2007 · Vol 4 · Issue 2

2007 . Vol 4 . Issue 2

Patterns of Care in Medical Oncology

Management of Breast Cancer in the Adjuvant and Metastatic Settings

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Includes audio CD with faculty interviews discussing the enclosed Patterns of Care survey

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Continuing Medical Education (CME) Information

STATEMENT OF NEED/TARGET AUDIENCE

It is important for practicing oncologists to be aware of similarities and differences between his or her practice patterns, those of others in community practice and those of breast cancer clinical investigators. It is also important for oncologists to recognize that heterogeneity exists in the oncology community, especially in clinical situations for which there is suboptimal research evidence.

This program focuses on the self-described practice patterns of randomly selected medical oncologists on a variety of key clinical issues in cancer. Also included are clinical investigator commentary and references addressing these issues. This CME program will provide medical oncologists with information on national cancer patterns of care to assist with the development of clinical management strategies.

GLOBAL LEARNING OBJECTIVES FOR THE *PATTERNS OF CARE* SERIES

- Compare and contrast management strategies of community oncologists and cancer clinical investigators for the treatment of breast cancer in the adjuvant and metastatic settings.
- Discuss cancer management issues for which relative agreement and heterogeneity exist in patterns of care.
- Counsel cancer patients about multiple acceptable treatment options when they exist.

PURPOSE OF THIS ISSUE

The purpose of this issue of *Patterns of Care* is to support these objectives by comparing the perspectives of 150 community medical oncologists with 50 breast cancer specialists and to offer in-depth commentary from faculty regarding their practice patterns in the management of breast cancer.

ACCREDITATION STATEMENT

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

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COMMERCIAL SUPPORT

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

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Dr Burstein — No financial interests or affiliations to disclose.

Dr Schwartzberg — Consulting Fees: Sanofi-Aventis; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: AstraZeneca Pharmaceuticals LP, Genentech BioOncology.

Financial disclosures for other oncologists quoted in this issue may be found in the cited CME pieces of origin.

COMMENTS IN THIS MONOGRAPH

To highlight the practice issues presented in this survey, a number of excerpts are included from CME publications. For financial disclosures of authors, please refer to the original publications. Audio programs from Research To Practice can be accessed at **www.BreastCancerUpdate.com**.

ABOUT THIS SURVEY

This survey was completed in October 2007 by 150 community-based medical oncologists and 50 oncologists who specialize in breast cancer management (see list on pages 3-4) in the United States. The community-based oncologists were selected from a proprietary mail list used by Research To Practice for distribution of its CME programs, and the specialists included physicians who have participated in education programs with Research To Practice and others referred for this project.

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Editor's Note: Third opinion

Our CME group constantly seeks new methods to delve into the deepest reaches of the minds of clinicians to tease out precisely how these individuals care for patients with cancer. Our most recent experiment in evidence-based psychology is a little tune we call "second opinion."

In many surveys and interactive polling conferences, we have queried docs about their usual recommendations for patients in various clinical situations. For this issue of *Patterns of Care*, we add a new twist to this time-tested strategy and focus on how physicians react to the recommendations of other docs.

The purpose of this exercise was to identify situations where concordance and discordance exist in the application of evolving clinical research findings.

For example, for the enclosed October 2007 survey, we presented the cases of three women with node-negative breast cancer to our cohort of 150 medical oncologists and 50 research leaders, and specified a "first opinion" from a different source for each case.

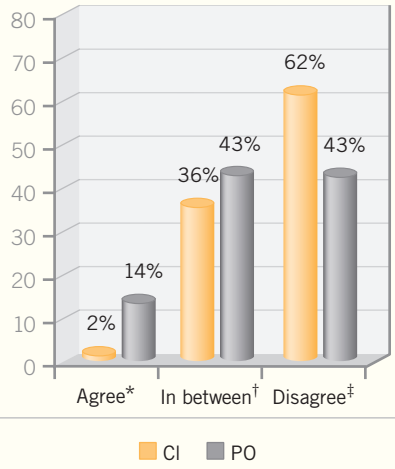
We then asked these individuals if they agreed with the first recommendation and, if not, whether they felt strongly enough to state that the first opinion was not an acceptable option.

It is an interesting reflection of how this field has developed that the approaches to these three patients vary based on variables like HER and ER status and patient age.

The responses suggest some strong disagreement in clinical practice that have profound implications for patient care. In essence, we found situations in which the preferred treatment recommendations of a substantial number of docs are not acceptable to many others, and these relate to major decisions such as the decision to recommend adjuvant chemotherapy or not.

Below, find a few thoughts on these test balloons, including a "third opinion" that reflects my views of how the risk-benefit tradeoffs might look to me as a patient.

CASE 1 (SEE FIGURE 16, PAGE 17): ***A 45-year-old premenopausal woman with a 0.8-cm, ER-positive, PR-positive, HER2-negative, node-negative tumor and a high recurrence score on the Oncotype DX™ assay (35) — First opinion: LHRH agonist and an AI, no chemotherapy***



* This is what I would recommend; † This is an acceptable treatment option but not what I would recommend; ‡ This is not an acceptable option

Way back in 2000, the NIH Consensus Conference on Adjuvant Therapy for Breast Cancer would not have recommended adjuvant chemotherapy for this woman, based on the small size of the tumor. What the consensus panel had no way of predicting was that after decades of less-than-exciting studies and papers on prognostic and predictive factors in breast cancer, someone finally got it right in the form of the Oncotype DX assay.

How much has this test changed practice? For this case, we noted that the recurrence score was high but that the first doc recommended only endocrine therapy — a standard approach in 2000, although in this case, the treatment recommended (an LHRH agonist and an AI) would not have been considered at the time.

Today, almost all investigators and practicing oncologists would use chemotherapy in this situation, and most feel

so strongly about it that they essentially would refute the first opinion for withholding chemo.

The choice of hormone therapy in this case is also interesting in that for this woman, who was premenopausal at diagnosis with a node-negative tumor, most docs would use an AI at some point, either up front with ovarian suppression or after menopause had interceded.

One important aspect of the NSABP data set on Oncotype DX is that patients with high recurrence scores generally derived much less or no benefit from tamoxifen. As such, clinicians may be taking this as a clue to consider new or more promising therapies — for example, an AI and LHRH agonist — even without definitive trial data.

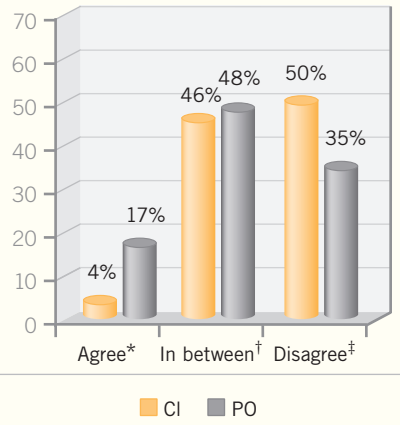
In 2008, the Oncotype DX assay will, for the first time, include reporting of quantitative ER and PR, and it will be interesting to observe whether docs start altering decisions in challenging cases like this one based on these numbers.

As the third opinion on this vexing case, here's what I might be thinking if I were the patient looking at a prognosis without chemo similar to a patient with a node-positive tumor and with the potential to reduce my risk of recurrence by 75 percent. I'd force myself to consider chemotherapy, and like the majority of survey respondents, I'd go with TC (docetaxel/cyclophosphamide) — another intervention that pretty much didn't exist in 2000.

In terms of hormone therapy, I'd like to see that quantitative ER, but even if it was high, I would likely be nervous that this was an aggressive tumor that just got caught early. If I were not interested in childbearing — and at 45 and about to receive chemo followed by hormones for at least five years, that might be a far away thought — perhaps I'd just check into the closest laparoscopy center for an

oophorectomy and maybe add tamoxifen or more likely an AI and see how it goes.

CASE 2 (SEE FIGURE 17, PAGE 18):
A 65-year-old woman with a 0.8-cm, ER-positive, PR-positive, HER2-negative, node-negative tumor and a high recurrence score on the Oncotype DX assay (35) — First opinion: 4 cycles of dose-dense AC followed by tamoxifen for 5 years, then no further treatment



* This is what I would recommend; † This is an acceptable treatment option but not what I would recommend; ‡ This is not an acceptable option

These are the same numbers as in case 1 but for a postmenopausal woman. The difference here is that the first opinion recommended chemotherapy (dose-dense AC) but the endocrine treatment suggested was tamoxifen.

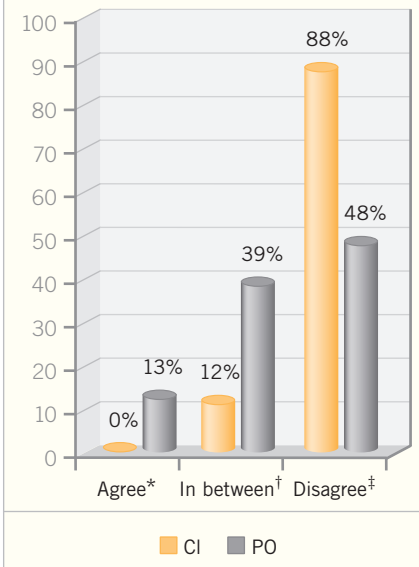
As with the first case, most docs didn't much like the first opinion, but in this case, mainly due to the endocrine recommendation. It's interesting to reflect back to December 2001, when Mike Baum presented the first AI adjuvant data (ATAC) in San Antonio. On that day, Mike and Aman Buzdar, another ATAC trialist, in separate interviews both flat out said, "It's time to say goodbye to tamoxifen as first-line adjuvant endocrine therapy in postmenopausal women."

It took several years of teeth gnashing and committee pronouncements before the breast cancer "intelligencia" finally agreed, but currently, the sentiment is strong enough that most docs reject a first opinion of tamoxifen, at least in this case.

For me as a patient, the AI is a no-brainer, and I am also not sold on AC as the best chemo option, as I am particularly struck by Dennis Slamon's recent comments on several of our programs about his belief that anthracyclines no longer have a role in the adjuvant breast cancer setting — not in HER2-positive or HER2-negative disease, regardless of nodal status.

Not many other investigators take such a strong stance, but Dennis's track record and his slide set convinced me. So I'm back to TC, this time with five years or maybe even more of an AI, depending on how I tolerate it.

CASE 3 (SEE FIGURE 6, PAGE 10):
A 70-year-old woman with a 1.2-cm, ER-negative, PR-negative, HER2-positive, node-negative tumor — First opinion: Trastuzumab alone



* This is what I would recommend; † This is an acceptable treatment option but not what I would recommend; ‡ This is not an acceptable option

This case raises the issue of adjuvant trastuzumab without chemotherapy. Everyone knows we don't have definitive randomized data on this important clinical question and are stuck with indirect comparisons and laboratory predictions. Most docs prefer adding some type of chemo to trastuzumab unless it's just too risky.

The question is, how old is too old? Or maybe, how comorbid is too comorbid? Given the high rate of early relapse in both ER-negative and HER2-positive disease, patients without major medical problems might need to be in their nineties to avoid a recommendation for a chemo/trastuzumab cocktail.

As for me — at age 70 and in otherwise good health, G–d willing — I'm going with a taxane alone with trastuzumab. I might even be tempted to take a shot at weekly *nab* paclitaxel/trastuzumab, although the thought of Cremophor® paclitaxel and the thought of my manic self on corticosteroids might be worth the price of admission to friends, family and colleagues, as there is a pretty good chance I'd find myself down at the local Sizzler just before closing time, devouring everything on the pasta bar while my hypothalamus was driven insane by a cortisol bath.

In reviewing these and other findings in the enclosed survey, and particularly trying to put myself in the place of people facing these vexing situations, one other thought is relevant, namely that patients themselves might find these types of data interesting and useful. Most people don't seek second, third or tenth opinions, but surveys like this might serve that function by providing a snapshot of the variability that currently exists in clinical oncology practice.

— Neil Love, MD
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December 6, 2007

SELECT PUBLICATIONS

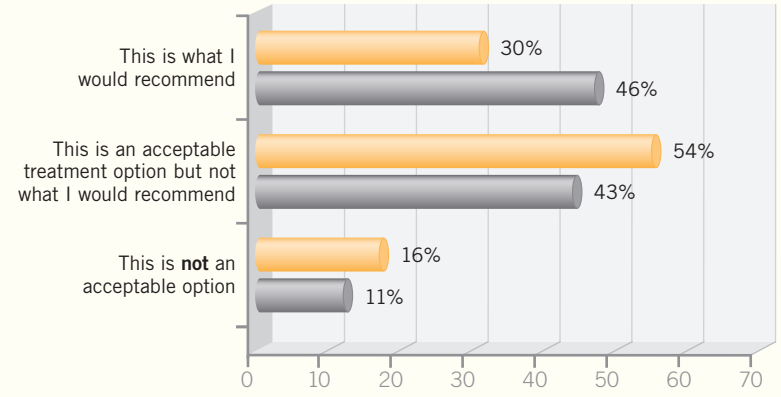
Jones SE et al. **Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer.** *J Clin Oncol* 2006;24(34):5381-7. Abstract

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

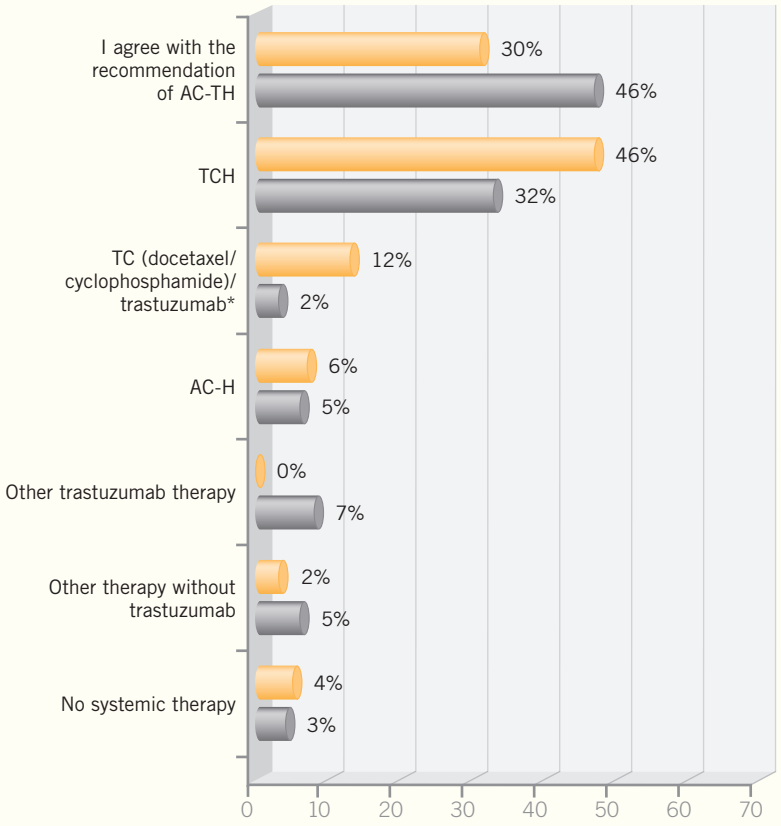
Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive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

FIGURE 1

Case 1: *A 65-year-old woman with a 0.8-cm, ER-negative, PR-negative, HER2-positive, node-negative tumor consults you for a second opinion.* ***The first oncologist she saw recommended AC-TH*** *(AC followed by paclitaxel/trastuzumab). What would you tell this patient regarding the recommendation?*



Which therapy would you recommend?



* Either concurrent or sequential trastuzumab

Adjuvant trastuzumab for smaller, node-negative, HER2-positive tumors (Figure 1)

DR HAROLD J BURSTEIN: This question for the patient with a node-negative, HER2-positive tumor comes up often in the clinical setting because the value of trastuzumab for higher-risk, node-positive breast cancer is clearly established.

The tumor board question we most frequently encounter for HER2-positive disease relates to these particularly small tumors, with which patients generally have a good prognosis.

As a general strategy, trastuzumab appears to reduce the risk of recurrence by one half. Across all of the adjuvant trials, that 50 percent risk reduction stands out as a consistent finding. The questions are, what is the residual risk for these smaller, HER2-positive tumors, and would it make sense to offer a treatment that would cut that risk in half?

Most of us seriously consider offering trastuzumab-based therapy to women with tumors greater than six millimeters in size, which is admittedly an arbitrary cutoff. It resonates because, historically, that was about the absolute smallest tumor size for which we would consider adjuvant chemotherapy in the era before trastuzumab.

I would treat this patient with chemotherapy and trastuzumab. A regimen such as docetaxel/carboplatin/trastuzumab (TCH) would be reasonable, but I would more commonly use four cycles of AC followed by trastuzumab or AC → TH. We recently activated a clinical trial in which we are using 12 weeks of paclitaxel with trastuzumab followed by the remainder of a year of trastuzumab to see if we can use a single chemotherapy drug for a three-month duration and avoid an anthracycline for these patients with lower-risk disease as defined by tumor size.

FIGURE 2

What would you reply if an otherwise healthy 65-year-old woman with a 0.8-cm, node-negative, ER-negative, PR-negative, HER2-positive tumor asked you the following questions?

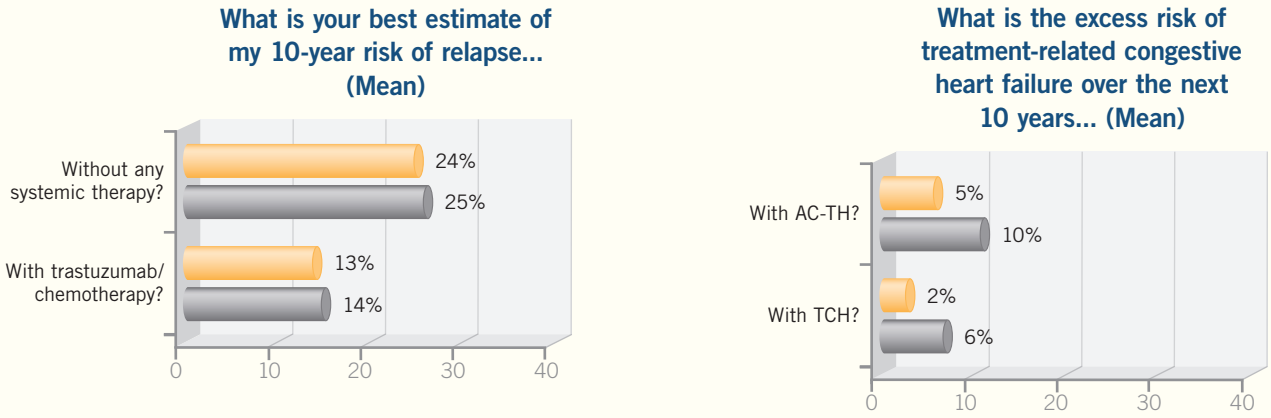


FIGURE 3

Case 2: *A 65-year-old woman with a 1.5-cm, ER-negative, PR-negative, HER2-positive, node-negative tumor consults you for a second opinion. She has a history of medically controlled hypertension.* ***The first oncologist she saw recommended AC-TH****. What would you tell this patient regarding the recommendation?*

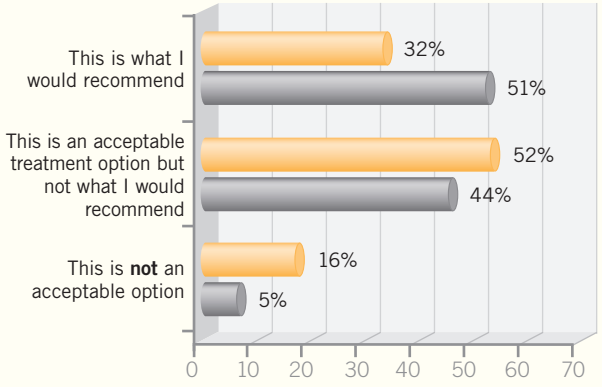
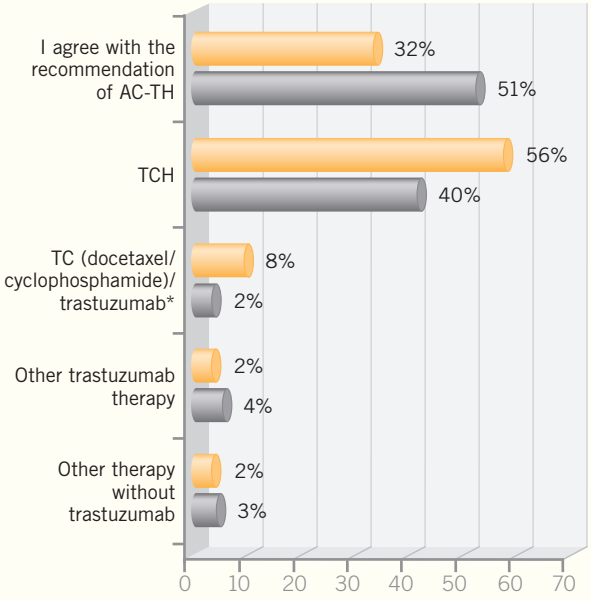


FIGURE 4

Which therapy would you recommend?



* Either concurrent or sequential trastuzumab

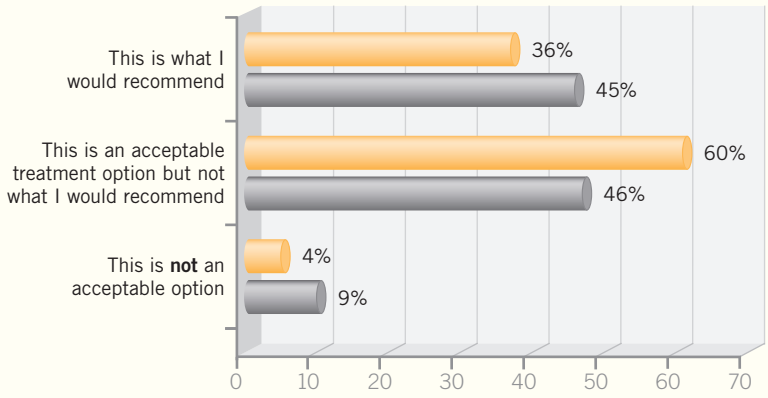
Estimated risk of relapse for smaller, HER2-positive tumors (Figure 2)

DR BURSTEIN: It's hard to find meaningful data on the clinical outcomes for tumors that are smaller than one centimeter, particularly for stratification by HER2 status. Our own group from Massachusetts General and Dana-Farber reported an abstract about a year ago at San Antonio, which reported on our patients with T1N0 breast cancer, who were historically treated with a variety of adjuvant therapies. We identified a risk of recurrence of about 15 to 20 percent over 10 years, which is not too far from what people were estimating in the survey.

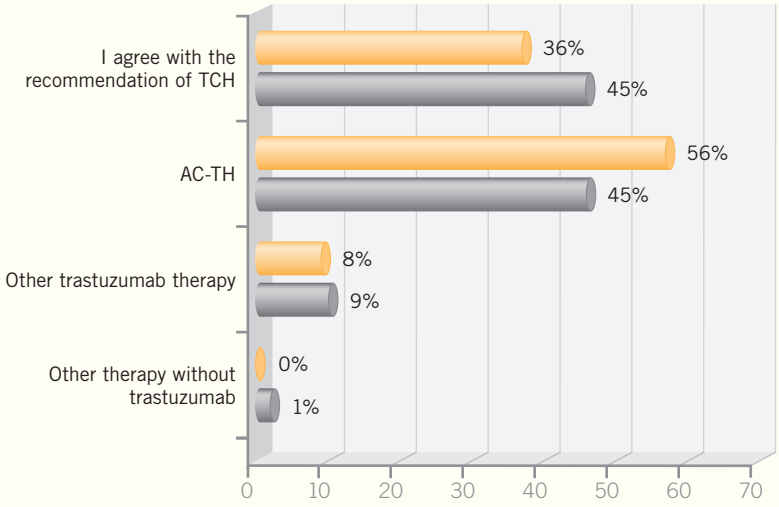
The NSABP has conducted several

FIGURE 5

Case 3: *A 42-year-old premenopausal woman in good health with a **1.2-cm**, ER-negative, PR-negative, HER2-positive tumor with 4 positive nodes consults you for a second opinion. **The first oncologist she saw recommended TCH**. What would you tell this patient regarding the recommendation?*



Which therapy would you recommend?



trials over the years that have included women with small tumors. In a publication a couple of years ago in the *Journal of the National Cancer Institute*, the NSABP showed that for women with 1-cm or smaller tumors, the risk of recurrence over about eight years of follow-up was approximately 10 to 15 percent. They did not have that broken out by HER2 status, but that would be the estimate for the subset of patients with ER-negative disease. I probably would have said about 15 percent, but I believe that's still a higher risk than we would have imagined for a tumor that was both ER-positive and HER2-negative.

Estimating the risk of cardiac toxicity associated with trastuzumab in combination with chemotherapy (Figure 2)

DR BURSTEIN: Cardiac toxicity is a major concern with trastuzumab-based regimens. Of the 10,000 women treated in the adjuvant trastuzumab trials, 9,000 received anthracycline-based regimens. In the best cardiac analyses conducted, which included independent cardiac review, comprehensive case tracking and assessment with follow-up including resolution of cardiac symptoms, the NSABP suggests about a four percent risk of clinically apparent congestive heart failure with an anthracycline- and trastuzumab-based regimen.

They seem to have identified some risk factors, which include preexisting hypertension, borderline cardiac ejection fraction at baseline and age greater than 60 or 65 years. The four percent estimate is probably the best number in the aggregate, but it probably is determined in part by some clinical features that most clinicians can easily tease out.

The TCH regimen, yet to be published, has not shown as high a rate of congestive heart failure in preliminary reports. The two percent estimate from the clinical investigators in the survey seems about right.

It might be a little higher than the one percent estimate that Dennis Slamon has reported. On the other hand, the case assessment has been somewhat less rigorous in this trial to date than has been reported in the North American Intergroup and NSABP experiences.

Adjuvant therapy selection for a 65-year-old patient with a 1.5-cm, node-negative, HER2-positive tumor (Figures 3-4)

DR BURSTEIN: For patients whose risk of relapse is greater, I feel somewhat more strongly about the concurrent as opposed to the sequential use of chemotherapy and trastuzumab.

We don't have definitive data yet, but the comparisons from N9831 (AC → T versus AC → T followed sequentially by trastuzumab versus AC → T with concurrent trastuzumab) suggest that using chemotherapy and trastuzumab concurrently may be particularly useful. So for patients whose risk is higher, I strongly prefer concurrent chemotherapy and

trastuzumab regimens, which include AC → TH or TCH.

We still principally use anthracycline-based regimens. Anthracyclines are historically important drugs in breast cancer. Comprehensive retrospective analyses suggest that the one group of patients in whom these drugs work is those with HER2-driven breast cancer. I believe they probably still have a role even with trastuzumab.

All of us are eager to see how the more mature data from BCIRG 006 develop. That study, which used docetaxel for the T, was never designed to compare the TCH to AC → TH. Numerically, they appear similar. The differences in clinical events are few, though obviously those data are still maturing.

Adjuvant therapy selection for a 42-year-old patient with a 1.2-cm, node-positive, HER2-tumor (Figure 5)

DR BURSTEIN: The risk of recurrence has gone up because the tumor is node-positive. With that, the recommendations for an anthracycline-based regimen have risen. I don't disagree with that because, as I mentioned, that's our preferred regimen.

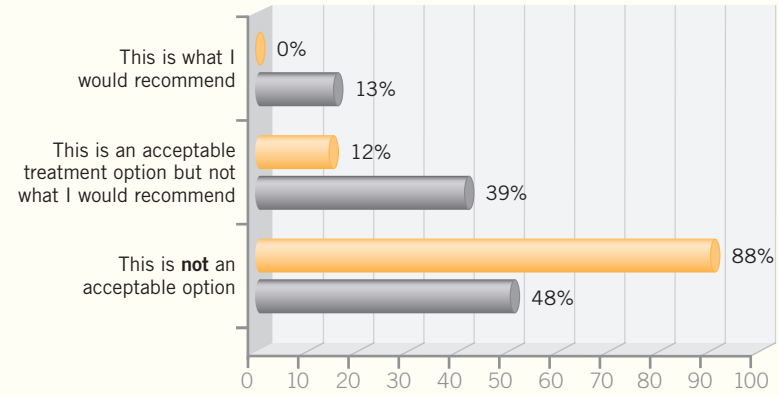
I don't know of data to tell you whether to use an anthracycline-based regimen or TCH based on those clinical features. None of the studies have reported that anthracyclines are particularly valuable in younger versus older women. I suspect physicians may be making this recommendation based on cardiotoxicity risk.

Clearly, younger women seem to bear a lower risk of cardiotoxicity with the anthracyclines. We have not seen a detailed breakout of the cardiac risk associated with TCH as a function of age, though the events may be rare enough that it's hard to do.

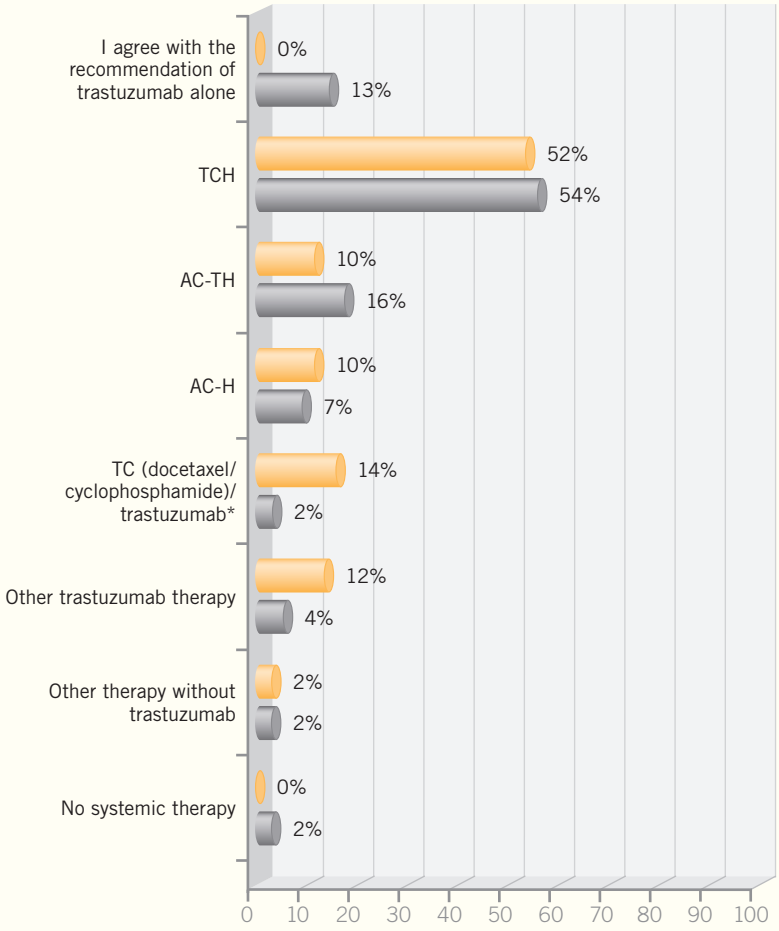
Trastuzumab may be the trump card. Therefore, whatever you use besides trastuzumab may not be relevant. This is why we feel that going ahead with a paclitaxel/ trastuzumab trial for patients with low-risk disease makes sense.

FIGURE 6

Case 4: A 70-year-old woman with a 1.2-cm, high-grade, ER-negative, PR-negative, HER2-positive, node-negative tumor consults you for a second opinion. ***The first oncologist she saw recommended trastuzumab alone****. What would you tell this patient regarding the recommendation?*



Which therapy would you recommend?



* Either concurrent or sequential trastuzumab

FIGURE 7

Would you be comfortable enrolling an otherwise healthy 65-year-old woman with an ER-negative, PR-negative, HER2-positive tumor in a randomized adjuvant clinical trial that has one arm administering lapatinib as the only anti-HER2 therapy in the following scenarios?

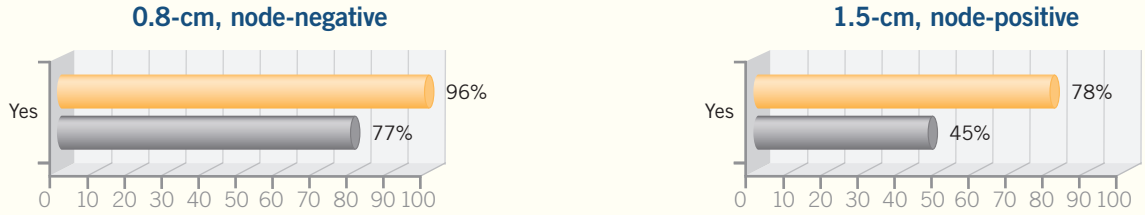
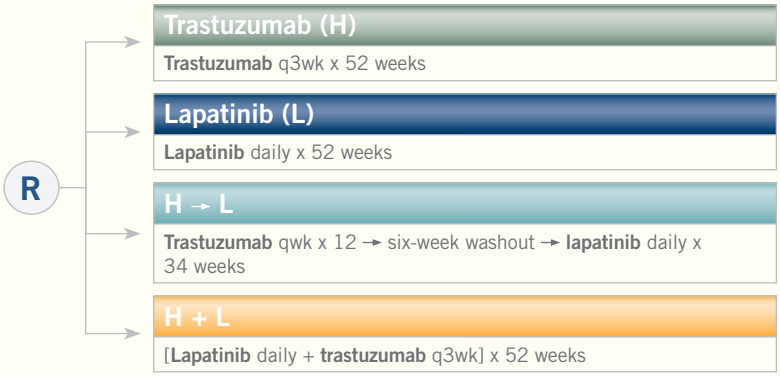


FIGURE 8

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

Protocol IDs: BIG 2-06, NCCTG-N063D, IBCSG 36-07
Target Accrual: 8,000



Eligibility

- HER2-positive breast cancer
- Prior treatment with at least four cycles of an approved anthracycline-based chemotherapy regimen

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

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

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

SOURCES: *Breast International Group Newsletter* Spring 2007;9(1); www.ibcsg.org; NCI Physician Data Query, September 2007.

Adjuvant therapy selection for elderly patients with HER2-positive disease (Figure 6)

DR BURSTEIN: HER2-driven disease is far more frequent in younger than in older women. You shouldn't be seeing too much HER2-positive breast cancer among women in their seventies and eighties. In large registry-type studies, we would expect fewer than five or eight percent of those tumors to be HER2-positive.

I expect relatively few people in your survey had used TCH for an 80-year-old woman, to know what that experience is like. I've used it for some septuagenarians, and it's a tough regimen. It's not a trivial chemotherapy regimen to get people through.

I believe for older women, it becomes ever more the "art of medicine" to assess their comorbid conditions, their existing cardiac function and the importance of these treatments. If they're healthy enough to tolerate the treatment and healthy enough that they merit consideration of treatment, then I believe any of these regimens would still be reasonable.

These regimens work in older women to the extent that they're at risk for breast cancer recurrence. Hyman Muss and others have shown, through retrospective work, that chemotherapy works as well in older patients as in younger patients if they have chemotherapy-sensitive tumors. So practitioners need more clinical seasoning to feel strongly that one regimen is preferable to another.

I would most likely recommend four cycles of AC followed by trastuzumab for a 70-year-old patient with a 1.2-cm, node-negative, ER-negative, PR-negative, HER2-positive tumor. If you wanted to try TCH, that would be reasonable, but it's not a trivial regimen. Trastuzumab monotherapy would not be my choice

if the tumor were ER-negative. No data support the role of adjuvant trastuzumab for patients not treated with chemotherapy.

ALTTO trial design (Figure 8)

DR BURSTEIN: ALTTO is a randomized trial in which patients receive chemotherapy with either trastuzumab alone, trastuzumab and lapatinib, lapatinib alone, or a sequence of lapatinib followed by trastuzumab.

One wrinkle to this study is that clinicians have the option of administering chemotherapy first, followed by the biologic therapy, or chemotherapy concurrently with the biologic therapy. It's a somewhat complicated study. For that reason, it's a large trial — an 8,000-person trial. A simpler study might have compared chemotherapy with trastuzumab to chemotherapy with trastuzumab and lapatinib. Preclinical data suggest that trastuzumab and lapatinib is better than either drug alone.

On the other hand, that trial would not have answered the lapatinib monotherapy question, which certainly is of interest because it might be appealing as an orally available drug, if it's shown to be as effective and tolerable as intravenous trastuzumab.

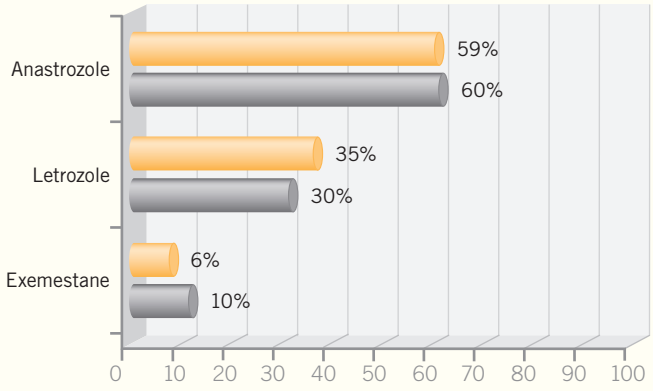
I agree with the sentiments expressed by some people that for a patient with a substantial risk of recurrence, the possibility of using lapatinib monotherapy in the adjuvant setting is of concern when we know that trastuzumab is a life-saving drug. This is evident in the survey results. I believe in the US, a bias will emerge toward enrolling patients with lower-risk disease in ALTTO. Whether the Europeans or the rest of the global community will feel the same way remains to be seen.

Clinical use of adjuvant aromatase inhibitors as initial therapy (Figure 9)

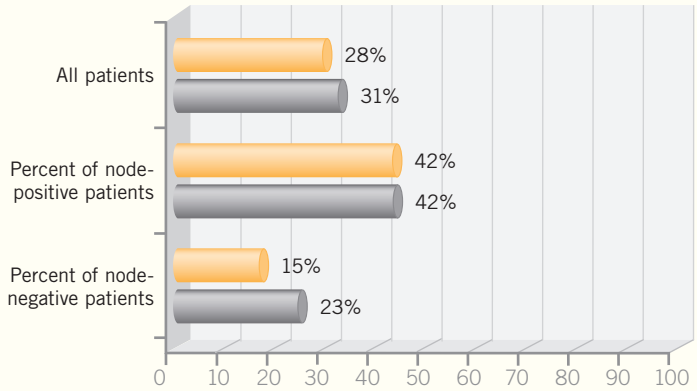
DR BURSTEIN: Three aromatase inhibitors are commercially available. If clinical differences between them exist, it's been impossible to tease them out to date. I

FIGURE 9

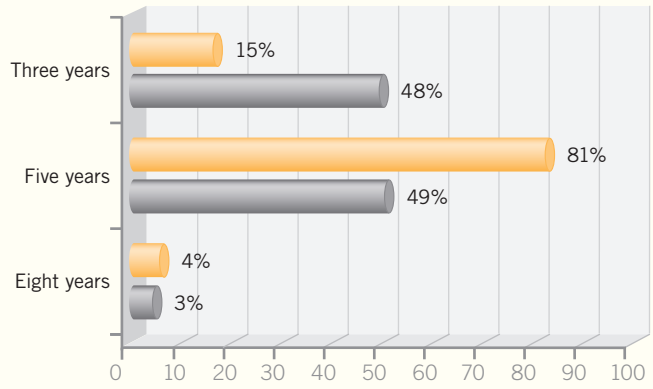
When you use an aromatase inhibitor (AI) in the initial adjuvant setting, what percent of those patients receives each AI? (Mean)



For approximately what percent of your patients who complete 5 years of an AI do you continue the AI? (Mean)



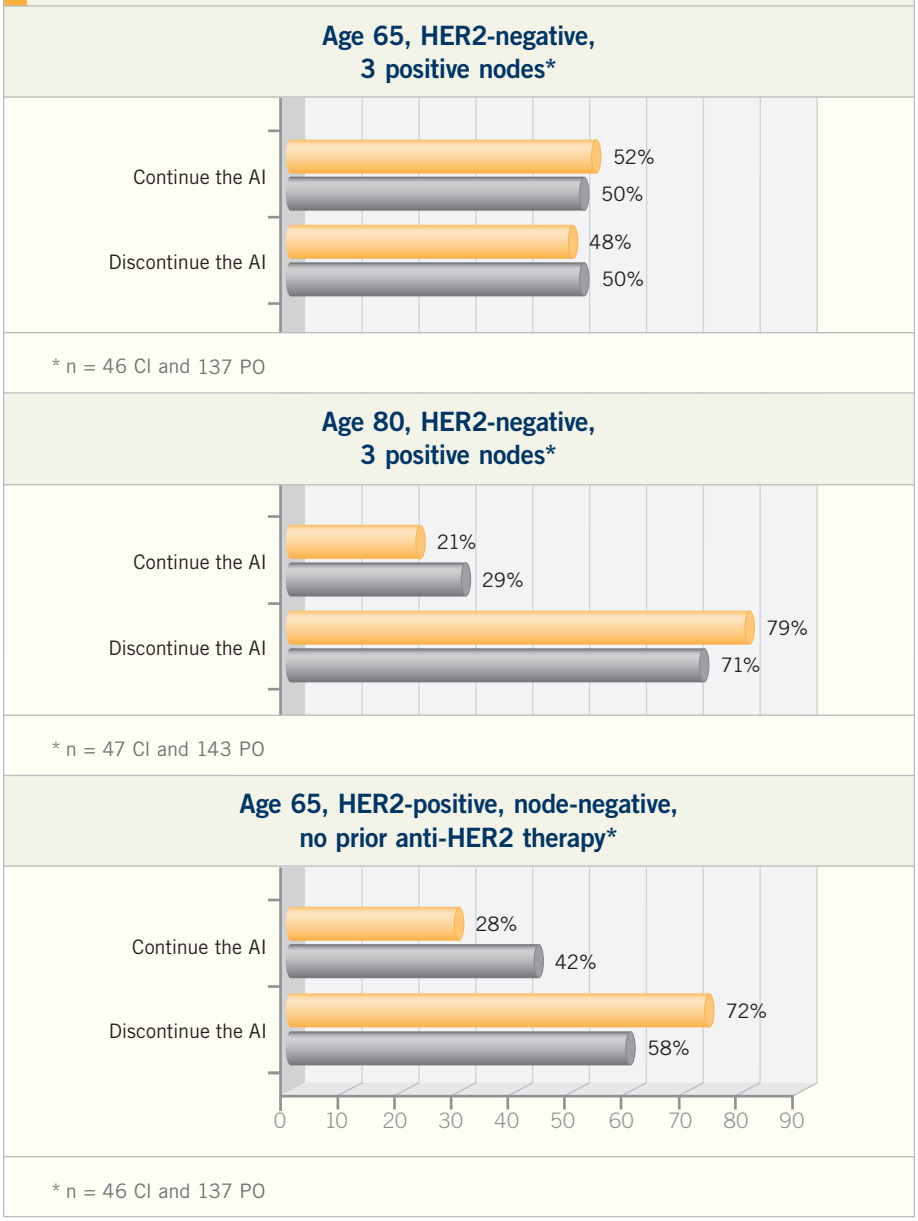
*For patients whom you have switched from tamoxifen to an AI after the first 2 years, what is your recommendation for the duration of the AI?**



* n = 46 CI and 143 PO

FIGURE 10

A woman with an ER-positive tumor is about to complete 5 years of an adjuvant AI and seeks your opinion about whether to continue the AI at this point (off protocol). She had no problems on the AI and previously received adjuvant AC → paclitaxel. What would you recommend in the following patient scenarios?



believe that any one of these is probably a reasonable clinical choice.

Having said that, we have data for the use of both anastrozole and letrozole as initial adjuvant treatment, and we do not have those data to date from trials involving exemestane, although such studies have been concluded and eventually we will have the data.

So it wouldn't be my style preference, but I don't believe it's a big mistake to use exemestane. It probably wouldn't be my first choice, but if a patient comes to me six weeks into treatment and says, "I feel great on this drug," I wouldn't derail that plan, if she were tolerating it.

Duration of therapy with an adjuvant aromatase inhibitor (Figure 10)

DR BURSTEIN: Before we had data from the NSABP-B-14 extension trial and the Scottish trial, patients were often receiving more than five years of tamoxifen. It turned out, at least based on the literature we have so far, that this was not clinically valuable. We need answers to the question, does extending adjuvant therapy beyond five years of an aromatase inhibitor improve long-term clinical outcomes?

Ongoing studies by the NCIC and the NSABP are randomly assigning women who have finished five years of an aromatase inhibitor to ongoing therapy with an aromatase inhibitor or placebo. We will have data, but there are none right now. What we can say is that we have a large safety experience for five years of treatment.

Parenthetically, I believe that one of the cleanest of the adjuvant aromatase inhibitor trials to interpret is MA17, which evaluated five years of tamoxifen followed by placebo or an aromatase inhibitor. Clearly, switching to an aromatase inhibitor was helpful. That study also reawakened us to the importance of the second and the third five years after diagnosis.

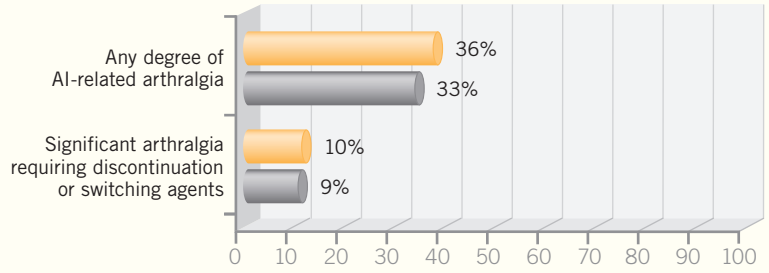
If you conceptualize hormone receptor-positive breast cancer as a disease with a 10- to 15-year latency period, then it is possible that ongoing durations of antiestrogen therapy with aromatase inhibitors might be helpful, but we don't actually have those data.

In contrast, we do have data suggesting that a successful strategy could be five years of tamoxifen and then five years of an aromatase inhibitor.

For women who have finished five years of tamoxifen and then five years of an aromatase inhibitor, we certainly don't have data showing that therapy for longer than 10 years is valuable, and we usually conclude therapy at that point. Women who have received tamoxifen for

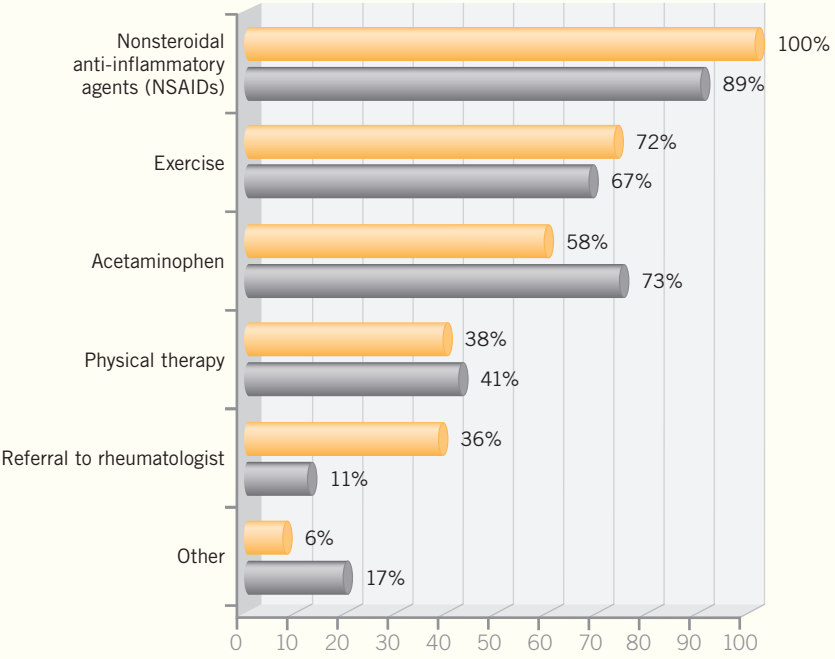
FIGURE 11

*When initially prescribing an AI, what percent chance do you generally quote to patients for developing the following conditions? (Mean)**



*n = 50 CI and 142 PO who mention the possibility of developing an AI-related arthralgia when initially prescribing an AI

Which of the following treatment options do you recommend to manage AI-related arthralgias? (May have more than one response)



a couple of years and then an aromatase inhibitor for five years are then out to year seven or eight.

I don't have a big problem extending their therapy to year 10, but again, we only have safety data for five years of an aromatase inhibitor. For a woman who starts an aromatase inhibitor at year zero, we have no data suggesting that ongoing therapy would be helpful. We all thought that tamoxifen indefinitely would be helpful, which has turned out to not be the case so far.

You can observe several different kinds of patients. You have the women who, three years ago, circled the date on their calendar on which they would finish their adjuvant endocrine therapy, and they've been counting down. For such women, I believe it's certainly reasonable to stop treatment at that time. Then you have women who feel fine or may not feel perfect but love the idea of taking something because it feels reassuring to undergo some treatment to prevent breast cancer recurrence.

For those women, I don't have a major objection to extending the duration of treatment with the aromatase inhibitors, but we don't know how valuable that would be.

Arthralgias related to the aromatase inhibitors (Figure 11)

DR BURSTEIN: Increasingly we are finding that patients have musculoskeletal symptoms related to the use of aromatase inhibitors. This is a fairly old observation. It was first reported in the literature, in patients with metastatic disease, seven or eight years ago, when the aromatase inhibitors became widely used in that setting. Now it's increasingly prevalent in the early-stage setting.

An interesting study of 200 consecutively screened women who were receiving an aromatase inhibitor in the early-stage setting was conducted at Columbia in New York.

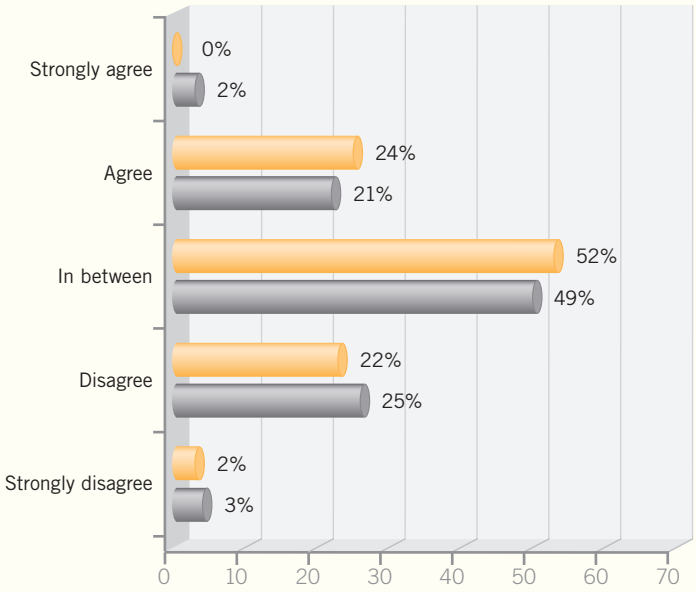
The important methodological point from this paper was that investigators didn't ask the doctors whether patients were experiencing arthralgias — they asked the patients. And over 80 percent of patients said, "Yes, I'm experiencing arthralgias."

Musculoskeletal symptoms are enormously prevalent in our society. Interestingly, for two thirds of the patients the onset of these symptoms seemed directly related to the use of the aromatase inhibitor. In fact, half of the patients had begun on their own to take something, an over-the-counter anti-inflammatory medicine, acetaminophen or something else, to minimize the arthralgias. This says to me that these are clinically real phenomena. I believe that the doctors' one-in-three estimate is something that they're making up because that's what we hear about.

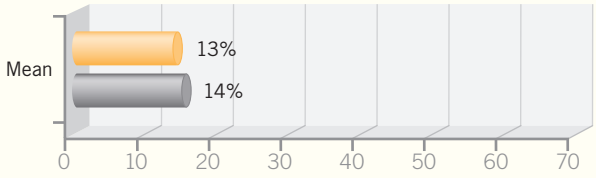
Without a strong comparator group, it's hard to know how much of the arthralgias are from any antiestrogen

FIGURE 12

AI-associated arthralgias seem to occur more frequently among my patients who have also received adjuvant chemotherapy.



Clinically significant arthralgias occur as the result of chemotherapy itself in the following percent of my patients:



intervention or from some concurrent baseline, nonspecific arthritic-type condition, which is common.

Studies define these difficulties in different ways, so it's hard to assess the toxicity experience in the major trials, in which severe toxicity was reported by way of case report forms, and relate that to the experience of patients.

What do you do about the arthralgias? We all talk about acetaminophen and nonsteroidals. Anecdotally, it's not clear that those help much. What does seem to help has been some moderate level of regular exercise. Patients who can get some exercise often find that this alleviates some of their discomfort.

In early 2008, we will begin a placebo-controlled intervention study on alleviating these symptoms. Our strategy is similar to the successful method that Chuck Loprinzi has used at the Mayo Clinic to study hot flashes. We're hoping to use some novel agents to pharmacologically treat these symptoms. Using a placebo-controlled trial design, we will identify which ones might work.

Arthralgias related to chemotherapy (Figure 12)

DR BURSTEIN: A classic paper from the Mayo Clinic in the *Journal of Clinical Oncology* in the late 1980s or early 1990s reported what they called chemotherapy-induced arthritis. It was a series of eight or 10 women, all of whom were in their late forties, who received chemotherapy and presumably experienced chemotherapy-induced amenorrhea and menopause. Then they began to develop these significant arthritis symptoms.

In the recent *JCO* paper (Crew 2007), investigators found that taxane-based adjuvant chemotherapy seemed to increase the risk of musculoskeletal complications. I'm not sure that's my experience in the clinic. The answers from your survey were all over the map on that one. So I believe more data are needed to verify that.

Certainly, paclitaxel is associated with a myalgia syndrome, which typically arises four to five days after treatment. Patients who are receiving growth factor support often have some bone marrow swelling and develop diffuse musculoskeletal achiness about a week into treatment. These are a fairly common set of symptoms among patients with breast cancer.

Chemotherapy-induced amenorrhea (Figure 13)

DR BURSTEIN: The standard treatment for a young woman who has breast cancer is tamoxifen. Good case-report experience indicates that many of these women in their early forties or younger will actually recover ovarian function in the months and even years after chemotherapy. In those cases, monitoring FSH and LH at a single time doesn't tell you what will happen with the ovarian function in the future.

Both our group and Ian Smith's group in London have published cases of women just like this who had begun menopause with chemotherapy. They were started on an aromatase inhibitor.

In many of these cases, their FSH levels were actually in the postmenopausal range. Their ovarian function recovered and they were not receiving effective endocrine therapy. I feel strongly that the correct answer here is tamoxifen until menopause is demonstrated unequivo-

cally. Single or even serial measurements of FSH and LH don't tell you what will happen with these women in the future. So I discourage the monitoring of these levels and clinical decision-making based on those measures.

Hormonal therapy for premenopausal women (Figure 16)

DR BURSTEIN: Since the patient is premenopausal, I believe the answers in the survey reflect the desire to treat her with tamoxifen initially, which I would agree with because it works irrespective of menopausal status.

I believe many favor the idea of switching treatment once it's clear she's menopausal. So in two to three or five years after chemotherapy, with the expectation she would be menopausal, they would switch her to an aromatase inhibitor.

We don't know what her menopausal status would be after four cycles of AC or TC. In clinical practice, this is a situation in which you would have to find

FIGURE 13

A 40-year-old premenopausal woman stopped menstruating when she began chemotherapy. In this situation, monitoring estradiol, FSH and LH hormone levels is an effective way to determine menopausal status.

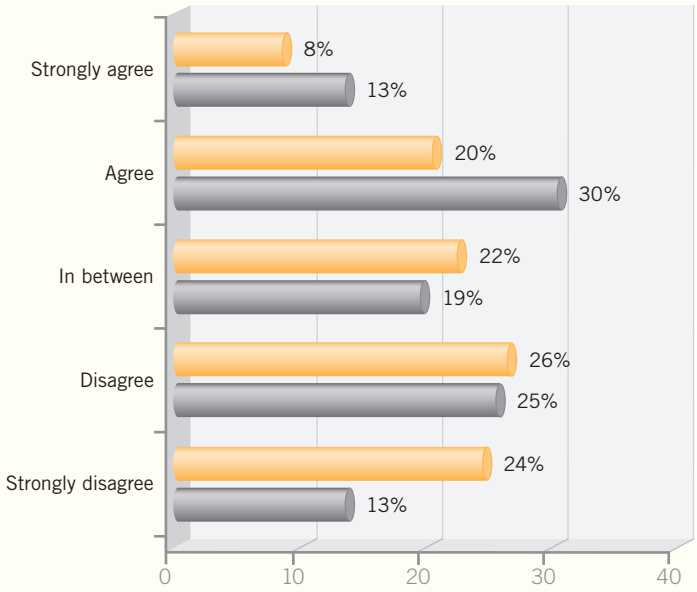
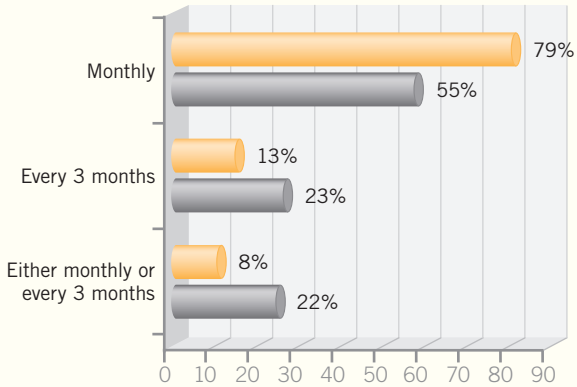


FIGURE 14

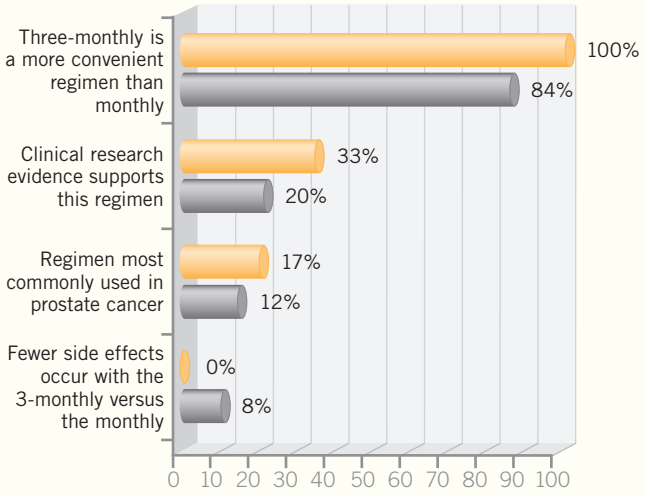
*What is your general approach to scheduling an LHRH agonist as adjuvant therapy for a premenopausal patient with ER-positive disease?**



* n = 48 CI and 107 PO who use adjuvant LHRH therapy for this patient type

FIGURE 15

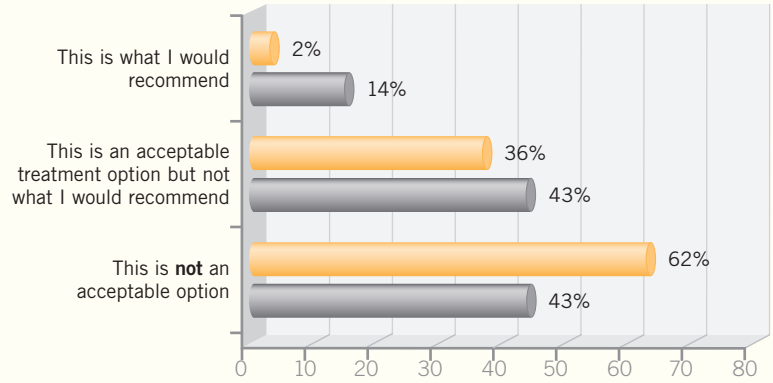
For the 3-monthly schedule, which of the following most closely describes the reason(s) for your recommendation? (May have more than one response)*



* n = 6 CI and 25 PO who generally use 3-monthly LHRH agonists

FIGURE 16

Case 5: *A 45-year-old premenopausal woman with a 0.8-cm, Grade II, ER-positive, PR-positive, HER2-negative, node-negative tumor consults you for a second opinion. The Oncotype DX assay shows a high recurrence score of 35.* ***The first oncologist she saw did not recommend chemotherapy but did recommend an LHRH agonist and an AI****. What would you tell this patient regarding the recommendation?*



out what happens as time goes by. I feel pretty strongly that an aromatase inhibitor with an LHRH agonist is not a preferable option.

The TEXT study is observing young premenopausal women who are receiving ovarian suppression and tamoxifen or ovarian suppression and an aromatase inhibitor.

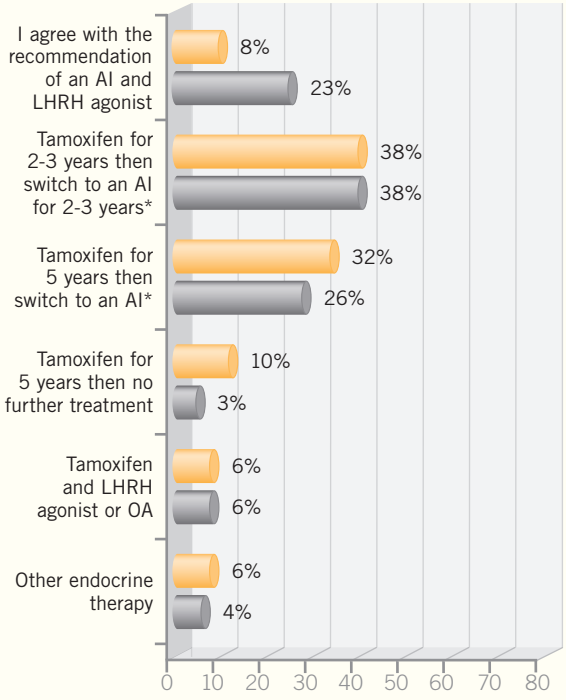
We will have data in the future about whether the aromatase inhibitors are as active as tamoxifen in younger women if used with ovarian suppression.

The worry is that a small fraction of women may not reach complete ovarian suppression with an LHRH agonist.

If you've treated many women, you know that in a small proportion of them, their ovaries won't functionally shut down. So you run the risk, if you treat them with an aromatase inhibitor and

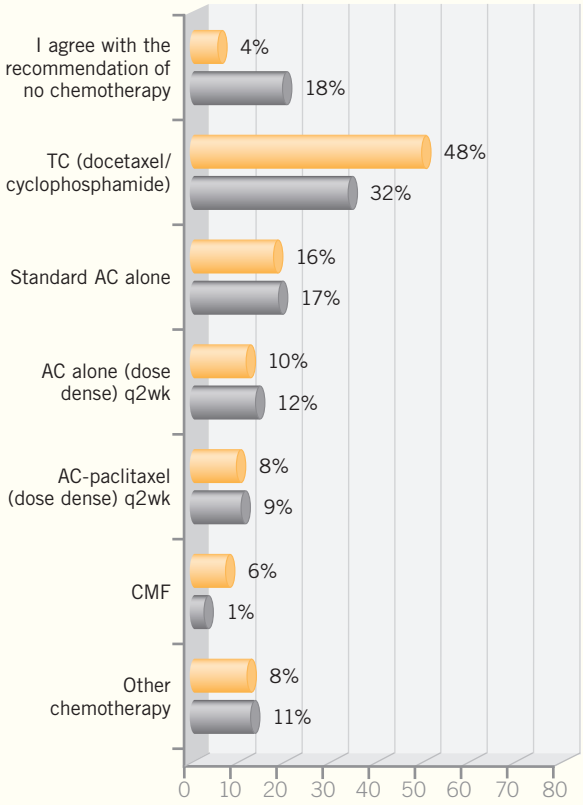
Which therapy would you recommend?

Endocrine therapy



* If patient becomes postmenopausal

Chemotherapy



an LHRH agonist, of their receiving no effective endocrine therapy. I would start with tamoxifen if they were still premenopausal and I wanted to consider ovarian suppression.

Only when they were truly postmenopausal would I consider switching them to an aromatase inhibitor.

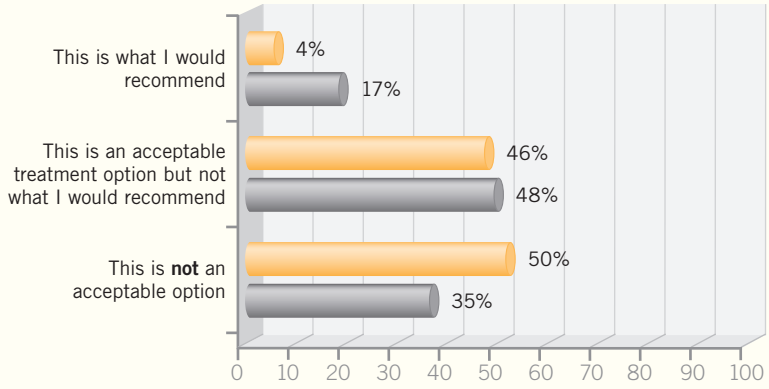
Selecting therapy for a patient with a high Oncotype DX recurrence score (Figure 16)

DR BURSTEIN: The point of ordering the Oncotype DX assay for a patient like this is to find out whether she has either a low or a high score. A low score would suggest she doesn't need chemotherapy.

A high score would suggest she does need chemotherapy. An intermediate score would narrow the range of the potential benefits of chemotherapy but

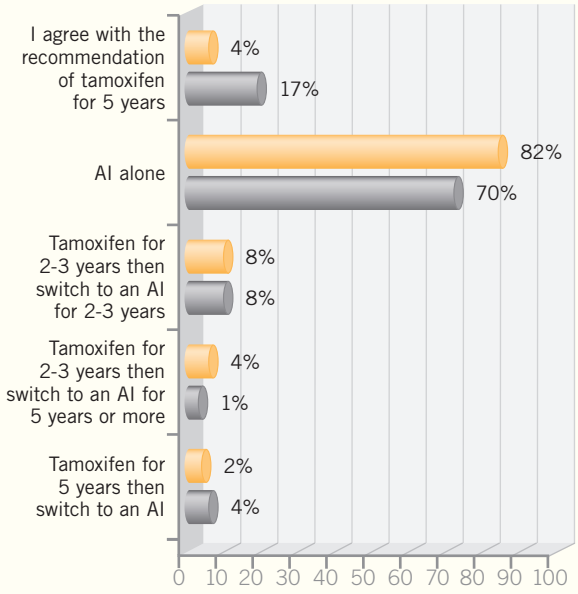
FIGURE 17

Case 6: *A **65-year-old woman** with a 0.8-cm, Grade II, ER-positive, PR-positive, HER2-negative, node-negative tumor consults you for a second opinion. The Oncotype DX assay shows a high recurrence score of 35. **The first oncologist she saw recommended 4 cycles of dose-dense AC followed by tamoxifen for 5 years and then no further treatment**. What would you tell this patient regarding the recommendation?*



Which therapy would you recommend?

Endocrine therapy



Chemotherapy

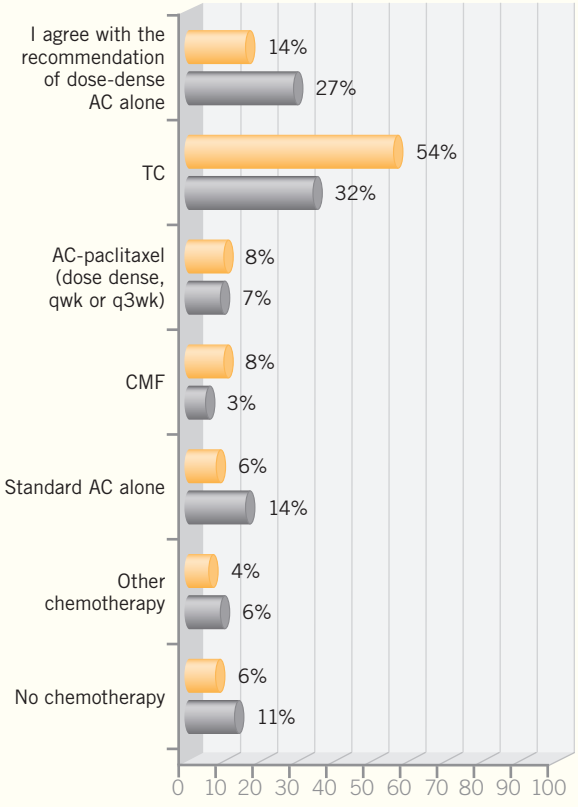
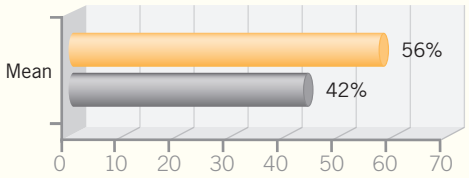


FIGURE 18

About what percent of patients with node-negative, ER-positive, HER2-negative tumors do you think would benefit by having an Oncotype DX assay performed?



(October 2007) The Oncotype DX assay will eventually prove useful for some patients with ER-positive, node-positive disease.

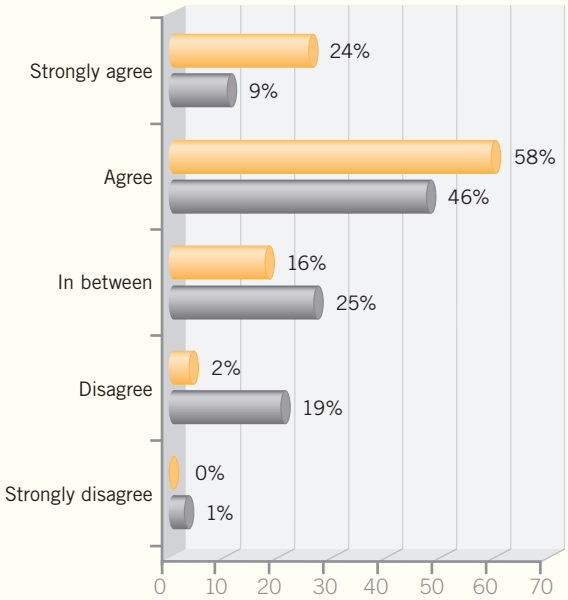
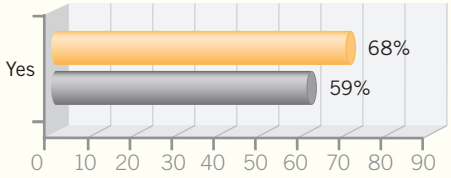


FIGURE 19

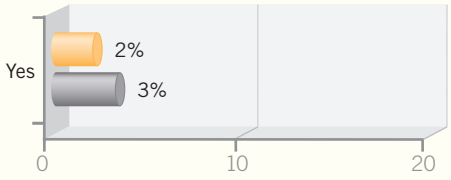
Is size a driving factor in your decision to utilize the Oncotype DX assay for a patient with an ER-positive, node-negative, HER2-negative tumor?



n = 50 CI and 133 PO who use the Oncotype DX assay

FIGURE 20

Have you ordered the MammaPrint® assay?



still leave you in an indeterminate posture. I certainly would have recommended adjuvant chemotherapy for this patient based on that score. None of the most commonly used regimens specified here have been explored in combination with the Oncotype DX assay in the reports from NSABP-B-20. That study was built around CMF and MF.

I believe most of us would use our typical adjuvant regimen for patients with node-negative disease. Ours happens to be AC, typically every two weeks. If people want to use TC, I believe that's a reasonable regimen, but it's not one we routinely use.

DR LEE S SCHWARTZBERG: The Oncotype DX test allows you to select those patients who are exquisitely sensitive to chemotherapy and, by the way, probably don't need aggressive chemotherapy. If you examine the data from the NSABP studies, you see that the chemotherapy administered was a combination of CMF and MF.

Today no one uses MF, and I believe everyone would agree that it's minimal chemotherapy, but despite that, the patients who were in the high recurrence score group, when they received CMF or MF, had a conversion of their disease-free survival rate up into the 90 percent range and a 75 percent relative reduction in the risk of relapse.

Those patients are exquisitely sensitive, and I'm comfortable using CMF for many of them. I still use every three-week CMF because the few times I've tried the oral CMF regimen, I found it difficult for the patients.

Selection of chemotherapy in the adjuvant setting (Figures 21-22)

DR SCHWARTZBERG: We're in a bit of a bind as practitioners right now, based on the retrospective analysis recently published by Dan Hayes in *The New England Journal of Medicine*. The data suggested, or at least the media picked up that they suggested, that taxanes administered after adjuvant AC confer no benefit for patients with estrogen receptor-positive breast cancer. The fact that it was published in *The New England Jour-*

nal and, for some reason, received a lot of uptake from the lay media, I believe, was the most important aspect of that trial.

At the same time, we have other esteemed investigators, like Dennis Slamon, saying that we shouldn't use anthracyclines at all. So which regimen do you use in that common patient population of women with hormone receptor-positive early breast cancer?

The data from Hayes had been presented a year before and were not a surprise to me whatsoever. The surprise to me is that a much more abundant data source of at least seven or eight randomized trials that have analyzed retrospectively or, in some cases, prospectively, suggests that the benefit of anthracyclines accrues only to patients with HER2-positive disease and, therefore, the benefit of both anthracyclines and taxanes may

FIGURE 21

Case 7: *A 40-year-old premenopausal woman with a 1.2-cm, Grade II, ER-positive, PR-positive, HER2-negative tumor with 3 positive nodes consults you for a second opinion.* ***The first oncologist she saw recommended TAC followed by an LHRH agonist q3m and an AI****. What would you tell this patient regarding the recommendation?*

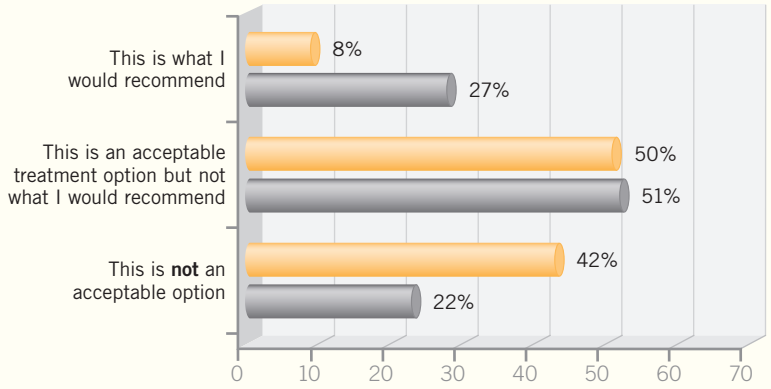
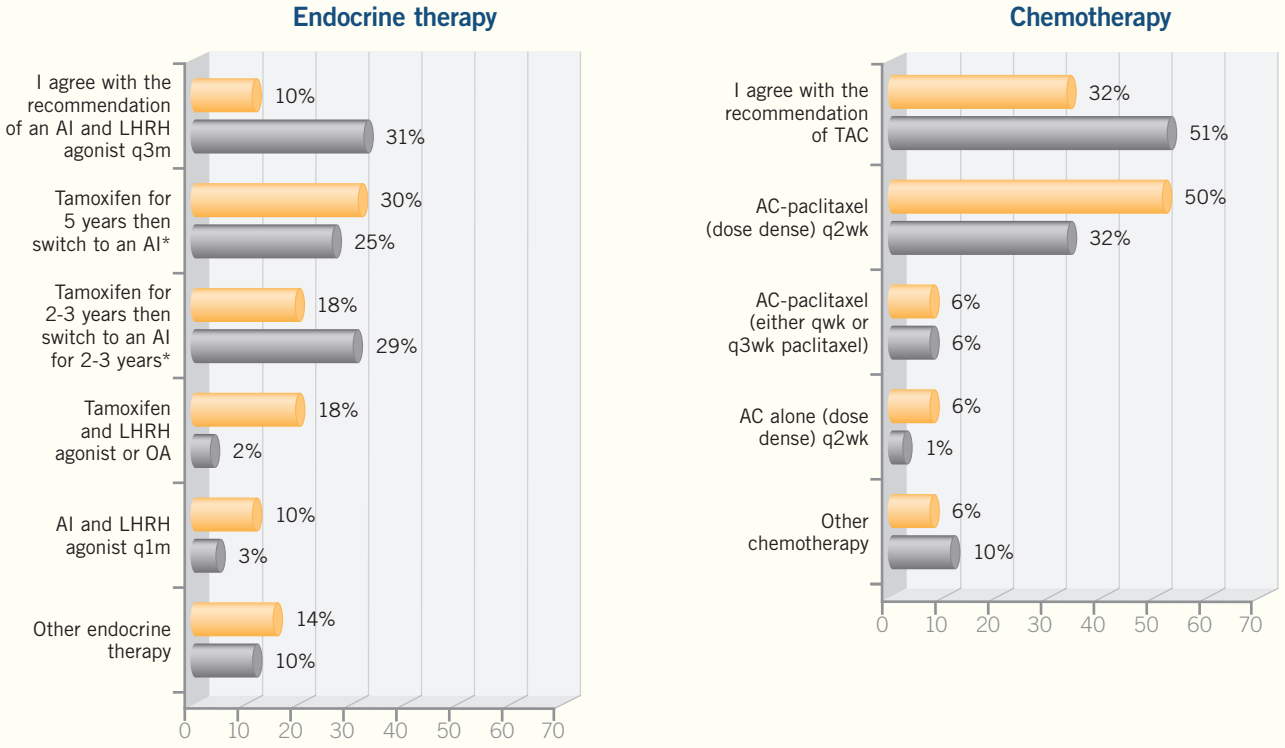


FIGURE 22

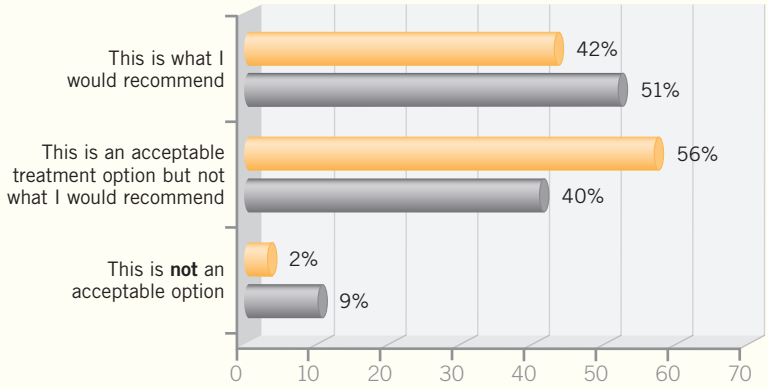
Which therapy would you recommend?



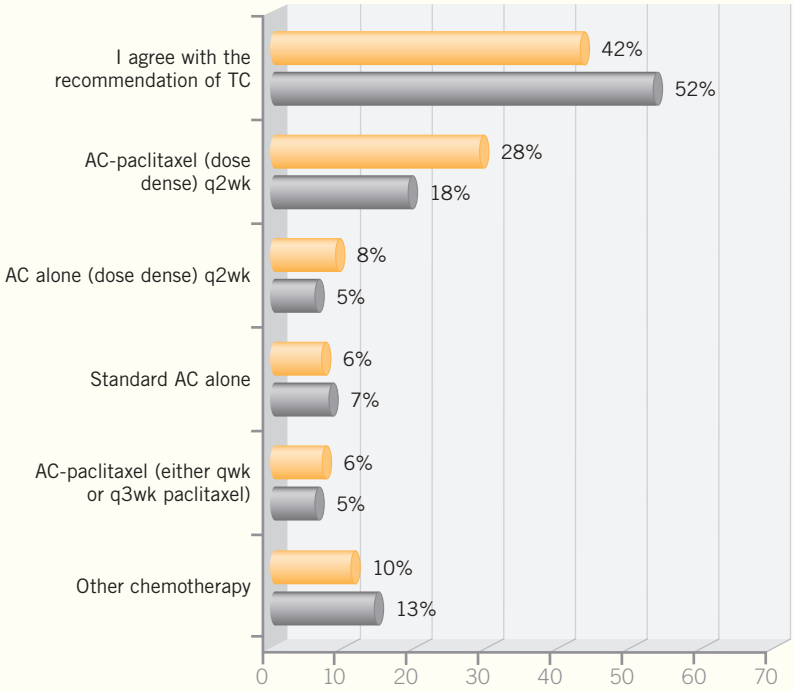
* If patient becomes postmenopausal

FIGURE 23

Case 8: *A 48-year-old premenopausal woman with a 1.2-cm, Grade II, node-negative, ER-negative, PR-negative, HER2-negative tumor consults you for a second opinion.* ***The first oncologist she saw recommended TC****. What would you tell this patient regarding the recommendation?*



Which specific chemotherapy regimen would you recommend?



occur only in that group of patients.

Further data have been published, including the retrospective review of multiple CALGB trials in the *Journal of the American Medical Association*, that show that the incremental benefit of chemotherapy accrues to patients with ER-negative tumors, and not so much or not at all to those with ER-positive disease.

Breast Cancer Update 2007 (1)

DR STEPHEN E JONES: The objective of our US Oncology trial was to compare the disease-free survival between AC and TC for women with operable breast cancer. About half of the women had node-negative disease, and half had node-positive disease. We recruited approximately 1,000 patients and had 5.5 years of median follow-up.

We conducted a preliminary analysis at about three years, in which a difference in favor of TC was emerging. At five years, however, this had become a significant difference, with a *p*-value of 0.015. We saw a one third reduction in the risk of a breast cancer event among the patients who received TC, which is a significant impact and translates into a six percent absolute difference at five years.

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

A trend toward an overall survival benefit ($p = 0.131$) and nearly a 25 percent lower chance of dying were evident among the patients treated with TC. If you present it that way to patients, most will opt for TC. I believe if this trial were larger or we had longer follow-up, we might see a survival difference. The conclusion from the trial was that TC is a new standard nonanthracycline adjuvant regimen.

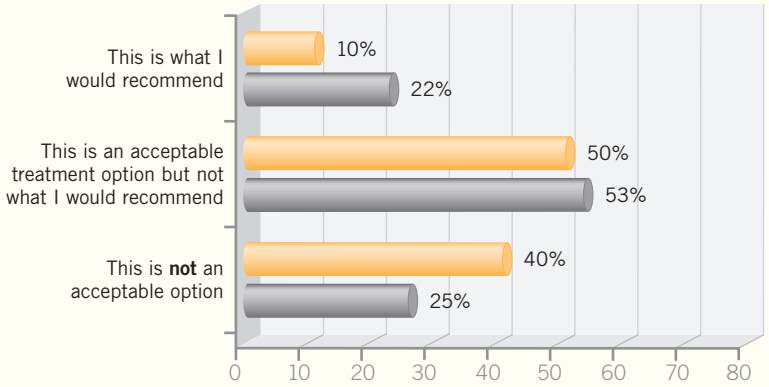
Personally, I would use TC in the population of patients we studied in this trial: Those with node-negative disease or those with one to three positive nodes. It provides a good reduction in the risk of recurrence.

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

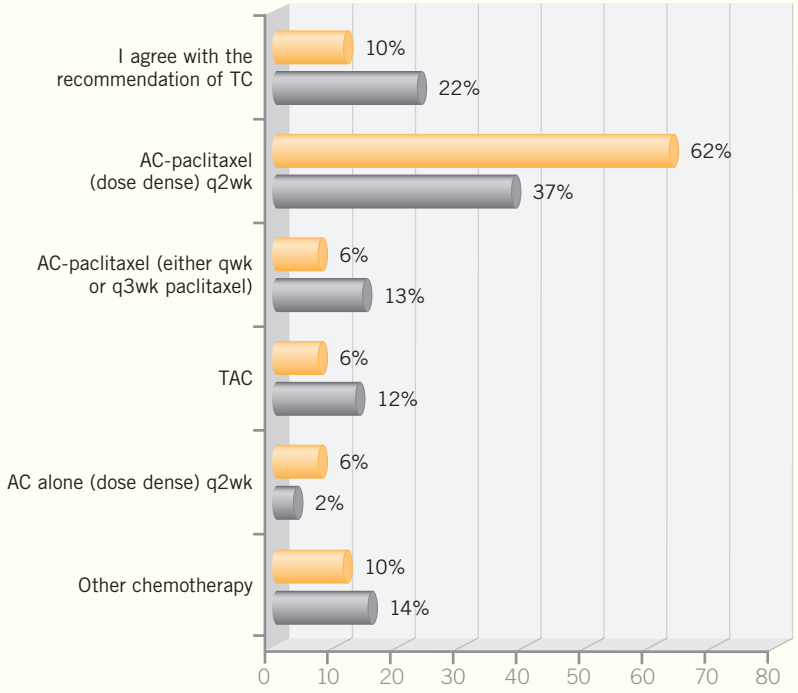
With longer follow-up, TC was associated with improved DFS and OS compared to standard AC. TC should now be a standard nonanthracycline combination for early BC. In addition, TC was well tolerated in older women without exces-

FIGURE 24

Case 9: *A **60-year-old** woman with a 1.2-cm, Grade II, ER-negative, PR-negative, HER2-negative tumor **with 2 positive nodes** consults you for a second opinion. **The first oncologist she saw recommended TC**. What would you tell this patient regarding the recommendation?*



Which specific chemotherapy regimen would you recommend?



sive toxicity compared to their younger counterparts, and may be preferable due to its lack of cardiotoxicity.

Breast Cancer Update 2007 (2)

DR FRANKIE ANN HOLMES: The US Oncology trial was a straightforward, simple idea embraced by the community, many of whom have concerns about the anthracyclines. We have now seen not only a better outcome in the total population with TC but also benefits in every subset, although these were not preplanned analyses.

It is one study, and it was a small study by modern adjuvant standards. However, it's not inconsistent with the data in the literature, which suggest that docetaxel is superior to the anthracyclines in head-to-head studies conducted in the metastatic setting. I don't have any problems with this study because it is reasonably sized, and the dose intensity was maintained.

I've started to incorporate the TC regimen much more frequently in my practice, especially in situations in which I have concerns about chemotherapy tolerance. However, at this time, I have not given up on the standard AC/taxane regimen for my patients with node-positive disease.

AC is now recognized as a highly emetogenic regimen, and patients experience delayed nausea and vomiting. I was once on a panel that was discussing emesis, and somebody said, "Oh, that's just AC." Well, AC is associated with a lot of delayed nausea and vomiting. You find a lot of hidden toxicity if you step into the shoes of a patient. It can be incapacitating. With TC, you don't have that burden of emesis and nausea.

Breast Cancer Update Think Tank 2007 (1)

DR ERIC P WINER: I haven't had trouble administering TC, and I agree that it may be less toxic than AC. However, I am concerned that the well-executed Intergroup trial, ECOG-E2197, which compared doxorubicin/docetaxel (AT) to AC, showed no benefit to AT versus AC, and yet the Jones data suggest that docetaxel is better.

If anything, I would have expected that substituting docetaxel for cyclophosphamide would provide a bigger hit. I find it troublesome. 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 that TC is better based on one study of 1,000 patients, considering the fact that the ECOG-E2197 study has a result that causes concern.

FIGURE 25

How would you compare the efficacy and safety/tolerability of TC versus what you view as the most effective anthracycline-paclitaxel regimen (eg, AC-paclitaxel qwk, q3wk or dose dense q2wk)?

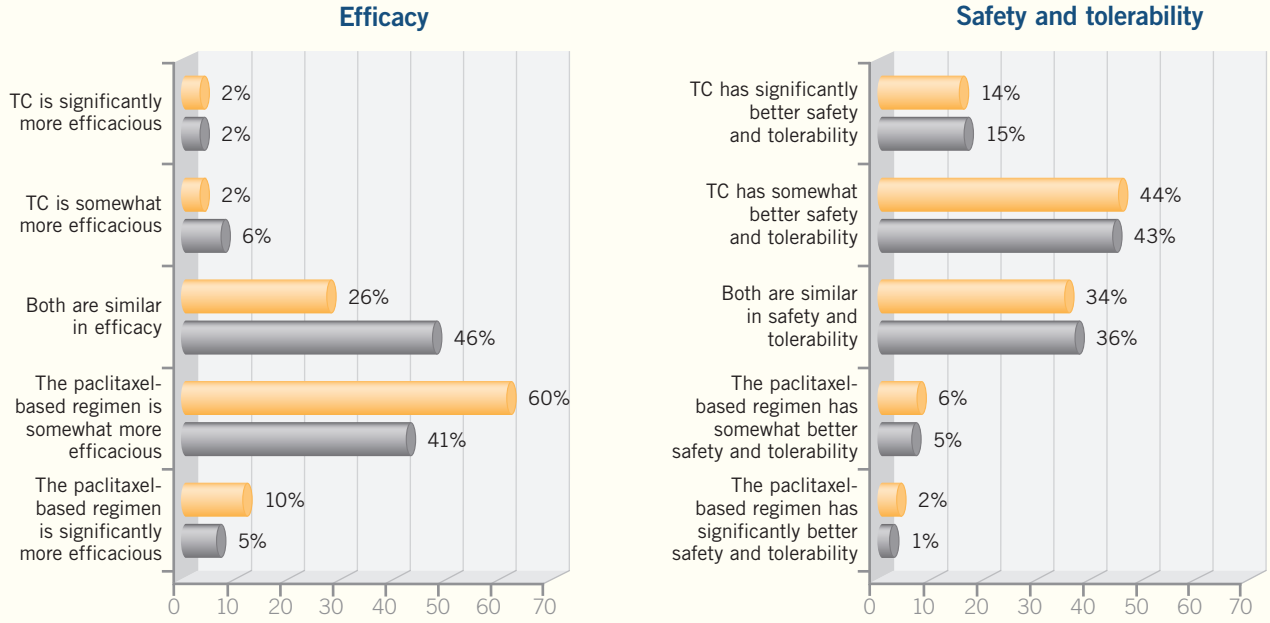
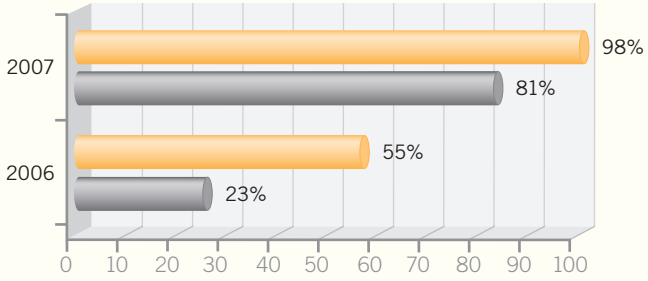
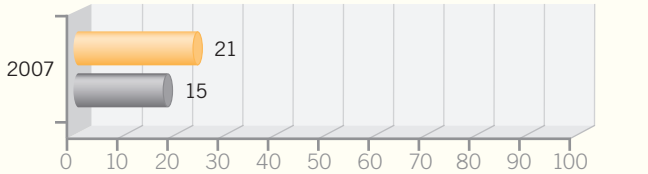


FIGURE 26

Have you utilized the TC regimen as adjuvant therapy? (Percent answering yes)



*For how many patients have you utilized the adjuvant TC regimen? (Mean)**



* n = 49 CI and 121 PO who have utilized the adjuvant TC regimen

Breast Cancer Update Think Tank 2007 (2)

DR BURSTEIN: Perhaps in contrast to what I'm hearing about TC, AC is still my standard adjuvant therapy for patients with lower-risk disease. I typically administer it on a dose-dense, every two-week schedule. It is a shorter regimen, and I find it remarkably well tolerated.

I've seen more subjective toxicity with TC, with regard to fatigue and other problems. In addition, AC is still the mainstay of the ongoing Intergroup trial for patients with lower-risk breast cancer who have zero to three positive nodes.

The dose-dense AC regimen has not been compared to TC. According to the US Oncology data, AC and TC are fairly comparable, perhaps with a small advantage for TC, but how the dose-dense schedule impacts that, we don't know.

Trial of adjuvant dose-dense AC → nab paclitaxel

DR BURSTEIN: We conducted a 56-person feasibility study with dose-dense

AC → *nab* paclitaxel in which we substituted *nab* paclitaxel at 260 mg/m^2 for paclitaxel at 175 mg/m^2 on the every two-week, so-called dose-dense schedule. We found it necessary to use white blood cell growth factor support with *nab* paclitaxel.

One determination we were trying to make was whether we could get away without using drugs like pegfilgrastim or filgrastim when we used *nab* paclitaxel instead of paclitaxel. The answer was no. If you want to keep to the every two-week schedule, you have to use the growth factor support. We used pegfilgrastim mostly.

Otherwise the regimen appeared comparable to our historical experience with dose-dense AC → T in terms of the rate of febrile neutropenia, delivery on schedule and other major toxicity complications. So I believe it's a regimen one could substitute.

SELECT PUBLICATIONS

Carlson RW et al. **Adjuvant endocrine therapy in hormone receptor-positive postmenopausal breast cancer: Evolution of NCCN, ASCO, and St Gallen recommendations.** *J Natl Compr Canc Netw* 2006;4(10):971-9. **Abstract**

Crew KD et al. **Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer.** *J Clin Oncol* 2007;25(25):3877-83. **Abstract**

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

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

Perez EA et al. **Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer.** *Proc ASCO* 2007;**Abstract 512**.

Rastogi P et al. **Five year update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC) → paclitaxel (T) vs AC → T with trastuzumab(H).** *Proc ASCO* 2007;**Abstract LBA513**.

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**.

FIGURE 27

For patients with endocrine receptor-negative breast cancer who do not achieve a pathologic complete response (pCR) following treatment with an anthracycline and a taxane as neoadjuvant chemotherapy, which of the following postsurgery treatment options do you generally recommend?

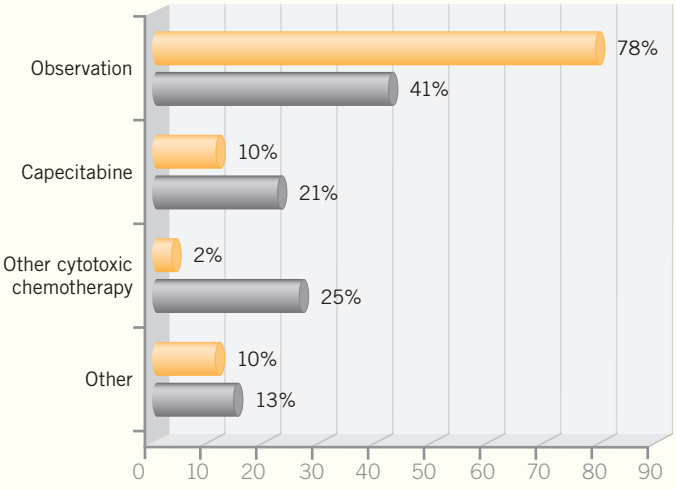
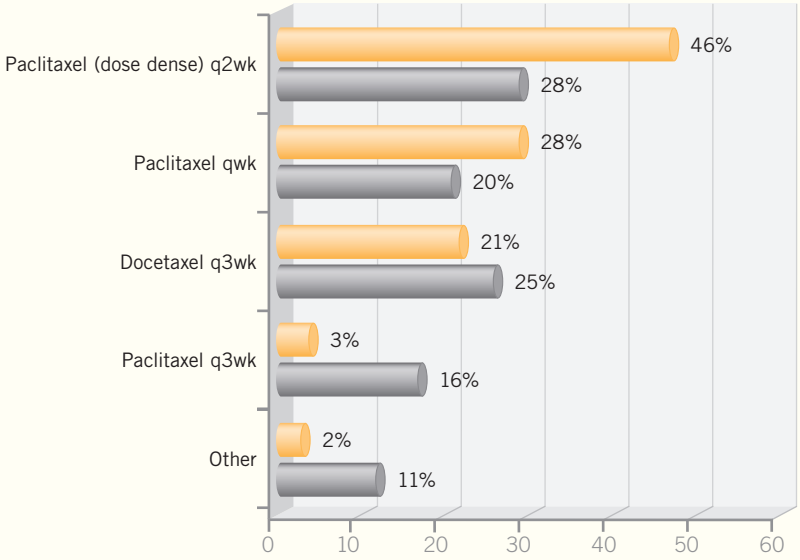


FIGURE 28

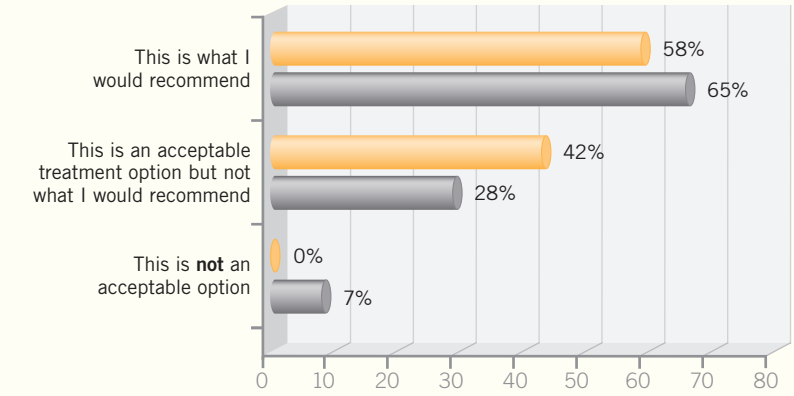
*When using taxanes in the adjuvant setting, approximately what proportion of the time do you use the following taxanes? (Mean)**



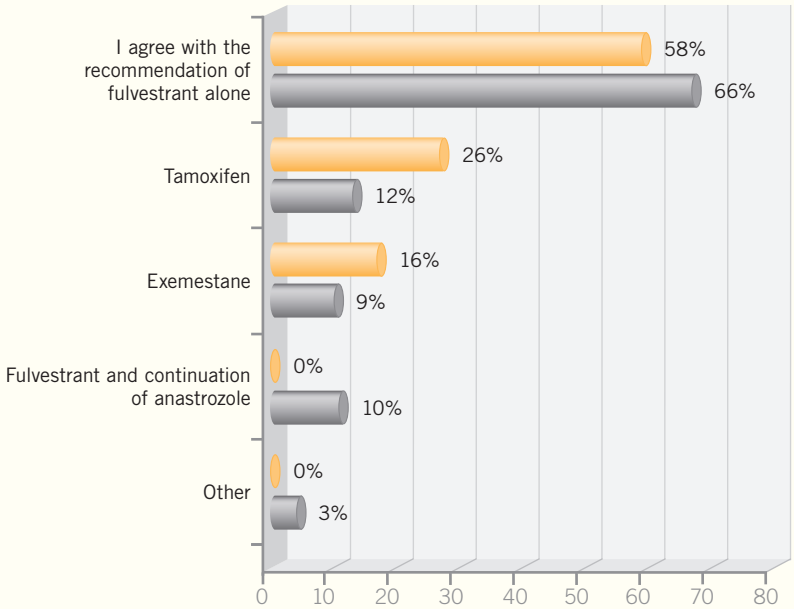
* n = 50 CI and 148 PO who use taxanes as adjuvant treatment of breast cancer

FIGURE 29

Case 10: *A 60-year-old woman was diagnosed 3 years earlier with ER-positive, PR-positive, HER2-negative breast cancer and consults you for a second opinion. She received AC followed by anastrozole, which she has received for 3 years. She now has bone metastases and no other sites of disease on staging.* ***The first oncologist she saw recommended fulvestrant alone as endocrine therapy.*** *What would you tell this patient regarding the recommendation?*



Which ***endocrine*** *therapy would you recommend?**



* n = 50 CI and 149 PO

CLINICAL INVESTIGATORS (CI)
PRACTICING ONCOLOGISTS (PO)

Second-line endocrine therapy for postmenopausal women with metastatic disease (Figure 29)

DR SCHWARTZBERG: This is a common case that we're faced with every day — the patient who received chemotherapy, an adjuvant aromatase inhibitor and then relapses — and a bone-only relapse is typical in patients with hormone receptor-positive disease.

We have few clinical trial data to suggest which therapy to use next in cases like this. The information we have on patients who relapse on an adjuvant aromatase inhibitor is recent, so we don't have long-term results to examine and we have to extrapolate from studies in the metastatic setting where a front-line aromatase inhibitor was used.

Those data suggest we have three different options: (1) switch to a second aromatase inhibitor — either a steroidal or another nonsteroidal agent, (2) switch to fulvestrant, which is an estrogen receptor downregulator or (3) use a SERM, and most commonly one would use tamoxifen in this case because the patient has not been exposed to it previously.

In head-to-head clinical trials in the second-line metastatic setting, the data suggest that fulvestrant is equivalent to an aromatase inhibitor and that fulvestrant might offer slight advantages in some of the endpoints, although not the primary endpoint.

Also, in the first-line setting, a trial comparing fulvestrant to tamoxifen demonstrated equivalence between these two agents for the patients with hormone receptor-positive disease.

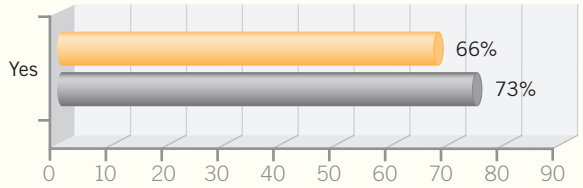
I believe that hormonal therapy is absolutely the best option in this case. For a patient with bone-only, hormone-positive disease, even though she relapsed on adjuvant therapy, one might still get considerable mileage out of further endocrine therapy.

As for which endocrine therapy I would select, I prefer not to use another drug that works by the same mechanism. I would choose fulvestrant in this case, and I would use it alone.

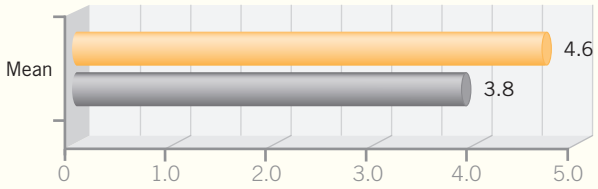
If I were to use another aromatase inhibitor, the data don't suggest that one agent is better than another. Typically,

FIGURE 30

*Do you think that fulvestrant will be demonstrated to be of value in the **adjuvant** setting, either alone or with one or more other agents?*



*If yes, in how many years do you think fulvestrant will be demonstrated to be of value in the adjuvant setting, either alone or with one or more other agents?**



* n = 33 CI and 110 PO who think that fulvestrant will be demonstrated to be of value in the adjuvant setting

if a patient relapsed on a nonsteroidal agent, I would switch to a steroidal agent, and vice versa, because of the belief that some differences might exist in the mechanisms of resistance. So in this case I would select exemestane.

Fulvestrant loading dose

DR SCHWARTZBERG: I do use a loading dose with fulvestrant — that's become the standard practice in my clinic. We start with an initial dose of 500 milligrams and then administer 250 milligrams two weeks and four weeks later, and then we begin the 28-day dosing schedule.

That regimen is based on preclinical data that suggest it takes a long time to reach a steady-state level of fulvestrant if you use the standard dosing that was initially approved, which is 250 milligrams every 28 days.

If you carefully examine the more recent studies, particularly those in which patients had previously been treated with an aromatase inhibitor and then received a second aromatase inhibitor, an aromatase inhibitor with another agent or fulvestrant, you see that progression-free survival decreases quickly in the first two to four months. Attaining a steady-state level of the drug so that it can work the way it's supposed to as soon as possible and before the disease progresses is an important strategy.

In the EFECT study, which compared fulvestrant to exemestane, they used a loading dose. While that's not the label dosing, I believe many people have come to adopt that strategy and, in my experience, no increase in toxicity occurs with the loading dose.

We don't have the head-to-head studies comparing a loading dose to the monthly 250-mg schedule, but I see little disadvantage to using the higher dose.

Fulvestrant causes little toxicity. Some patients experience a local reaction from the intramuscular injection, and a small number experience hot flashes, gastrointestinal upset or headache, but it's an extremely well-tolerated drug, and for patients who don't mind coming in once a month to receive an injection, as opposed to taking a daily pill, it's a nice alternative.

Rationale for trials combining fulvestrant with an aromatase inhibitor (Figure 31)

DR SCHWARTZBERG: Combining fulvestrant with an aromatase inhibitor is an interesting research strategy. A good amount of preclinical data supports the idea that we might observe greater efficacy if we not only shut off estrogen production, as an aromatase inhibitor would do, but also downregulate the estrogen receptor.

We know that in the preclinical animal models, a downregulator like fulvestrant can cause a feedback loop that increases the available estrogen. Thus, shutting off estrogen, which can then bind to the estrogen receptor as well as downregulating, theoretically leads to greater efficacy. We need to conduct a clinical trial to prove this.

I believe that if you had asked this question before the ATAC data were available, the majority would have predicted that the combination would show greater efficacy.

The results of the ATAC trial probably explain why over half of the clinical investigators responded that no difference would be evident between the two arms, even though the preclinical data are compelling otherwise.

I was surprised that the combination in ATAC was no better than either agent alone and, to my mind, why that is remains to be explained. We don't understand everything.

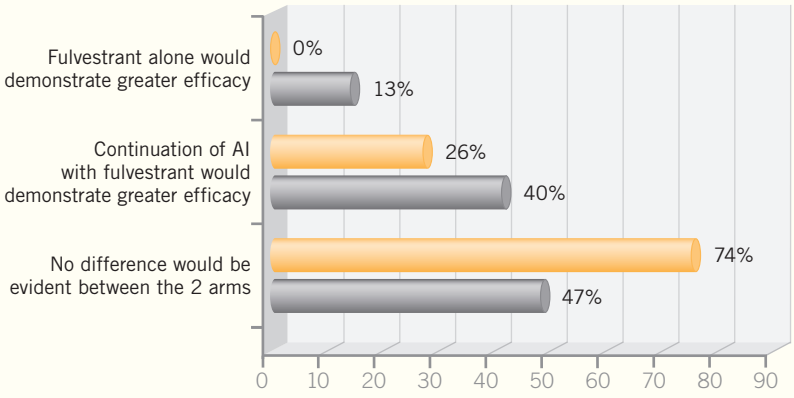
The models are not necessarily perfect, but they're exciting and show that we may obtain greater efficacy from combination therapy that is rationally designed — and an aromatase inhibitor with fulvestrant is a rational design. This combination makes more sense from a preclinical model.

Breast Cancer Update 2007 (7)

DR IAN E SMITH: Fulvestrant seems to be as good as tamoxifen in up-front

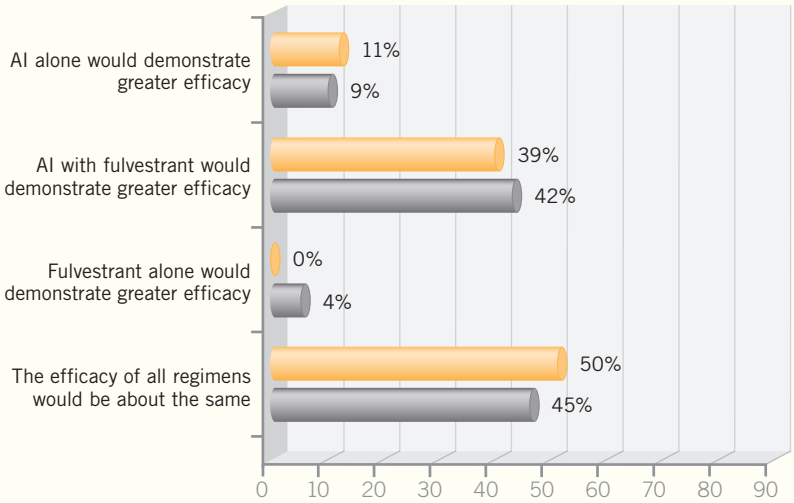
FIGURE 31

*If a randomized Phase III study for patients with disease progression on a nonsteroidal AI were able to adequately evaluate fulvestrant alone versus continuation of the AI with fulvestrant, what do you expect the trial would demonstrate?**



* n = 43 CI and 106 PO

*If a randomized Phase III study of first-line therapy for metastatic disease in postmenopausal patients with no prior AI or fulvestrant therapy were able to adequately evaluate an AI alone, an AI with fulvestrant or fulvestrant alone, what do you expect the trial would demonstrate?**



* n = 46 CI and 110 PO

trials. It also seems to be as good as anastrozole, but it isn't better.

One question is about the estrogen receptor becoming hypersensitized when it is reset. If the estrogen receptor is exposed to low doses of estrogen for a long time — as, for example, during prolonged aromatase inhibitor therapy — the receptor then seems to become hypersensitive to minute amounts of estrogen. So the question is whether fulvestrant would work better if you used an aromatase inhibitor concomitantly.

Two or three trials address this — one in the United Kingdom is called SoFEA. Patients who experience relapse on aromatase inhibitors are randomly assigned to fulvestrant or fulvestrant in combination with the aromatase inhibitor to test this question.

If another issue is that prolonged exposure to low estrogen doses hypersensitizes the receptor, then maybe we should be administering these therapies intermittently.

The latest idea being tested in clinical trials is intermittent aromatase inhibitor therapy — for example, three months on, three months off. In metastatic disease, the tumor marker CA15-3 may be useful in guiding therapy.

As soon as the levels go down, you stop and wait. Treatment can be restarted when the marker levels rise again to determine whether that approach is superior.

The Breast International Group trial 1-07 — the Study of Letrozole Extension (SOLE) — is like the MA17 trial, in which people who've been receiving endocrine therapy for five years are switched to either continuous or intermittent aromatase inhibitor therapy.

Nanoparticle albumin-bound (nab) *paclitaxel versus standard taxane therapies (Figure 32)*

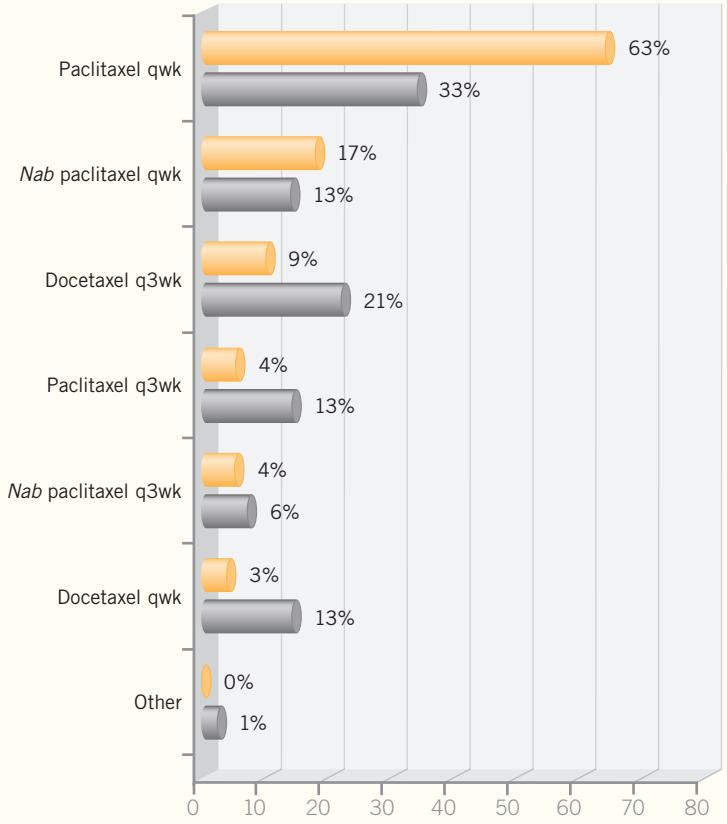
DR SCHWARTZBERG: It's always interesting to see the disparity among the clinical investigators and the community. Sometimes there's no consensus within either group, but in this case, we clearly see that a large majority of the clinical investigators chose paclitaxel.

If you examine the data, which must be extrapolated a little, in my opinion it's clear now that weekly is the best schedule for administering paclitaxel.

The CALGB data support paclitaxel as weekly therapy in the first-line metastatic setting, showing it to be superior in terms of response rate in addition to having less overall toxicity. Although a little more neuropathy occurs with the weekly versus the every three-week schedule, the hematologic toxicity is much less. The large adjuvant trial, ECOG-E1199, eval-

FIGURE 32

When you use a taxane as first-line chemotherapy for metastatic disease (no previous taxanes), alone or in combination, approximately what proportion of the time do you use each of the following? (Mean)



n = 50 CI and 149 PO who use taxanes for the treatment of metastatic breast cancer in the first-line setting

uated four schedules of taxane therapy: paclitaxel administered weekly and every three weeks and docetaxel administered weekly and every three weeks.

While no significant difference was evident in the main comparison, in the subgroup analyses, I believe weekly paclitaxel was clearly the winner in terms of less toxicity and greater efficacy, even in that large adjuvant setting in which it's harder to tease out the effect in terms of disease-free survival.

As for docetaxel, I believe it's been clearly shown that every three weeks is superior to the weekly schedule. Weekly docetaxel stirred a lot of interest around 2000, and some early data from Hainsworth and his group were provocative. Many people adopted that strategy, but I've always found fatigue to be a problem.

With docetaxel administered every three weeks, particularly at the full dose of 100 mg/m^2, quite a lot of neutropenia occurs.

However, growth factors can be used prophylactically, which is the standard according to the NCCN and ASCO guidelines, to avoid that toxicity, and a lower dose of 75 milligrams every three weeks is also effective.

I'm a little puzzled by the respondents who chose weekly docetaxel and paclitaxel every three weeks, given the abundance of data demonstrating that those are less effective regimens.

Personally, I voted for *nab* paclitaxel in this question. We have done a fair amount of research using weekly *nab* paclitaxel and have found that it's not only an effective drug, either alone or in combination, but it's also easy to administer and is not associated with much toxicity. In addition, *nab* paclitaxel delivers somewhat higher doses and does not require premedications.

Also, some data from the clinical trials suggest the neuropathy, which is the dose-limiting side effect of paclitaxel in general, resolves faster with *nab* paclitaxel than with Cremophor-based paclitaxel.

Use of premedications with* nab *paclitaxel (Figure 33)

DR SCHWARTZBERG: I am surprised by these responses and find the reasons for using premedications interesting. The emetic potential of paclitaxel is considered low, so there is no standard reason to use steroids for that purpose with *nab* paclitaxel as half of the oncologists suggested.

Most of us are concerned about the use of steroids, particularly when patients are receiving therapy on a weekly basis. Women frequently have problems with insomnia and nervousness, and older patients are frequently diabetic or have a prediabetic condition. Although steroids are wonderful drugs that we use every day, we should use them only when it's appropriate.

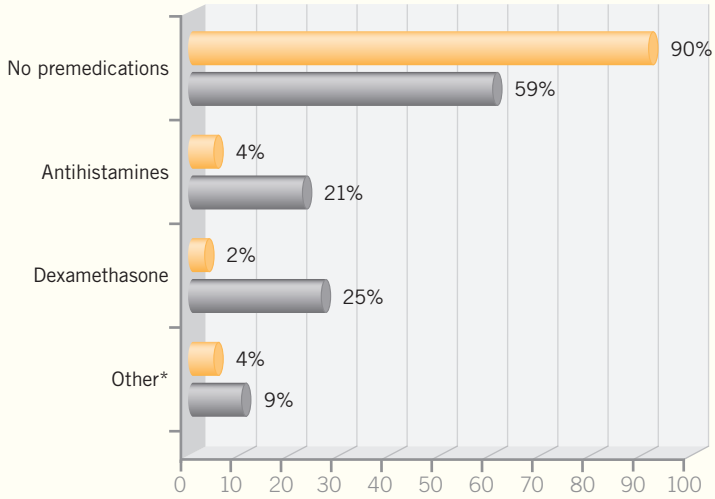
The fact that a third of the practicing oncologists have a treatment algorithm that includes premedications when administering *nab* paclitaxel must be changed immediately.

We're moving into an era of evidence-based therapy, of quality medicine and pay for performance. The insurers are increasingly scrutinizing the way we're treating patients and the supportive measures we use, and this practice would be difficult to justify.

In an era in which electronic medical records are used increasingly, it seems it would be simple to alter the algorithm and take out the premedications for *nab* paclitaxel while retaining them for Cremophor-based paclitaxel.

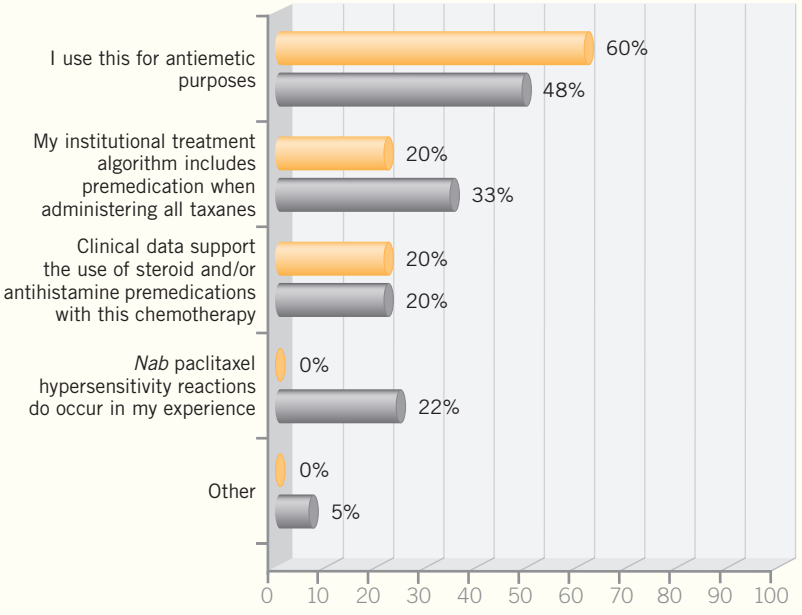
FIGURE 33

A 53-year-old woman with metastatic breast cancer, bone-only metastases and minimal symptoms will receive nab *paclitaxel (qwk or q3wk). Please indicate the premedications you would use, regardless of whether or not this is your preferred regimen. (May have more than one response)*



* Primarily antiemetics

*If premedications are chosen, which of the following most closely describes the reason(s) for your premedication recommendation? (May have more than one response)**



* n = 5 CI and 61 PO who use premedications with *nab* paclitaxel

As for hypersensitivity reactions, they are rare with *nab* paclitaxel in my experience, nor do I recall seeing any in our Phase II study of *nab* paclitaxel combined with capecitabine.

In this trial, approximately 50 patients received *nab* paclitaxel, 125 mg/m^2 on days one and eight, and capecitabine, 1,000 mg/m^2 BID on days one through 14 every 21 days.

We recorded a high response, approximately 60 percent overall, and the mean time to progression was nine months, which compares favorably to other combination regimens.

We are encouraged by this regimen and are hoping to repeat the study with a similar schedule and the addition of bevacizumab, which we believe we can add because the reported toxicity was reasonable.

A few patients experienced neutropenia and required dose delays or reductions, but in general no unusual toxicity occurred and we found full doses could be combined easily.

Efficacy and tolerability of* nab *paclitaxel (Figure 34)

DR SCHWARTZBERG: At the San Antonio Breast Cancer Symposium in 2006, Bill Gradishar presented data from a randomized Phase II trial comparing weekly or every three-week *nab* paclitaxel to q3wk docetaxel as first-line therapy for metastatic breast cancer.

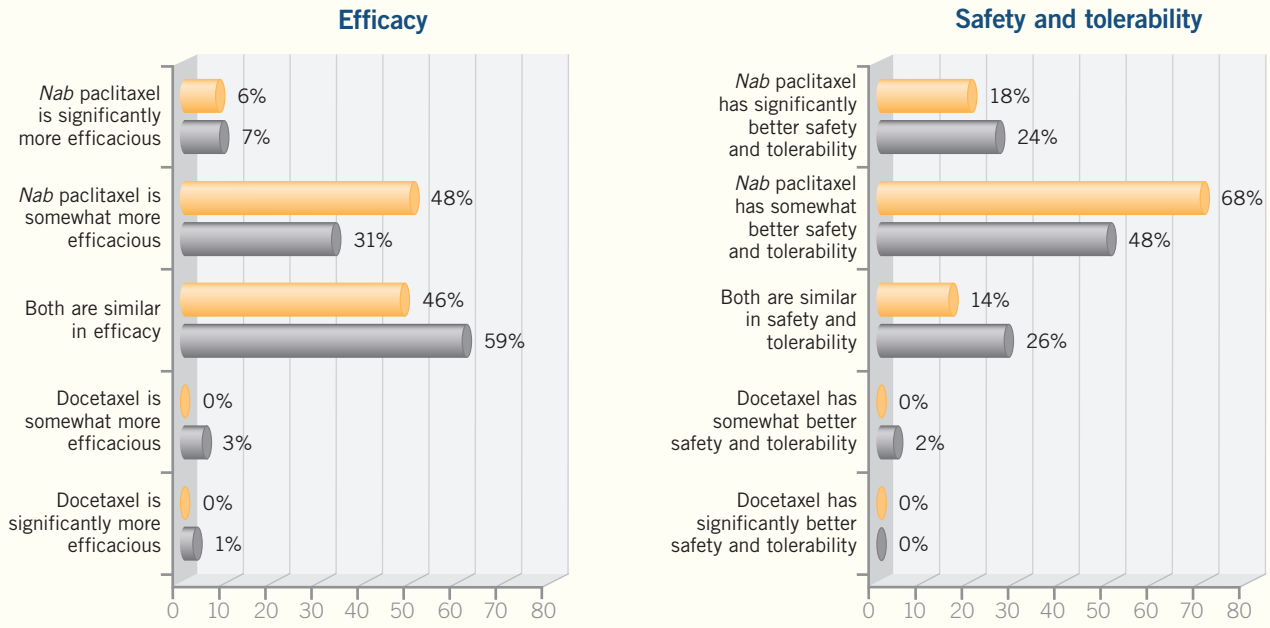
In that study, the weekly *nab* paclitaxel appeared to be superior to the every three-week schedule and also to docetaxel. They also evaluated weekly *nab* paclitaxel at 100 mg/m^2 and 150 mg/m^2, and while the higher dose appeared to work a little better, it brought more toxicity.

Still, the toxicity of weekly *nab* paclitaxel was substantially less than that of docetaxel. I believe these data are the reason why the majority of both doctors in practice and the clinical investigators responded that they believe *nab* paclitaxel is safer and more tolerable.

Assessing the efficacy depends on how you interpret the data because it is a randomized Phase II study. I would

FIGURE 34

How would you compare the antitumor efficacy and safety/tolerability of nab *paclitaxel to docetaxel?*



vote for weekly *nab* paclitaxel as somewhat more efficacious than the best dosing of docetaxel, which is the every three-week schedule that was used in Gradishar's trial.

I hope we have the opportunity to study *nab* paclitaxel in the adjuvant setting as a treatment option. Currently, the use of docetaxel is resurgent in the adjuvant setting, particularly with the nonanthracycline regimens — TCH for HER2-positive tumors and TC for HER2-negative disease.

Breast Cancer Update 2007 (6)

DR WILLIAM J GRADISHAR: *Nab* paclitaxel was developed to take advantage of the significant antitumor activity of the taxanes but also to avoid some of their side effects. Solvents typically used with drugs such as docetaxel or Cremophor-based paclitaxel are absent, and instead the paclitaxel is administered in an albumin delivery system to increase the amount of drug that reaches the tumor tissue. That's the underlying rationale.

What's been shown to date, both through some of the early Phase I and Phase II trials and ultimately the Phase III trial, is that when administered every three weeks, *nab* paclitaxel was superior to solvent-based paclitaxel administered every three weeks.

Despite more of the paclitaxel being administered in the *nab* preparation than with the every three-week solvent-based paclitaxel, less neutropenia occurred. A different kind of neuropathy appeared to be present that resolved more quickly. A greater antitumor effect was also observed in terms of response rate and improved progression-free survival.

In an era when we're increasingly using weekly therapy and when many perceive docetaxel to be the most active single-agent anticancer therapy for breast cancer, what most people want to know is, how does *nab* paclitaxel compare to a weekly taxane schedule? How does it compare to docetaxel?

We conducted a randomized Phase II trial, which we reported at the 2006 San Antonio meeting and updated at ASCO 2007. Patients with metastatic breast cancer were randomly assigned to first-line treatment with a dose of 300 mg/m^2 of *nab* paclitaxel every three weeks, 100 mg/m^2 of docetaxel every three weeks or *nab* paclitaxel administered weekly three out of four weeks at a dose of either 100 or 150 mg/m^2.

In December 2006, we reported that the weekly *nab* paclitaxel schedules were more active from the standpoint of antitumor activity than either every three-week docetaxel or every three-week *nab* paclitaxel. The weekly treatment arms were not only active but were also well tolerated, particularly the 100-mg/m^2 dose, which appeared at the time to be the optimal schedule.

The weekly schedule with 150 mg/m^2 had a slightly higher response rate, but it also is associated with slightly more toxicity. We did not see much of a difference in terms of progression-free survival between these two arms.

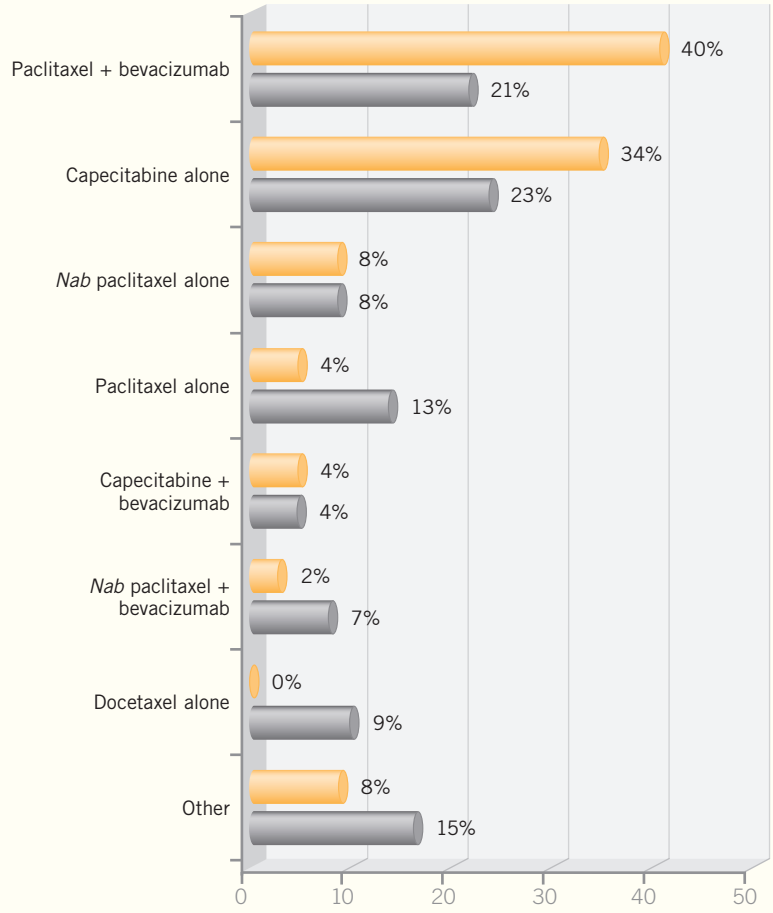
The weekly treatment arms were associated with response rates in the 60-plus percent range, markedly higher than the every three-week treatment arms of either *nab* paclitaxel or docetaxel.

Part of the more recent ASCO presentation was the response rate findings

FIGURE 35

A patient with HER2-negative, ER-positive breast cancer receives AC followed by 5 years of anastrozole. She develops metastatic disease, is treated with 2 lines of subsequent endocrine therapy, and the tumor is now hormone resistant. The patient has minimal tumor symptoms.

*Which of the following would be your most frequent **first-line** chemotherapy for this patient?*



from the independent radiology review. As expected, there was a drop-off in response rates among all four treatment arms.

However, consistent with the original investigator-reported findings, response rates for both weekly *nab* schedules remained numerically superior to every three-week docetaxel or every three-week *nab* paclitaxel.

In the December 2006 analysis, we would have said that the progression-free survival is not different across the *nab* paclitaxel treatment arms, but all are superior to docetaxel administered every three weeks.

What's emerging now is that both the every three-week *nab* paclitaxel and the weekly schedule of 150-mg/m^2 *nab* paclitaxel arms appear to be the superior treatments.

However, from the standpoint of efficacy and tolerability, the 150-mg/m^2 schedule appears to be the treatment arm to be pursued in a pivotal Phase III trial.

I believe one of the things that will come out of the upcoming randomized trial is whether the added antitumor efficacy that's presumed to be associated with the weekly schedule will offset what might be slightly more toxicity than we see with lower-dose weekly schedules of *nab* paclitaxel.

One of the interesting observations made across all the reported *nab* paclitaxel trials is the notion that the neuropathy might be different.

One of the first things people would have considered is that with this agent, when you eliminate the Cremophor, no neuropathy should occur.

But what has been observed in every trial — even in the Phase I trials — is that with high doses, you see neuropathy even in the absence of Cremophor. This might be attributable to the chemotherapy drug itself. So neuropathy occurs with *nab* paclitaxel — that seems to be a consistent finding.

The numbers are not huge, but there appears to be resolution of the neuropathy to the point at which you can readminister the chemotherapy drug within approximately three weeks.

In other words, you see a decrease in the severity of the neuropathy to the point at which you feel comfortable readministering the drug.

That's in contrast to what we typically see when patients develop Grade III neuropathy with solvent-based paclitaxel, with which the duration of the neuropathy is much longer.

In terms of other side effects, the degree and frequency of significant neutropenia are decreased with the *nab* paclitaxel every three-week and weekly schedules, relative to the three-weekly docetaxel, and minimal febrile neutropenia is associated with *nab* paclitaxel at the doses evaluated.

Additionally, in contrast to docetaxel, in our study the incidence of stomatitis is clearly less frequent whether you're using every three-week or weekly schedules of *nab* paclitaxel.

Chemotherapy and bevacizumab for hormone-resistant metastatic disease (Figure 35)

DR SCHWARTZBERG: I find these responses provocative.

The investigators are apparently driven by clinical trials, whereas the practicing oncologists are more creative in terms of different options. Based on these responses, there's clearly no consensus among practitioners about the right approach.

When I answered this question, I selected capecitabine alone based on the description of the patient as having minimal tumor symptoms.

In the long run, this patient will be exposed to multiple agents, so I want to ease her into chemotherapy. Obviously, in a case like this the physician should speak frankly with the patient about the need for chemotherapy and describe the different options. It in fact becomes the patient's decision.

FIGURE 36

Case 11: A 65-year-old woman in otherwise good health with ER-positive, PR-positive, HER2-positive disease consults you for a second opinion. She presents with her first cancer relapse with minimally symptomatic bone metastases and a few small, asymptomatic lung nodules after receiving adjuvant AC-paclitaxel followed by tamoxifen, which she has now received for 3 years. The patient received no prior anti-HER2 therapy. ***The first oncologist she saw recommended endocrine therapy alone.*** *What would you tell this patient regarding the recommendation?*

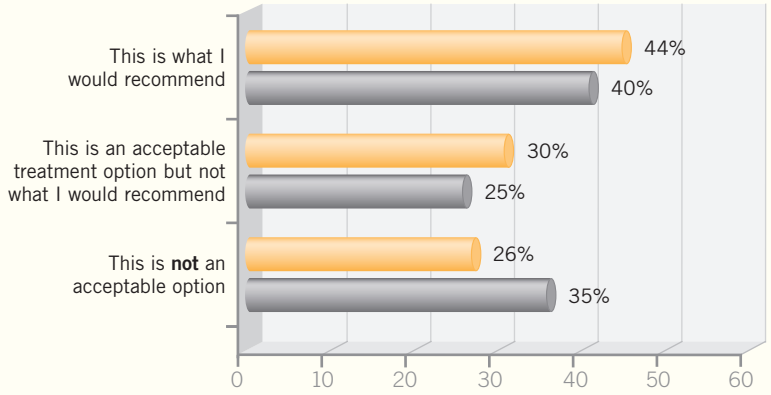
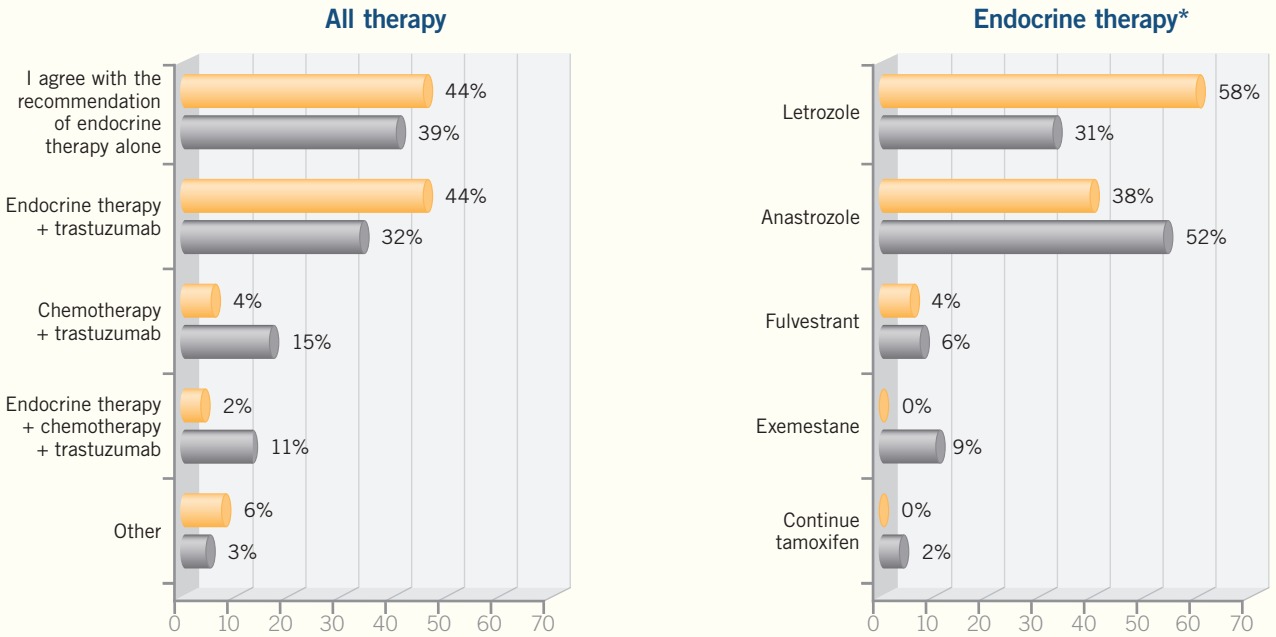


FIGURE 37

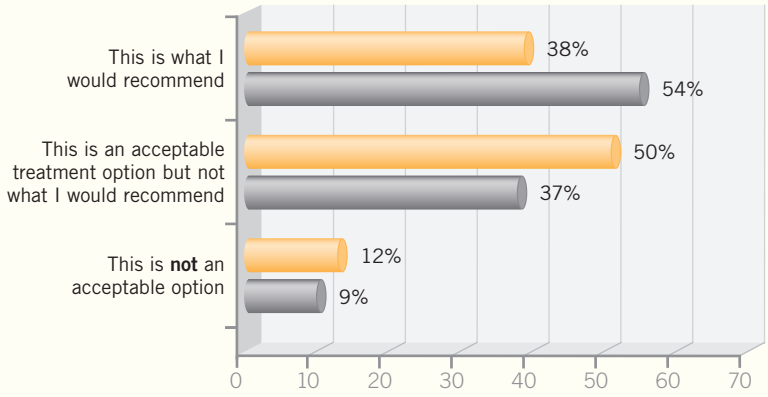
Which therapy would you recommend?



* n = 24 CI and 65 PO who would recommend endocrine therapy alone or in combination

FIGURE 38

Case 12: *A 65-year-old woman in otherwise good health with ER-positive, PR-positive, HER2-positive disease consults you for a second opinion. She presents with her first relapse with minimally symptomatic bone metastases and a few small asymptomatic lung nodules after receiving adjuvant AC followed by paclitaxel/trastuzumab (trastuzumab continued for 1 year) and anastrozole, which she has now received for 3 years.* ***The first oncologist she saw recommended endocrine therapy and trastuzumab.*** *What would you tell this patient regarding the recommendation?*



Another option I would consider would be paclitaxel and bevacizumab because that combination seems to have the best time-to-progression data in randomized trials, although this issue hasn't been evaluated head to head.

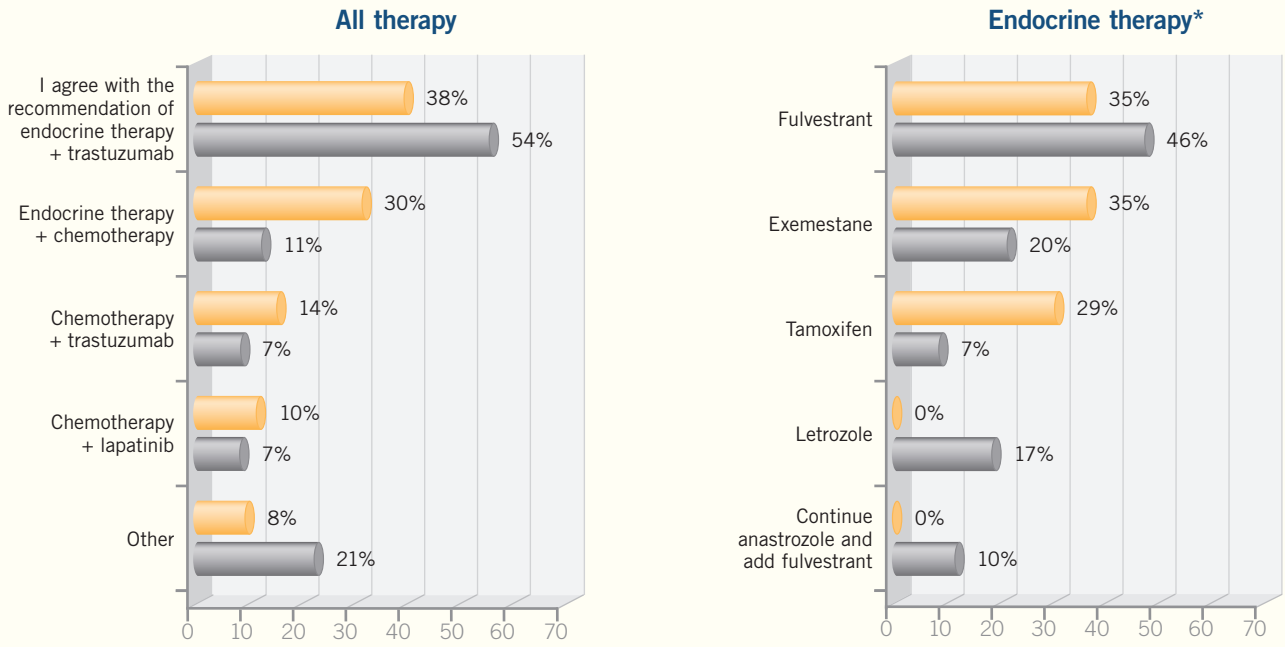
This regimen is complicated, however, involving weekly infusions and a second drug. It changes the lifestyle of the patient, whereas capecitabine alone is an oral therapy and it's similar to what she has already been on, so that is frequently the choice of patients as they ease back into chemotherapy.

TAnDEM trial data and treatment of hormone receptor-positive, HER2-positive, metastatic disease (Figures 36-37)

DR SCHWARTZBERG: This case is realistic because three years of tamoxifen therapy is approximately the point patients had reached before the adjuvant trastuzumab data were released, so we have a fair number of these patients.

FIGURE 39

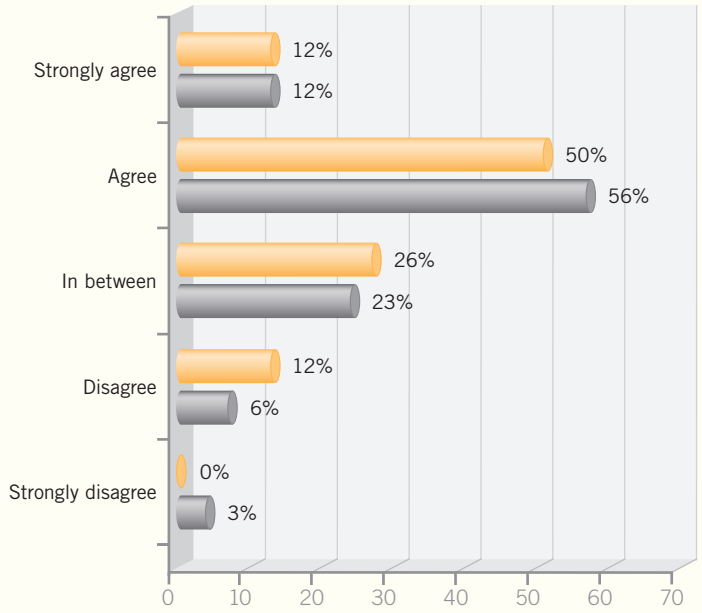
*Which therapy would you recommend?**



* n = 17 CI and 42 PO who would recommend endocrine therapy alone or in combination

FIGURE 40

Patients with metastatic disease that is hormone receptor-negative or hormone refractory who experience prolonged useful responses to first-line trastuzumab with chemotherapy should be continued on trastuzumab when switched to another chemotherapy at the time of disease progression.



The TAnDEM data confirmed that the subgroup of patients who have ER-positive, PR-positive breast cancer that is also HER2-positive are the least likely to respond to hormonal therapy alone.

Their median time to progression was approximately two and a half months, which is rather short. The addition of trastuzumab increased that by 60 or 70 percent, to four months or more.

While trastuzumab increased the disease-free survival and time to progression, these results are still somewhat modest. One might ask what would have been the efficacy of single-agent trastuzumab in these patients? We might have seen the same effect, but we don't know because that wasn't studied, which is one criticism of this study.

To me, the most important feature of the TAnDEM trial is that investigators saw a survival advantage, and that's why I would vote for endocrine therapy with trastuzumab in this case.

The trial data suggest that patients with HER2-positive metastatic disease should begin an anti-HER2 therapy right away, and that might impact their overall survival. Specifically, I would use a nonsteroidal aromatase inhibitor with trastuzumab for this patient.

On the other hand, if a patient presented with a similar history, relapsing on endocrine therapy, but was symptomatic with visceral disease, I would move on to chemotherapy with trastuzumab. I would do that because the response rates are high, as is symptom control, with that combination.

In addition, it has shown a survival advantage, and I don't believe we have time to wait for progression when a patient is symptomatic.

If half the patients will experience disease progression at four months anyway, they may be very sick, and then you may not have an opportunity to salvage the situation.

Clinical trial evaluating fulvestrant with capecitabine for disease progression after adjuvant endocrine therapy

DR SCHWARTZBERG: I found it fascinating to see in these responses that clinicians are starting to consider combining endocrine therapy and chemotherapy again, which was anathema in the field for many years.

I have a particular interest in that strategy and have recently launched a trial for the ACORN Network evaluating fulvestrant and capecitabine for patients who are failing at or within 12 months of completing an adjuvant aromatase inhibitor.

The goal is to evaluate the idea that the patients who fail an aromatase inhibitor have relatively endocrine-resistant disease and that many of them experience disease progression within the first few months of therapy.

That may be due to the pharmacodynamics and pharmacokinetics of the drug and a matter of getting the drug in fast enough, or maybe it's due to the fact that this disease is more intrinsically resistant, if patients fail an aromatase inhibitor, and they may not respond as well to a second-line hormonal therapy.

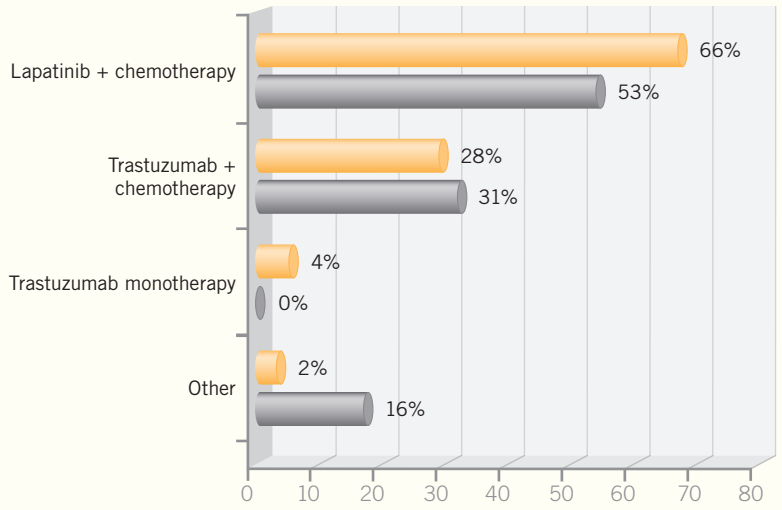
We simply don't know the data on that yet, although some suggestion has emerged that the second-line therapy won't be as effective for a patient who has already received an aromatase inhibitor and maybe not as good as after having failed front-line tamoxifen, as in a patient who is naïve to therapy.

In this trial we're using a metronomic approach to capecitabine, administering a low dose daily, which we believe will be well tolerated. It's a Phase II trial, but the goal is to improve time to progression for these patients with hormone receptor-positive disease who fail an aromatase inhibitor and are still receiving endocrine therapy.

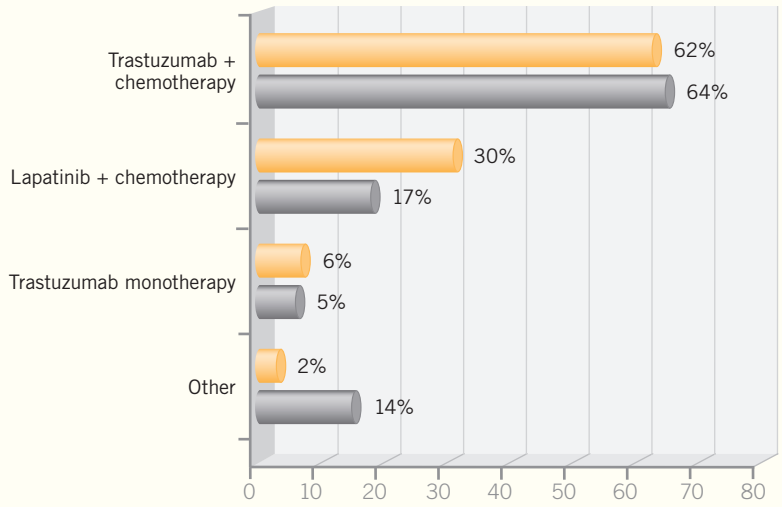
We also believe that the data on the antagonism between hormonal therapy and chemotherapy are scant. No work has been done since the 1970s, and that work was done with tamoxifen, which is an estrogen agonist, so those data may not relate at all to the interac-

FIGURE 41

A 65-year-old woman initially diagnosed with ER-negative, PR-negative, HER2-positive, node-positive breast cancer was treated with adjuvant TCH (docetaxel/carboplatin/trastuzumab). Six months after completing her full year of adjuvant trastuzumab (approximately 18 months from initial diagnosis), she complains of pain with coughing and is found to have rib metastases, in addition to 2 asymptomatic liver lesions. Which of the following treatment options would you recommend?



*If the patient does not exhibit evidence of disease recurrence until **2 years after completion** of a full year of adjuvant trastuzumab (approximately 3 years from initial diagnosis), which of the following treatment options would you recommend?*



tion between chemotherapy and an ER downregulator like fulvestrant or, for that matter, an aromatase inhibitor.

Anti-HER2 therapy for disease progression status-post adjuvant trastuzumab (Figures 38-39, 41)

DR SCHWARTZBERG: I agree with the general approach of deciding which anti-HER2 therapy to use based on the length of the disease-free interval.

Extrapolating from what we know about chemotherapy, the longer the interval between adjuvant therapy and relapse, the more likely the patient is to respond to similar agents or even the same agent. In previous years, that was tested and shown to be true. How long is long enough to go back to trastuzumab is an arbitrary decision.

We're fortunate now to have a second anti-HER2 agent, lapatinib. However, when you're considering these patients who unfortunately relapse with HER2-positive disease, you have to consider the long haul.

Undoubtedly, these patients will be exposed to both lapatinib and trastuzumab again, so it comes down to a sequencing question rather than simply picking one agent over the other.

I have patients who are living with extensive metastatic disease three, four or five years with a variety of anti-HER2-directed therapies. You have to simply make the decision as to which agent to use initially.

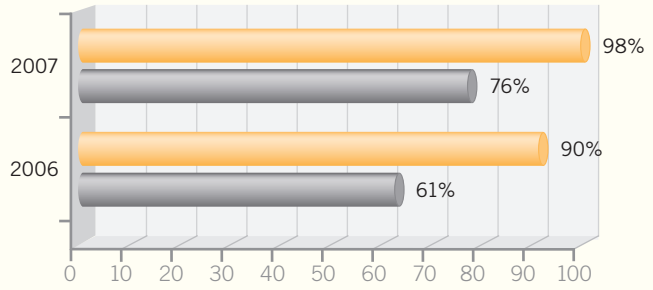
In years to come, we may learn that if a patient has failed trastuzumab, even at three years, lapatinib is the best drug to use, but our data set on that agent is much more limited than our data set on trastuzumab.

For patients who you believe may respond again, trastuzumab-based therapy makes sense. It is well known and has minimal toxicity. For patients who are refractory — that is, they relapse while on trastuzumab or within a few months or even a year — I'll use lapatinib.

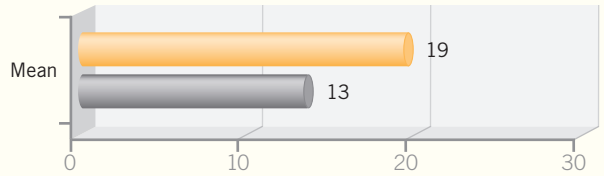
The cutoff I use is that if they finished trastuzumab less than a year or 18 months ago, I use lapatinib. We have

FIGURE 42

Have you used bevacizumab for metastatic breast cancer off protocol? (Percent responding yes)



If yes, for how many patients?



data now that show the combination of lapatinib and capecitabine is effective in those patients.

Breast Cancer Update 2007 (3)

DR BRIAN LEYLAND-JONES: A big controversy existed about continuing trastuzumab on progression. It seemed people would say, "Well, if the patient had a good, prolonged response to first-line therapy, I might be more likely to continue the trastuzumab." Will that now go totally out the window, and will people simply go to second-line lapatinib?

DR MARK D PEGRAM: A strong sentiment will probably emerge to change classes of inhibitors.

The lessons learned from other targeted therapy approaches — the estrogen receptor — are that by changing the strategy of therapeutic targeting, you might capture additional responses, albeit with perhaps somewhat lower frequency and not as long a duration, but nevertheless resulting in tangible clinical benefit.

This issue of trastuzumab duration in the metastatic setting has never been put to rest in a randomized clinical trial, which is unfortunate because once the tyrosine kinase inhibitors are available in the community, that question will probably become impossible to address.

Use of bevacizumab for metastatic breast cancer in clinical practice (Figure 42)

DR SCHWARTZBERG: I was surprised that 24 percent of the practicing oncologists indicated that they have not used bevacizumab for metastatic breast cancer.

It's clearly related to reimbursement. I can tell you that in my own practice, which is generally a relatively liberal reimbursement environment, I undergo tremendous scrutiny about this.

Many carriers do not pay for bevacizumab at all because it's not yet FDA approved, and from those that do pay for it, I am receiving approval only when it's combined with paclitaxel, based on the data submitted to the FDA. I've tried using it with *nab* paclitaxel, too, and sometimes it's reimbursed and sometimes it's not.

An amazing aspect of being an oncologist that is endlessly fascinating is the different way people respond to receiving chemotherapy.

Some patients when faced with chemotherapy will say, "This is the time I want to get aggressive. I want bevacizumab with chemotherapy because I've read that it's the best option."

Patients with metastatic disease know they're receiving therapy to keep their cancer under control.

Frequently they've received oral therapy, or sometimes a monthly injection, for years, but coming in for intravenous chemotherapy and all that goes with it — blood counts, antinausea agents, steroids and other supportive care medicines — changes the whole dynamic.

They see themselves in a different way, and treatment decisions are a collaboration between the patient and the physician.

Bevacizumab combined with endocrine therapy (Figure 43)

DR SCHWARTZBERG: I found it interesting that a quarter of the practicing oncologists have used bevacizumab with endocrine therapy for metastatic disease in practice. I have not used that.

We have a paucity of data, although at least one Phase II trial of letrozole and bevacizumab has been reported, and that showed a higher response rate with the combination than one would expect with an aromatase inhibitor alone.

The combination of bevacizumab and endocrine therapy does make preclinical sense, because some evidence exists for a feedback loop as you downregulate the estrogen receptor.

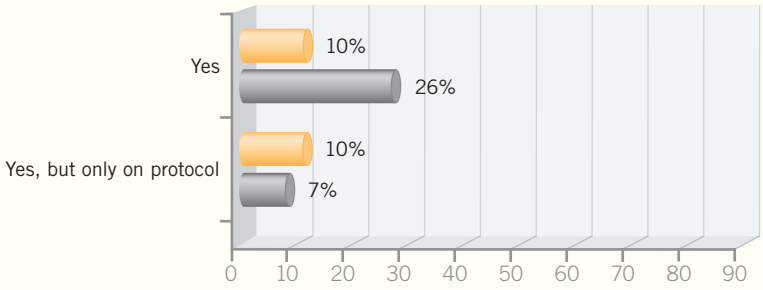
In this case, if you block estrogen production and ER activity decreases, then a compensatory increase in VEGF occurs, so some kind of feedback loop may be working in this situation through the hormonal system.

However, while it makes sense to do, I personally wouldn't do it in the absence of more data. The regimen requires the introduction of IV therapy and a great deal of expense.

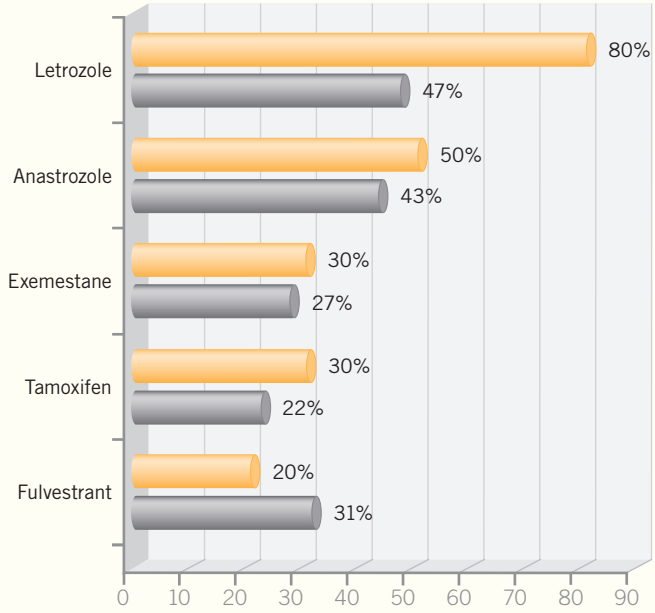
The increase in toxicity associated

FIGURE 43

Have you used endocrine therapy in combination with bevacizumab for treatment of metastatic breast cancer?



*If yes, which endocrine therapy have you used in combination with bevacizumab for treatment of metastatic breast cancer? (May have more than one response)**



* n = 10 CI and 49 PO who have used endocrine therapy in combination with bevacizumab for metastatic breast cancer

with the combination is probably modest, but in my opinion, it still needs more data support before it should be used off study.

Efficacy of bevacizumab combined with chemotherapy in the metastatic setting (Figure 44)

DR SCHWARTZBERG: In deciding whether to use bevacizumab in a case like this, I believe you have to go back to the clinical trial data.

If you examine ECOG-E2100, you see that it suggests that this type of patient treated with paclitaxel alone on the best schedule — weekly — will surprisingly have only about a 20 percent response rate.

However, with the addition of bevacizumab the response rate increases and, perhaps more importantly, the progression-free survival doubles, albeit with some increase in toxicity.

Generally, I believe it's a good idea to add bevacizumab to paclitaxel in these cases, particularly for a patient like this who is taxane naïve.

Nab *paclitaxel in combination with bevacizumab (Figure 44)*

DR SCHWARTZBERG: From a scientific perspective, I don't know of any reason whatsoever why *nab* paclitaxel should work any differently with bevacizumab than paclitaxel does. It's the same drug, simply a different delivery system.

In fact, some evidence suggests that you may actually deliver more drug to the tumor with this agent because of the way the particles are distributed on the nanoparticle albumin. That would account for its milligram-per-milligram increased efficacy or, at least, the fact that we can deliver more drug with less toxicity.

In the end, it's still paclitaxel, and I would agree that it's generally a good idea to add bevacizumab to *nab* paclitaxel.

I believe that's true in the adjuvant setting also, and if reimbursement were not an issue, I would use it in that setting because I believe it brings less toxicity and it's easier to deliver.

Use of bevacizumab in elderly patients (Figure 45)

DR SCHWARTZBERG: For the majority of 85-year-old patients, I would probably not advise adding bevacizumab to paclitaxel, but I would be comfortable with that being done. I wouldn't want to stress an 85-year-old heart with bevacizumab unless the patient had no comorbidities and was symptomatic from her disease, in which case I would consider it.

I believe it's fairly clear, particularly from the work of Hy Muss in CALGB, that among older patients, response rates to standard therapies are similar but toxicity is increased, so we have to balance toxicity and efficacy.

Adding bevacizumab to paclitaxel does increase toxicity, particularly cardiovascular toxicity and hypertension.

In the ECOG-E2100 trial, 15 percent of patients had Grade III hypertension and required therapy.

XCaliBr data: Response to capecitabine with bevacizumab based on estrogen receptor status (Figure 45)

DR SCHWARTZBERG: At ASCO in 2007, George Sledge presented data from the Phase II XCaliBr trial that evaluated capecitabine with bevacizumab as first-line treatment in the metastatic setting.

He presented some unexpected data, but that's why clinical trials are so endlessly fascinating — because they sometimes produce answers you don't expect. They send you in new directions, and I would describe the XCaliBr trial as one of those that is hypothesis generating.

It was not a comparative study, but it seemed to show only a modest benefit from capecitabine with bevacizumab for the whole patient group.

That mirrors the original trial that Kathy Miller reported of capecitabine and bevacizumab in heavily pretreated patients, which did not meet its primary endpoint.

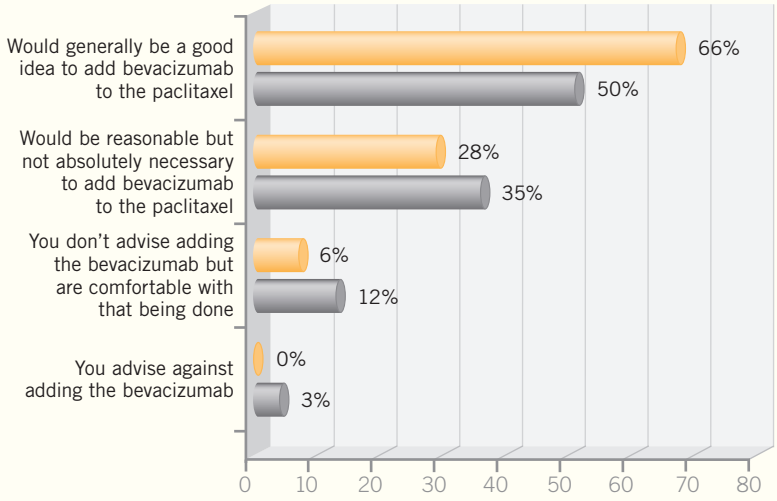
However, when George went back and analyzed the ER status, this study demonstrated a dramatically better response to the combination in patients with ER-positive versus ER-negative disease. The time to progression was more than doubled for the patients with ER-positive disease, and it was rather short for those with ER-negative tumors.

This is probably not what most people would have anticipated. Rather, one would have expected that the patients with ER-negative disease might actually respond better to chemotherapy, or at least as well as those with ER-positive breast cancer, but that's not what we saw.

Still, this was a small trial, and this issue should be explored prospectively. However, considering these data, perhaps in the future we'll confirm that it's the patients with ER-positive tumors that benefit the most from capecitabine and bevacizumab.

FIGURE 44

*A **65-year-old** otherwise healthy patient is facing her first relapse with metastatic disease after receiving **AC** 3 years ago for an ER-negative, PR-negative, HER2-negative tumor. She and her physician determine that her best treatment option is **single-agent paclitaxel.** They both are unsure about whether bevacizumab should be added and seek your opinion. Reimbursement and other financial issues aside, your response would be closest to which of the following?*



*A **65-year-old** otherwise healthy patient is facing her first relapse with metastatic disease after receiving **AC followed by paclitaxel** 3 years ago for an ER-negative, PR-negative, HER2-negative tumor. She and her physician determine that her best treatment option is **single-agent** **nab paclitaxel**. They both are unsure about whether bevacizumab should be added and seek your opinion. Reimbursement and other financial issues aside, your response would be closest to which of the following?*

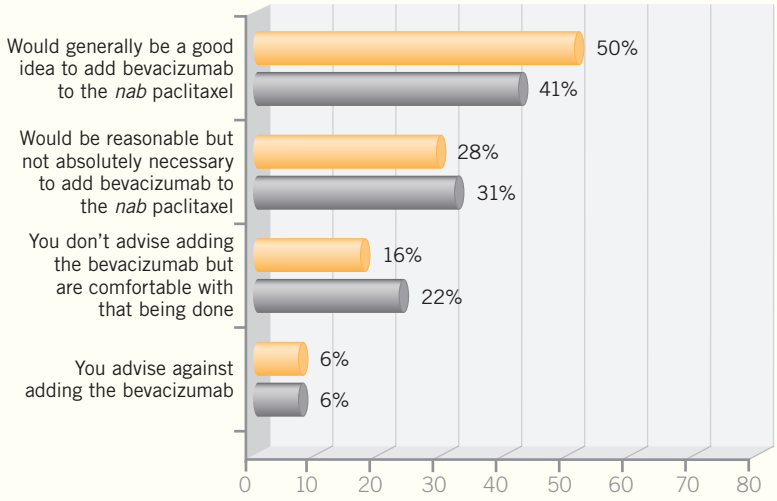
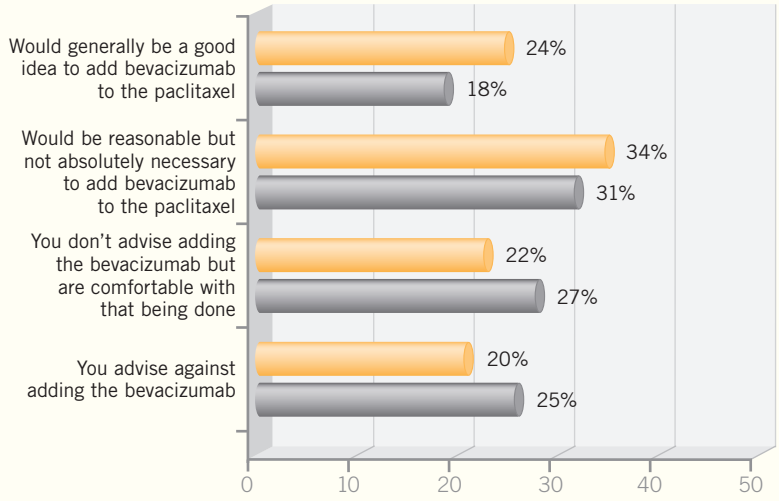
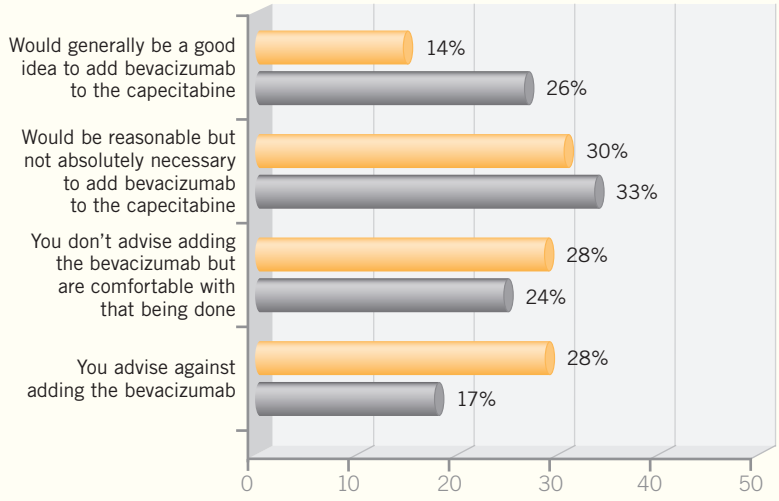


FIGURE 45

*An **85-year-old** otherwise healthy patient is facing her first relapse with metastatic disease after receiving **AC** 3 years ago for an ER-negative, PR-negative, HER2-negative tumor. She and her physician determine that her best treatment option is **single-agent paclitaxel**. They both are unsure about whether bevacizumab should be added and seek your opinion. Reimbursement and other financial issues aside, your response would be closest to which of the following?*



*A **65-year-old** otherwise healthy patient is facing her first relapse with metastatic disease after receiving **AC followed by docetaxel** 3 years ago for an ER-negative, PR-negative, HER2-negative tumor. She and her physician determine that her best treatment option is **single-agent capecitabine**. They both are unsure about whether bevacizumab should be added and seek your opinion. Reimbursement and other financial issues aside, your response would be closest to which of the following?*



DR ANDREW D SEIDMAN: Currently, outside of a clinical trial I generally follow the ECOG-E2100 paradigm.

For patients who are not participating in our AC/*nab* paclitaxel/bevacizumab pilot trial but for whom taxanes are appropriate, I use paclitaxel and bevacizumab.

Occasionally, I will have patients who have received an adjuvant taxane within the past year and have relapsed, and my inclination at that point is to use capecitabine and bevacizumab, based on Kathy Miller's reported Phase III trial. Those are probably the two most common scenarios.

Despite the doubling of the response rate, it does concern me that Kathy Miller's trial did not show a significant increase in the time to progression with capecitabine. Certainly a difference is evident between that population and that of the E2100 trial with regard to the extent of prior therapy.

I don't see any reason to suspect that the addition of bevacizumab to one particular cytotoxic agent in breast cancer versus another will make a big difference in terms of efficacy.

The RIBBON 1 trial, which allows a repertoire of commonly used chemotherapy regimens in the first-line setting, should inform us as to whether we need to worry about which agent we combine with bevacizumab.

My practice follows the highest level of evidence-based medicine. So when I use bevacizumab, for the majority of patients, I use it with paclitaxel.

There are certain unique circumstances in which paclitaxel is not appropriate, so I find the occasion to combine bevacizumab with other agents. Capecitabine would be the next most common agent followed probably by vinorelbine and gemcitabine.

I don't think I've ever used an anthracycline with bevacizumab for metastatic disease. Primarily, I use taxane-based therapy.

Controversies regarding the continuation of bevacizumab upon disease progression (Figure 47)

DR SCHWARTZBERG: In responding to this question, more than half of the practicing oncologists indicated that they would present patients with the option of continuing bevacizumab and switching to another chemotherapy at the time of disease progression, yet only about 20 percent of investigators said they would do so.

I believe this reflects the fact that the practitioners tend to see not only breast cancer but all types of cancer and they draw inferences — as I do, myself — from other diseases when appropriate.

In colon cancer, we have the BRiTE registry data that show a significant benefit to continuing bevacizumab beyond disease progression, although it's biased by the fact that they are longitudinal registry data. We participated in the registry, and it's possible that the majority of the clinicians you polled participated also because it was a large registry.

I believe clinicians are extrapolating those data from colon to breast cancer, but I suggest a couple of notes of caution. First, we have the negative capecitabine with bevacizumab trial in breast cancer, although that wasn't second line. It was in the third-line setting and beyond, so that's perhaps different from the colon data.

In addition, as the data are maturing in colon cancer, a suggestion is emerging that bevacizumab might have a ceiling effect in the sense that if you administer better first-line chemotherapy in colorectal cancer, you obtain less incremental benefit from the addition of bevacizumab. In other words, it worked well with IFL, which wasn't as good as FOLFOX or XELOX, and yet when you add bevacizumab to those regimens, one interpretation is that it confers some benefit, but it's a modest benefit.

If you extrapolate that to breast cancer, then we probably do need to see the results of the RIBBON 1 and other ongoing trials to make sure that bevacizumab added to chemotherapy is the same across different types of chemotherapy. We don't know the answer to that yet.

FIGURE 46

*A **65-year-old** otherwise healthy patient is facing her first relapse with metastatic disease after receiving **AC followed by paclitaxel** 3 years ago for an ER-negative, PR-negative, HER2-negative tumor. She and her physician determine that her best treatment option is **single-agent docetaxel**. They both are unsure about whether bevacizumab should be added and seek your opinion. Reimbursement and other financial issues aside, your response would be closest to which of the following?*

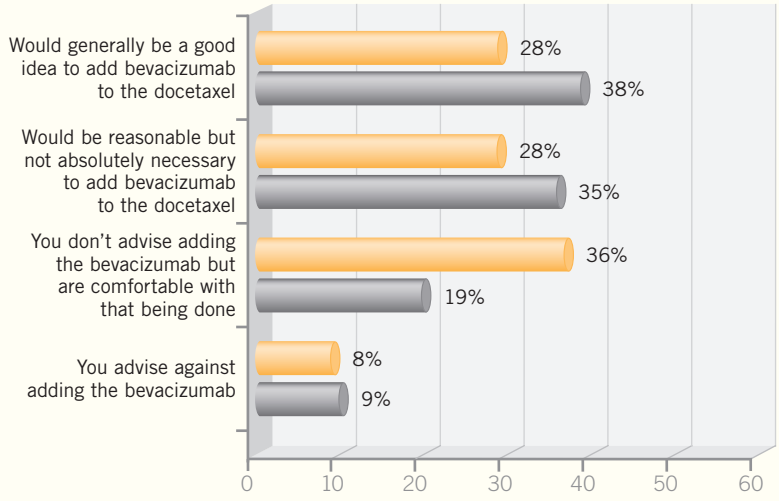


FIGURE 47

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

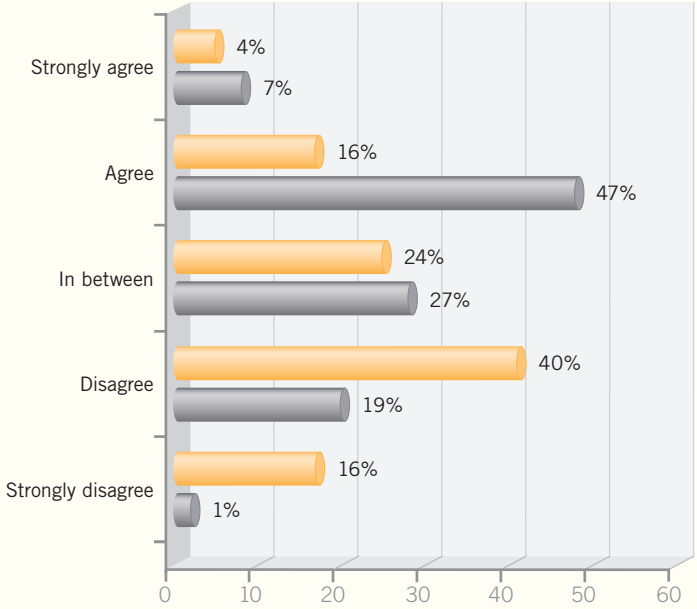
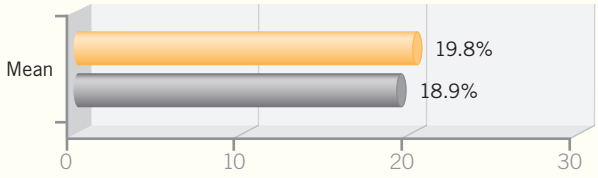


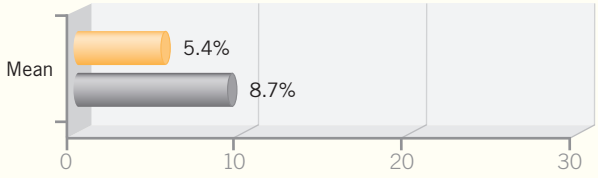
FIGURE 48

What would be your response to a 60-year-old patient with metastatic breast cancer, who is in good health and considering receiving bevacizumab as part of her treatment, if she asks you what the chances are that she will develop:

Hypertension that requires medical treatment?



A thromboembolic event that requires medical intervention?



Cardiovascular toxicities associated with bevacizumab (Figure 48)

DR SCHWARTZBERG: The clinical trials show that 15 to 20 percent of patients on bevacizumab will require antihypertensive therapy.

As for thromboembolic events, that might vary somewhat from disease to disease and is also probably age and comorbidity dependent. I believe that in the breast cancer trial, it was around four percent.

It's becoming clear now that most of the thromboembolic events with bevacizumab are arterial and probably associated with a minimal increased risk, if any at all, of venous thromboembolism.

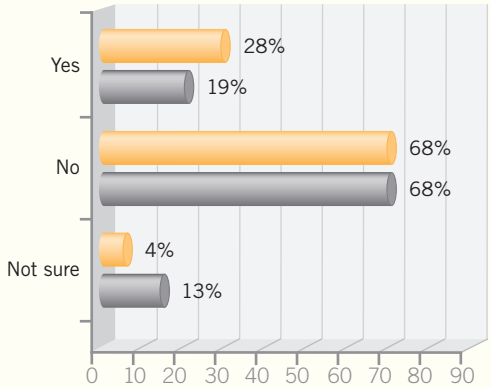
You have to screen your patients carefully, and those who have arterial problems or significant coronary artery disease need to be evaluated carefully before considering bevacizumab.

Those patients who have preexisting renal disease, particularly proteinuria of any degree, should probably not receive the drug. Nor should patients who have hard-to-control hypertension,

FIGURE 49

A woman presents in your office with de novo ER-negative, PR-negative and HER2-negative metastatic breast cancer with evidence of disease in her bone, liver and brain. Although previously functioning well, she is currently PS 2 due to symptomatic disease. She completes a course of radiation therapy for her 2 brain lesions, with partial response, and is now in stable condition and ready to begin systemic treatment. Would you recommend adding bevacizumab to this patient's first-line chemotherapy regimen if the patient was:

Age 35



Age 65

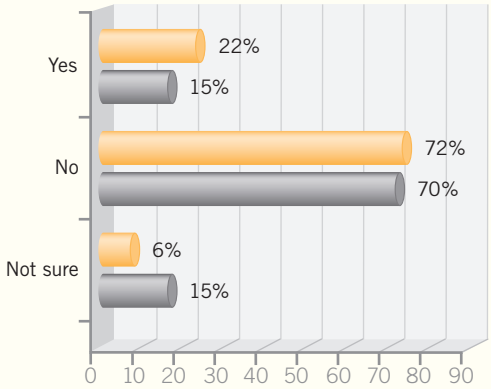
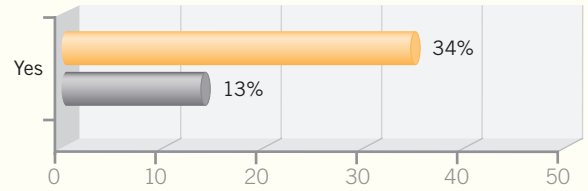


FIGURE 50

Have you enrolled patients in the RIBBON trials 1 and 2?



If yes, how many patients have you enrolled?

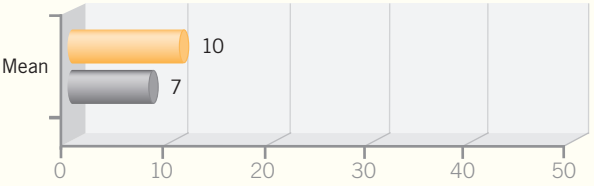
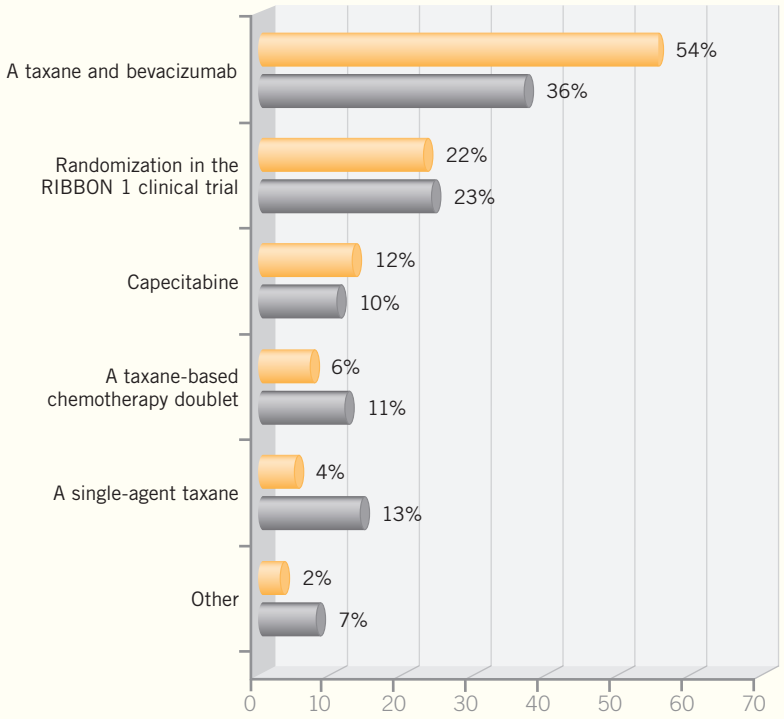


FIGURE 51

A 60-year-old woman received adjuvant AC following resection of a 2-cm, ER-negative, PR-negative, HER2-negative, node-positive tumor. Three years later, she is diagnosed with symptomatic bone metastases and 1 pulmonary nodule. Which treatment are you most likely to recommend, assuming all are available to you and the patient?



but all other patients are probably good candidates.

SELECT PUBLICATIONS

Geyer CE et al. **Lapatinib plus capecitabine for HER2-positive advanced breast cancer.** *N Engl J Med* 2006;355(26):2733-43. **Abstract**

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Muss H et al. **Toxicity of older and younger patients (pts) treated (Rx) with intensive adjuvant chemotherapy (Cx) for node-positive (N+) breast cancer (BC): The CALGB experience.** *Proc ASCO* 2006;**Abstract 559**.

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

Traina TA et al. **Letrozole (L) with bevacizumab (B) is feasible in patients (pts) with hormone receptor-positive metastatic breast cancer (MBC).** *Proc ASCO* 2006;**Abstract 3050**.

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

- Compare and contrast management strategies of community oncologists and cancer clinical investigators for the treatment of breast cancer in the adjuvant and metastatic settings. 5 4 3 2 1
- Discuss cancer management issues for which relative agreement and heterogeneity exist in patterns of care. 5 4 3 2 1
- Counsel cancer patients about multiple acceptable treatment options when they exist. 5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

Related to my practice needs. 5 4 3 2 1

Will influence how I practice 5 4 3 2 1

Will help me improve patient care 5 4 3 2 1

Stimulated my intellectual curiosity 5 4 3 2 1

Overall quality of material. 5 4 3 2 1

Overall, the activity met my expectations 5 4 3 2 1

Avoided commercial bias or influence 5 4 3 2 1

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POCB207

Patterns of Care in Medical Oncology

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This program is supported by educational grants from
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Last review date: December 2007
Release date: December 2007
Expiration date: December 2008
Estimated time to complete: 3.25 hours