the second-line setting, Mark is absolutely right. We have no data, but I have the feeling we will be seeing significant activity with bevacizumab in the second- and third-line settings for metastatic disease.

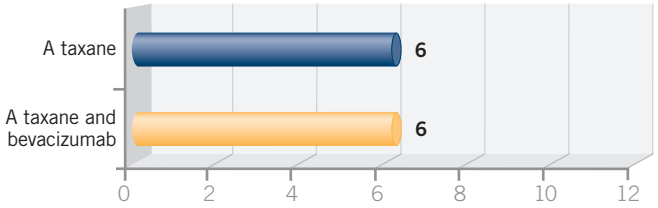
DR WINER: I don't believe you can think of this as another combination therapy like a taxane with capecitabine or gemcitabine. It's important to recognize that a previous randomized trial of bevacizumab with capecitabine in the second-line setting was largely negative, although a hint of activity was evident (Miller 2005b).

I don't believe we should be too rigid about defining first- and second-line therapy because so much of this depends on what someone has received in the adjuvant setting. A woman who received adjuvant TAC or AC → paclitaxel nine months ago and now has a relapse is technically in the first-line setting and far more refractory than many who are in the second-line setting who might not have received adjuvant chemotherapy.

FACULTY POLL QUESTION 22

A 60-year-old woman received AC for a triple-negative tumor. One year later, she is diagnosed with asymptomatic bone metastases and two small pulmonary nodules and receives capecitabine. She shows a response, but the disease progresses after a total of nine months of therapy.

Cost and reimbursement issues aside, which therapy is likely to provide the best therapeutic ratio?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

So for the woman who received adjuvant AC a few years ago and capecitabine as her first-line regimen, I'm willing to try paclitaxel and bevacizumab, recognizing that ECOG-E2100 limited eligibility to patients who had not received chemotherapy in the metastatic setting.

DR LOVE: Aman, what are your thoughts on this controversy?

DR BUZDAR: I don't believe there is much controversy. The data clearly demonstrated that inclusion of a biologic with paclitaxel substantially improved the response rate and time to progression (Miller 2005a). This is a viable positive lead, and we need to discuss it with every patient who meets those eligibility criteria.

The next generation of trials will answer more clearly whether in the second- and third-line settings the inclusion of bevacizumab will enhance the response rate.

DR LOVE: Would you consider combination chemotherapy (a taxane and capecitabine) and bevacizumab for a patient with rapidly progressive visceral disease?

DR BUZDAR: I would not because the safety data are not available. We don't know which dose of each drug we should use for that combination. That is not an appropriate recommendation outside of the context of a clinical trial.

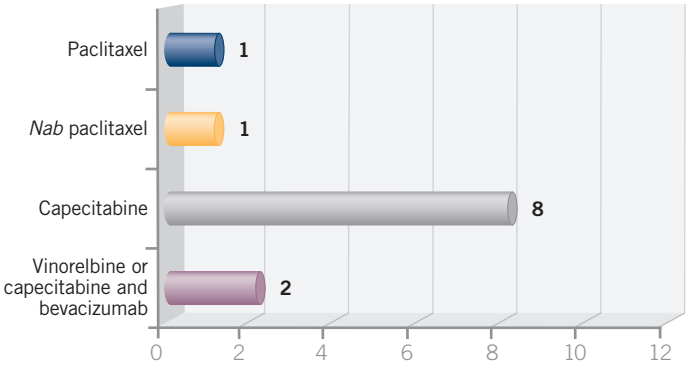
DR LOVE: Matt, what are your thoughts?

DR ELLIS: If ECOG-E2100 does not show an overall survival advantage,

FACULTY POLL QUESTION 23

A 60-year-old woman received AC for a triple-negative tumor. One year later, she is diagnosed with asymptomatic bone metastases and two small pulmonary nodules and receives docetaxel. She shows a response, but the disease progresses after a total of nine months of therapy.

Cost and reimbursement issues aside, which therapy is likely to provide the best therapeutic ratio?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

then bevacizumab is another palliative drug for the treatment of metastatic breast cancer with the potential to relieve symptoms. If that were the case, I would not use bevacizumab for asymptomatic patients because they have no symptoms to palliate. I would probably reserve it for patients who are heavily symptomatic with visceral crisis, for whom response is critical. If bevacizumab improves survival, my view will change.

DR BUZDAR: Let's say that no survival advantage is demonstrated. Still, in metastatic disease, the idea is to control the disease for as long as possible. If you start with a combination therapy of biologics and chemotherapy and you control the disease in a much higher number of patients for a much longer period, that is a major achievement from the patient perspective, even though long-term survival may not be affected.

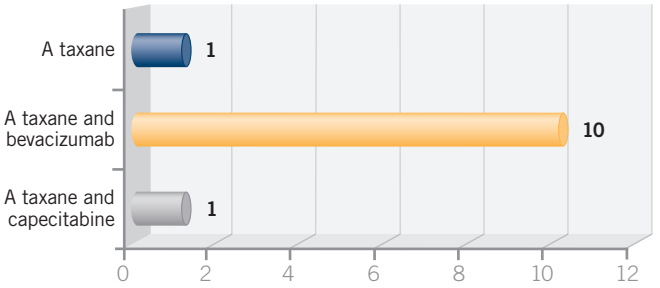
DR DICKLER: We have a lot to learn about bevacizumab. As we learn more about how it works and how to appropriately select patients, then we'll better know with whom we should use it.

Right now, however, I believe stringent rules about which line of therapy to use it in don't make a lot of sense, and toxicity is an issue that must be considered with this drug. Side effects include hypertension, which can be signifi-

FACULTY POLL QUESTION 24

A 60-year-old woman received AC for a triple-negative tumor. Three years later, she is diagnosed with very symptomatic bone metastases and multiple hepatic and pulmonary nodules.

Cost and reimbursement issues aside, which therapy is likely to provide the best therapeutic ratio?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

cant. Some patients require two drugs to control their blood pressure, but it is controllable. I've also had patients develop nephrotic-range proteinuria, and I monitor the urine protein-to-creatinine ratio every few months.

DR LOVE: Joe, if a patient who received adjuvant AC develops asymptomatic metastatic disease that is treated with capecitabine and then develops symptoms from her metastatic disease, what would you recommend?

DR SPARANO: I would absolutely offer that patient paclitaxel and bevacizumab.

DR ELLIS: So would I, probably.

DR WINER: As would I.

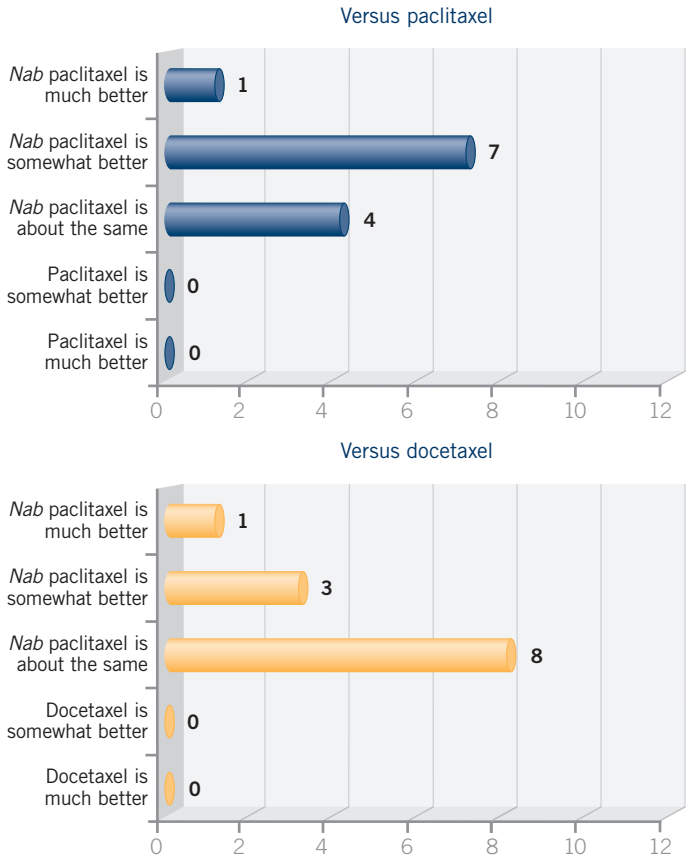
Tracks 7-8

DR LOVE: MJ, let's talk about the most recently available taxane, *nab* paclitaxel. Can you comment on the shorter infusion time for *nab*?

DR JAHANZEB: From the practice standpoint, chair time is an issue, so this is an advantage. Patients don't want to sit for an infusion any longer than necessary. Not having to administer premedications is another advantage with *nab* paclitaxel.

FACULTY POLL QUESTION 25

How would you compare the antitumor efficacy of *nab* paclitaxel versus paclitaxel or docetaxel?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

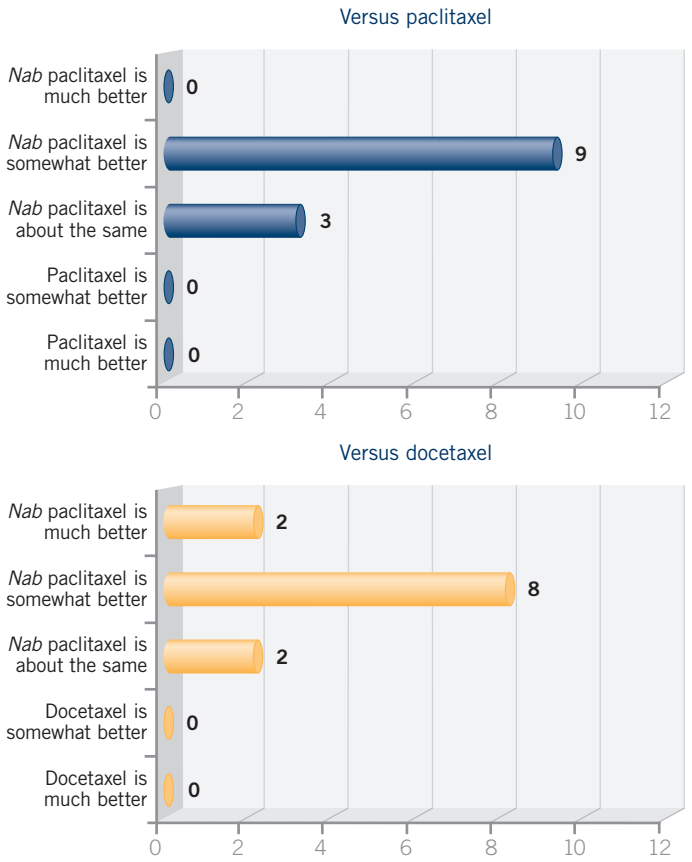
Also, the lack of allergic reactions and the shorter duration of neuropathy are desirable (Gradishar 2005).

Cost is the only remaining issue with *nab* paclitaxel from a practitioner's standpoint. That has been the reason, I believe, for slower uptake. Otherwise, it's a good advance in terms of making a widely used drug better with respect to its efficacy and toxicity.

DR LOVE: Let me quickly poll the group. If the cost of *nab* paclitaxel were exactly the same as paclitaxel, would you use paclitaxel? Show of hands is unanimous with one exception. Eric, you are the only one not raising a hand.

FACULTY POLL QUESTION 26

How would you compare the short- and long-term risks of serious complications with *nab* paclitaxel versus paclitaxel or docetaxel?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

DR WINER: Show me the Phase III trial that has compared *nab* paclitaxel to weekly paclitaxel. I believe the claim that the neuropathy is of shorter duration is based on a very small number of patients. I'm not aware of any symptom complex that is typically more severe but goes away more quickly with one drug versus another.

DR LOVE: From a quality-of-life point of view, Eric, how much of an advantage are the shorter infusion time and lack of premedications?

DR WINER: If you're talking about weekly versus weekly, weekly paclitaxel

is administered over an hour, which is not a tremendously long time. The need for ongoing steroid premedication when you're using weekly paclitaxel is something that one can question. Maybe *nab* paclitaxel will be a better drug, but it's important to investigate further.

DR LOVE: Rowan?

DR CHLEBOWSKI: Up to now, docetaxel at 100 mg/m^2 every three weeks hasn't been beaten by anything in the metastatic disease setting, but it has been tied by weekly paclitaxel.

The presentation by Gradishar at the 2006 San Antonio Breast Cancer Symposium was a Phase II trial, but an apparently substantial improvement occurred in the primary study endpoint, which was objective response, with weekly *nab* paclitaxel compared to every three-week docetaxel (Gradishar 2006). This is impressive.

DR LOVE: Maura, can you discuss your research experience with dose-dense AC → *nab* paclitaxel?

DR DICKLER: We have a feasibility study (MSKCC-06019) evaluating bevacizumab in the adjuvant setting, which is using dose-dense AC → dose-dense *nab* paclitaxel. The trial is currently accruing. Approximately 45 people have enrolled, and many haven't finished receiving the *nab* paclitaxel. I hope we'll have more information by ASCO.

DR LOVE: The US Oncology trial indicated that you need growth factors in that situation.

DR DICKLER: Correct. When they conducted their small pilot trial, they didn't use pegfilgrastim with *nab* paclitaxel at 260 mg/m^2 every two weeks. I believe a third of the patients couldn't receive *nab* paclitaxel on time (Robert 2005). We've also conducted a study at Memorial Sloan-Kettering in which we tried to avoid pegfilgrastim with dose-dense treatment, and we could not administer the treatment on time. It required delays. ■

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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**

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**

SECTION 5

Endocrine Therapy of Metastatic Disease

Tracks 1-3

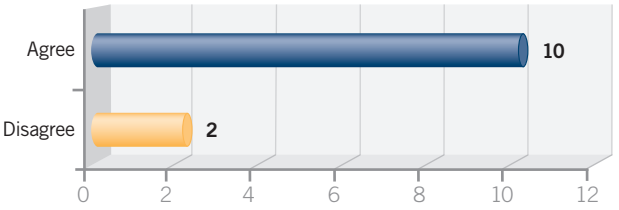
Track 1 EFECT: Equivalence of fulvestrant and exemestane as second-line or later therapy

Track 2 Patient preferences for oral versus parenteral therapy

Track 3 Clinical trial strategies evaluating fulvestrant in combination with the aromatase inhibitors

FACULTY POLL QUESTION 27

I generally use a loading dose when starting fulvestrant.



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

Select Excerpts from the Discussion

Track 1

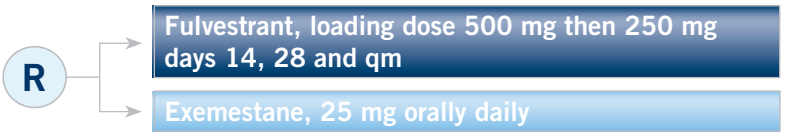
DR LOVE: Paul, what are your thoughts about the efficacy of fulvestrant and the use of a loading dose?

DR GOSS: Using a loading dose seems like the appropiate way to administer fulvestrant. Many people believe fulvestrant's pharmacology has impaired its activity. Several studies are being conducted that will provide additional data on this topic.

One strategy in metastatic disease is evaluating a loading dose and then maintaining a high dose of fulvestrant. A neoadjuvant trial, called the NEWEST trial, is comparing a loading dose to a standard dose.

2.1 **EFECT: Evaluation of Fulvestrant versus Exemestane Clinical Trial**

Protocol IDs: EFECT, NCT00065325, 9238IL/0048
Accrual: 660 (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	
DCB	9.3 months	8.3 months	

OR = objective response; CB = clinical benefit; TTP = median time to progression
DOR = median duration of response; DCB = median duration of clinical benefit

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

In that trial, an early rebiopsy will examine cell proliferation and other markers in the tumor to determine whether the loading dose has a biologic effect. I don't believe we have evidence that fulvestrant is better than an aromatase inhibitor as initial therapy for metastatic disease.

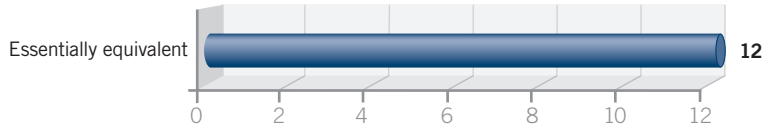
However, I believe the results from EFECT (Evaluation of Fulvestrant versus Exemestane Clinical Trial) are convincing that fulvestrant and exemestane are comparable for patients who have failed on a nonsteroidal aromatase inhibitor (Gradishar 2006; [2.1]).

DR WINER: We're all using a loading dose of fulvestrant. However, zero data are available regarding its efficacy because it wasn't compared to a standard dose.

It is interesting that we've had a number of discussions about wanting data from Phase III randomized studies before writing a prescription, and in this case, the pharmacokinetic data are on slides and we have no efficacy data. However, 10 out of 12 of us are using a loading dose, including myself.

FACULTY POLL QUESTION 28

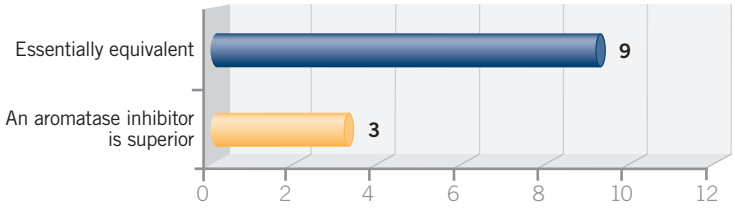
Overall, how do you evaluate the risk/benefit profiles of exemestane and fulvestrant in postmenopausal patients with metastatic disease progressing on a nonsteroidal aromatase inhibitor?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

FACULTY POLL QUESTION 29

Overall, how do you evaluate the risk/benefit profiles of an aromatase inhibitor and fulvestrant in postmenopausal patients with metastatic disease progressing on tamoxifen?



SOURCE: Survey of Think Tank Participants, January 25, 2007, Miami, Florida.

Track 2

DR LOVE: Paul, can you comment on the results of the EFECT study?

DR GOSS: I'm always skeptical about stable disease in chronic endocrine-responsive disease, but if it's true that about 35 percent of patients benefit from exemestane following failure with letrozole or anastrozole (Gradishar 2006), it implies a substantial lack of cross resistance between those two classes of aromatase inhibitors.

DR SPARANO: In the Phase III trials with patients whose disease progressed on tamoxifen (Robertson 2003) and patients whose disease progressed on an aromatase inhibitor (Gradishar 2006), the treatment arms (fulvestrant versus anastrozole and fulvestrant versus exemestane, respectively) produced comparable results. I still believe the aromatase inhibitor in both cases is a winner because the average patient would prefer to receive an oral agent.

Second, we have a fair amount of information now regarding the efficacy of fulvestrant following an aromatase inhibitor, whereas we don't have that information for the converse. For those reasons, most people still choose an aromatase inhibitor and reserve fulvestrant in the event of progression.

Track 3

DR LOVE: Kathy, where is fulvestrant heading in terms of ongoing and future clinical trials?

DR PRITCHARD: Ongoing trials are comparing an aromatase inhibitor with fulvestrant to an aromatase inhibitor alone in the metastatic setting. An evaluation of that same question in the adjuvant setting has been proposed.

DR LOVE: Paul, what do you think about the strategy of combining an aromatase inhibitor and fulvestrant?

DR GOSS: I like that strategy. I've said many times that I believe this type of trial is one of the pieces of an important puzzle about endocrine therapy. We need to continue pursuing the optimization of standard endocrine therapy.

DR LOVE: In a clinical setting, for patients with metastatic disease progressing on an aromatase inhibitor, are there situations in which you would continue the aromatase inhibitor and add fulvestrant?

DR GOSS: I do occasionally, but I talk to the patient carefully about it. I do it because I often wonder how many more endocrine therapies I have left to try with this patient. I can see chemotherapy approaching on the horizon, and I believe perhaps I have one more crack.

After progression on an aromatase inhibitor, we don't have a standard therapy. It's dealer's choice whether to switch to another hormone therapy or to add fulvestrant to an aromatase inhibitor. ■

SELECT PUBLICATIONS

Cheung KL et al. **Endocrine response after prior treatment with fulvestrant in postmenopausal women with advanced breast cancer: Experience from a single centre.** *Endocr Relat Cancer* 2006;13(1):251-5. **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**.

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

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

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Patients on the MA17 trial who originally received a placebo after five years of tamoxifen and then received letrozole after the study was unblinded experienced a significant reduction in the rate of recurrence.**
   a. True
   b. False

2. **In the adjuvant trial reported by Jones and colleagues comparing docetaxel/cyclophosphamide to doxorubicin/cyclophosphamide, a disease-free survival advantage was seen with _____.**
   a. Docetaxel/cyclophosphamide
   b. Doxorubicin/cyclophosphamide

3. **The TAILORx study is randomly assigning patients with _____ Onco*type* DX recurrence scores to hormonal therapy or combination chemotherapy followed by hormonal therapy.**
   a. Low
   b. Intermediate
   c. High

4. **The TAnDEM trial demonstrated a two-month improvement in progression-free survival with the addition of trastuzumab to _____ for patients with HER2-positive and ER-positive metastatic breast cancer.**
   a. Fulvestrant
   b. Lapatinib
   c. Exemestane
   d. Anastrozole
   e. Letrozole

5. **The planned NSABP/BCIRG adjuvant trial for patients with HER2-positive disease will evaluate docetaxel/carboplatin/trastuzumab (TCH) with or without _____.**
   a. Lapatinib
   b. Gefitinib
   c. Bevacizumab

6. **According to the second interim analysis of BCIRG 006, TCH was found to be comparable to AC → TH in terms of efficacy.**
   a. True
   b. False

7. **The ALTTO trial will randomly assign patients with HER2-positive disease to trastuzumab versus lapatinib versus trastuzumab followed by lapatinib versus trastuzumab plus lapatinib.**
   a. True
   b. False

8. **ECOG-E2100 demonstrated that the addition of bevacizumab to paclitaxel as first-line therapy for women with metastatic breast cancer improves _____.**
   a. Progression-free survival
   b. Overall survival
   c. Both a and b
   d. None of the above

9. **The RIBBON 2 trial will evaluate the efficacy of bevacizumab in the _____ setting.**
   a. First-line
   b. Second-line
   c. Both a and b
   d. None of the above

10. **In a Phase II trial, weekly *nab* paclitaxel had a better response rate than every three-week docetaxel as first-line therapy.**
    a. True
    b. False

11. **Results from EFECT indicate that fulvestrant and exemestane have comparable efficacy in patients with metastatic disease with progression on _____.**
    a. Tamoxifen
    b. A nonsteroidal aromatase inhibitor
    c. Either a or b
    d. None of the above

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

EVALUATION FORM

Breast Cancer Update — Think Tank Issue 1, 2007

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

To what extent do you feel the faculty members' comments were helpful or not helpful?

. . . . . .

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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 modules did you find particularly relevant to your practice? Please elaborate on what about the topics and comments was helpful to you.

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Breast Cancer Update — Think Tank Issue 1, 2007

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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:

.....

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BCUTT107

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This program is supported by education grants from
Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP,
Genentech BioOncology and Sanofi-Aventis.

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Sponsored by Research To Practice.

Last review date: May 2007
Release date: May 2007
Expiration date: May 2008
Estimated time to complete: 4.25 hours