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Patterns of Care in Medical Oncology

Management of Breast Cancer in the Adjuvant and Metastatic Settings

Adjuvant Endocrine Therapy

Adjuvant Chemotherapy

Treatment of Patients with HER2-Positive Disease

Systemic Therapy for Metastatic Disease

Editor
Neil Love, MD

A Case Survey Comparing Practices of Breast Cancer Investigators and General Oncologists

CME Certified

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Management of Breast Cancer in the Adjuvant and Metastatic Settings

2006 . Vol 3 . Issue 3

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PowerPoint files of the graphics contained in this document can be downloaded at **PatternsOfCare.com**.

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 research leaders 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 randomly selected community medical oncologists with 41 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.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 2.5 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This monograph is one issue of a CME series activity. To receive credit for this activity, the participant should read the monograph and complete the evaluation located in the back of this book or on our website **PatternsOfCare.com**. PowerPoint files of the graphics contained in this document can be downloaded at **PatternsOfCare.com**.

COMMERCIAL SUPPORT

This program is supported by education grants from AstraZeneca Pharmaceuticals LP, Genentech Inc, Genomic Health Inc, Roche Laboratories Inc and Sanofi-Aventis.

PHARMACEUTICAL AGENTS DISCUSSED IN THIS PROGRAM

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DISCLOSURE INFORMATION

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

COMMENTS IN THIS MONOGRAPH

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

ABOUT THIS SURVEY

This survey was completed in October 2006 by 150 community-based medical oncologists and 41 oncologists who specialize in breast cancer management (see list on pages 6-7) in the United States. The community-based oncologists were randomly 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.

Editor's Note: Age isn't just a number

If one were to identify individuals who have had the greatest recent impact on daily breast cancer clinical practice, way up on the list would be the mop-haired boy genius and numbers king, Peter Ravdin, MD.

Our prior Patterns of Care studies have clearly documented the extensive integration of Peter's Adjuvant! website and computer model into medical oncology practice (Figure 1).

More than half of practicing oncologists regularly incorporate numbers derived from Peter's program into consultation sessions with patients considering adjuvant systemic treatment, particularly people with node-negative tumors contemplating chemotherapy.

The impressive uptake of Adjuvant! has had a profound impact on patient care. Prior to its advent, medical oncologists were often criticized for providing relative risk reduction numbers to patients, a practice that was confusing and potentially misleading (eg, telling a woman with a baseline risk of relapse of 10 percent that her chance of cancer relapse could be decreased by 40 to 50 percent with chemotherapy).

Now physicians can just fill in specifics such as a patient's age, comorbidities and basic tumor characteristics, and Adjuvant! provides easy-to-read graphics showing the absolute benefit and actual likelihood that a therapy will prevent an event (Figure 2).

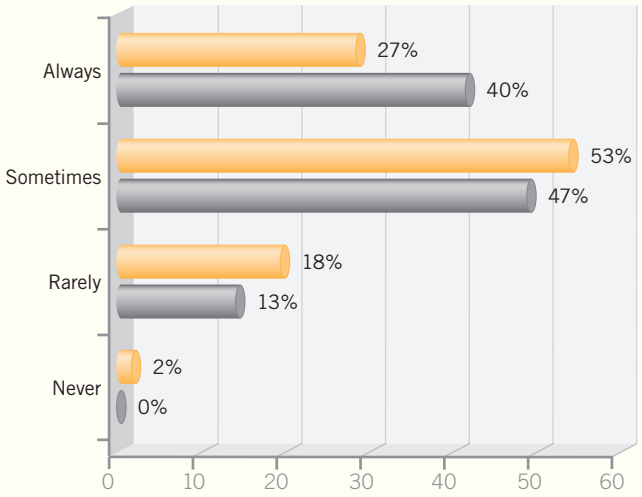
The program also enables docs to print the results for use during patient visits. Clearly, this has been a major boon to clinical decision-making.

Peter Ravdin, MD

CLINICAL INVESTIGATORS (CI) PRACTICING ONCOLOGISTS (PO)

FIGURE 1

How often do you use Adjuvant! in counseling breast cancer patients?



SOURCE: ***Breast Cancer Update Patterns of Care* 2005;2(3): Survey of 150 medical oncologists.**

In addition to providing specific numbers that can be reviewed with patients, Adjuvant! has become a profoundly useful tool in managing treatment specifically for older patients.

Because the program accurately predicts in aggregate competing causes of mortality, clinicians can use Adjuvant! to assess whether it really makes numeric sense to risk treating a 75- or 85-year-old patient with chemotherapy.

Peter adopted the raw numbers on nonbreast cancer mortality from the SEER Public Registries Files as a basis for Adjuvant! and it is apparent that age has a dramatic effect on the estimated absolute benefits of adjuvant systemic therapy (Figure 3).

He took the whole process to a new level in a collaboration with the British Columbia tumor registry when he verified the accuracy of the data (Olivotto 2005).

It is amazing to consider how Peter's desire to deliver superior and accurate information to doctors has now been translated to an enormous impact on patient well-being.

Perhaps tens of thousands of individuals have elected to receive therapy that prevented relapse or death based on their exposure to Adjuvant! estimates, and countless others have avoided the toxicity of treatments because Peter's numbers demonstrated that the benefit wasn't quite worth it.

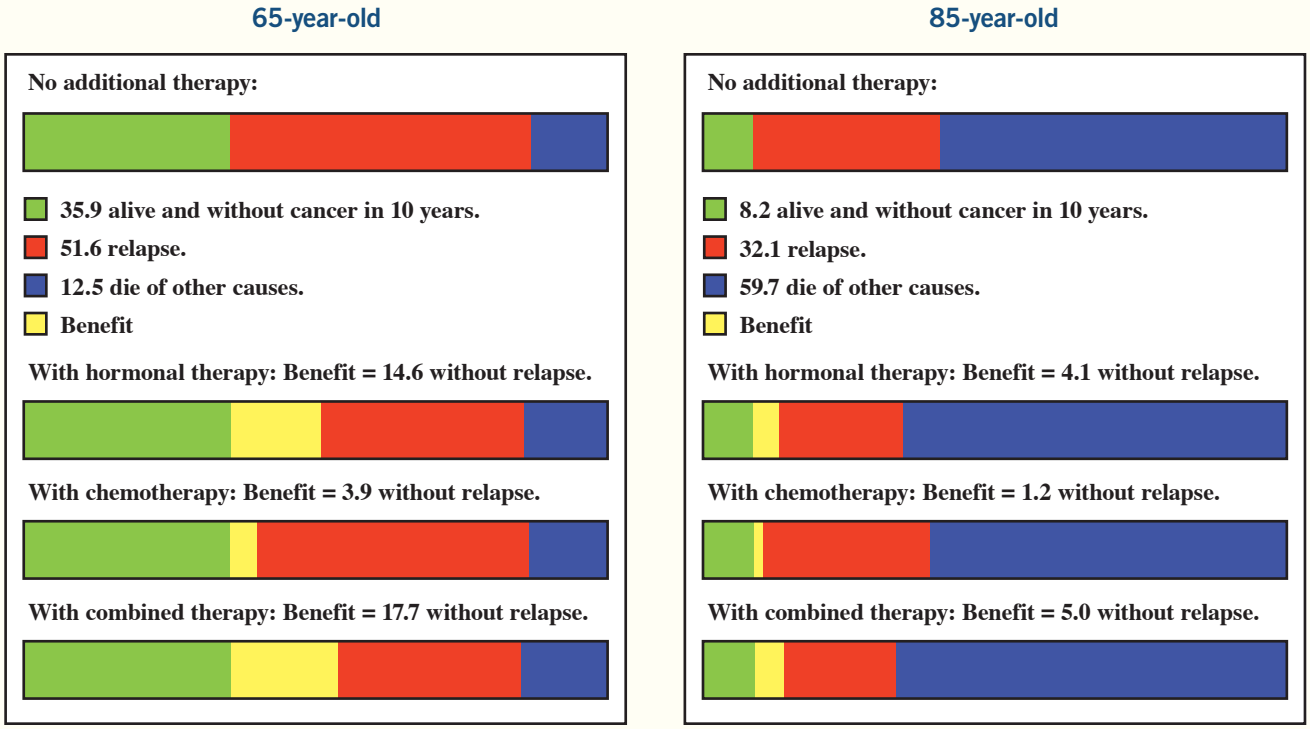
The program has become so important to clinicians that many are currently clamoring for Adjuvant! to incorporate HER2 and trastuzumab into the algorithm, but Peter notes that the adjuvant trastuzumab data really do not have adequate follow-up to be incorporated into his model, which focuses on 10-year risks of relapse and death.

However, on the way to his devoted audience is a new version (9.0) that will incorporate the HER2 story, and you can bet that the model will be used frequently, particularly for patients with lower-risk, node-negative, HER2-positive disease.

FIGURE 2

Adjuvant! Online: 10-Year Risk of Relapse

Patient in average health with a 1.5-cm, Grade II, ER-positive, PR-positive tumor and four positive nodes



SOURCE: Adjuvant! Online, Standard Version 8.0, Adjuvantonline.com

Even now, with a few twists and pulls you can derive numbers from Adjuvant! that should be reasonably accurate predictors of benefit of adding trastuzumab to chemotherapy (increase the baseline risk of recurrence by 50 percent, and decrease the risk of cancer relapse by 50 percent, or some similar machination), but it will be comforting to use the more familiar Ravdinian pathways.

One of the most interesting aspects of Adjuvant! is that for years Peter has feared that the site might be misleading to patients who wander in off the web, and he has tried hard to steer them away from it. For that reason, to enter Adjuvant! users must attest that they are in fact healthcare professionals.

Although Peter in no way wishes to deny patients access to Adjuvant! (he believes they should ask their oncologists to obtain the information), he is concerned about the potential adverse consequences of using the site in isolation without the appropriate background and understanding of its meaning.

Of interest is the enclosed US-based survey of 150 randomly selected practicing medical oncologists and 41 clinical investigators focusing on breast cancer. In contrast to Peter's restrictive position, many of these physicians believe patients should be encouraged to consider using the site (Figures 4, 5).

Peter is actually featured in an in-depth audio interview on our new patient education audio/web program, and his opinions raise a critical question: Can patients understand sophisticated models like Adjuvant!, and particularly the concept of the effect of age on treatment impact?

Certainly only a highly motivated subset of patients will wish to become that involved with their oncologic care, but "the waiting room and infusion center theory of cancer information dissemination" would postulate that educating 10 to 20 percent of a patient population will result in a significant spillover to other patients who chat together.

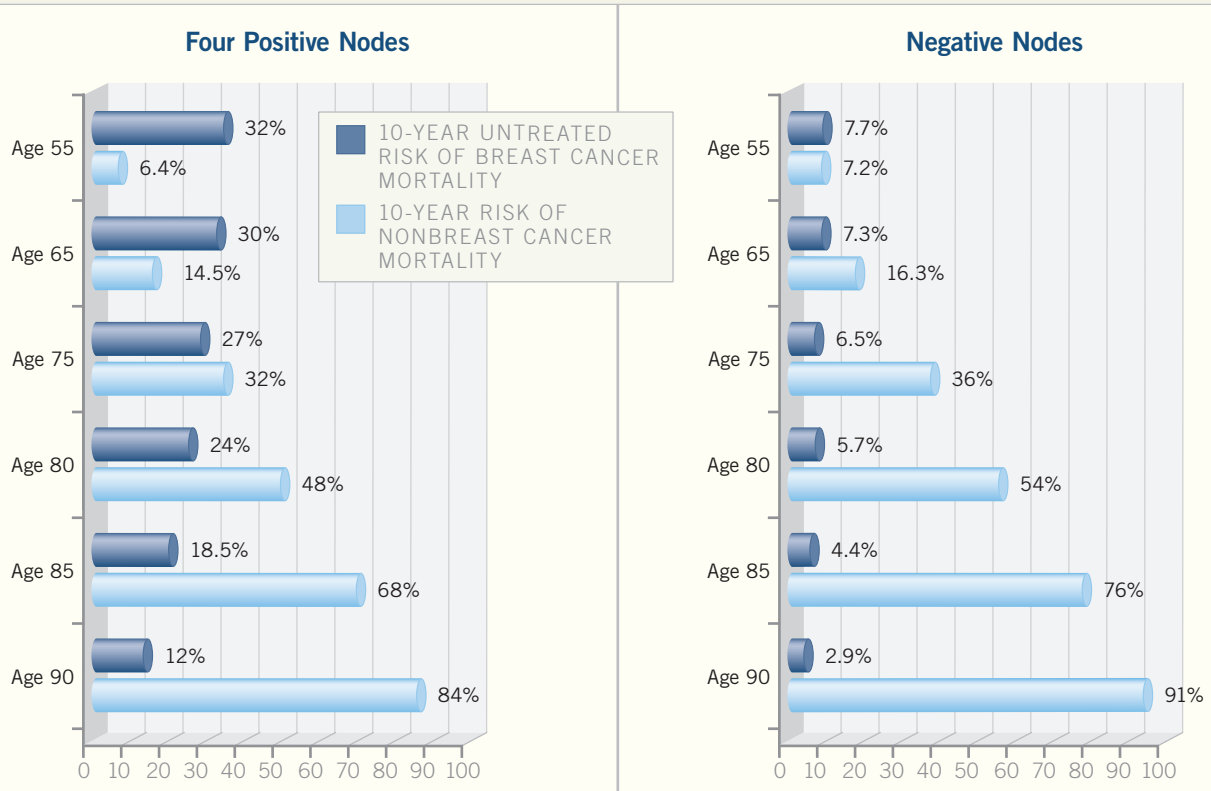
Thus it may be that many of the key concepts in Adjuvant! are already affecting the collective patient consciousness.

Peter is one of the coolest guys in oncology, and as is often the case with such people, he is truly humble about his work. We need to encourage other creative thinkers and inventors to come up with new methods to make the best decisions possible for people with cancer.

— Neil Love, MD
NLove@ResearchToPractice.net

FIGURE 3

Patient with a 1.5-cm, ER-positive, Grade II tumor in average-for-age health



SOURCE: Adjuvant! Online, Standard Version 8.0, Adjuvantonline.com

FIGURE 4

Breast cancer patients should be discouraged from going to the Adjuvant! Online website.

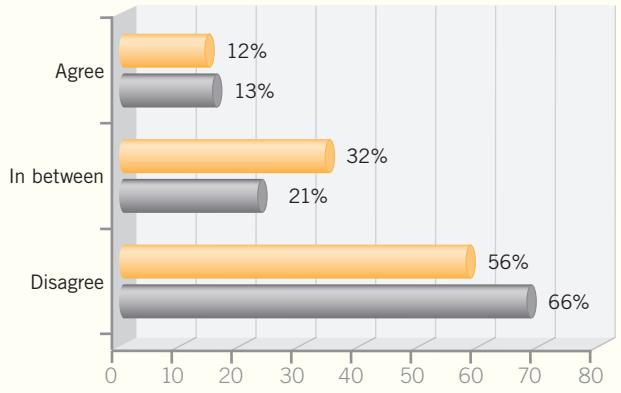


FIGURE 5

*Breast cancer patients should be **encouraged to ask their oncologists to retrieve data from Adjuvant! Online** (or a similar website) and discuss the data with them.*

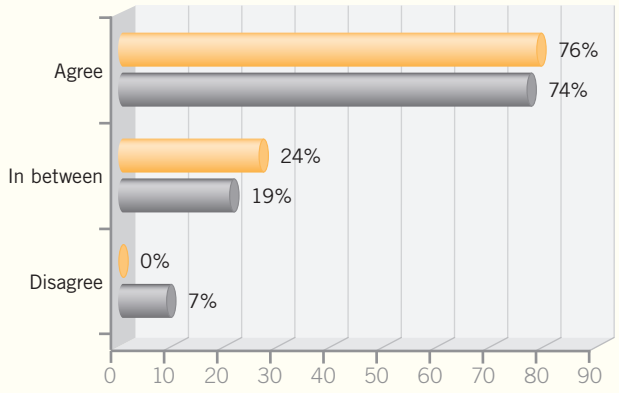


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FIGURE 6

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CONTINUED

FIGURE 6 (CONTINUED)

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Adjuvant Endocrine Therapy

FIGURE 7

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

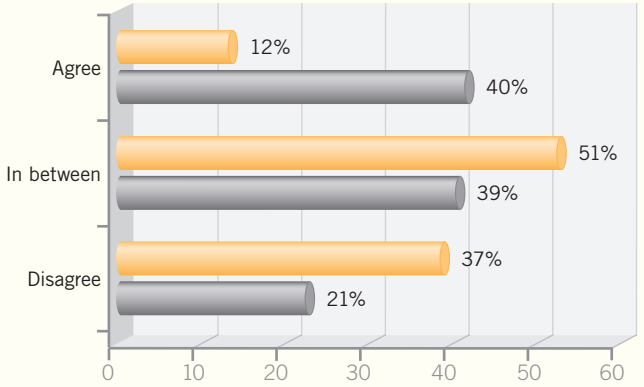
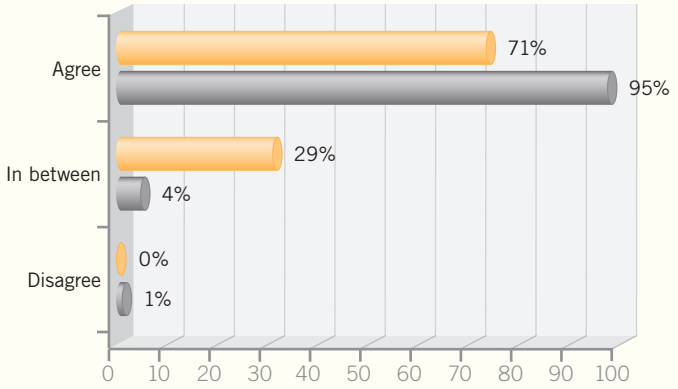


FIGURE 8

Postmenopausal patients with ER-positive tumors without osteoporosis should generally be started on an aromatase inhibitor.



Breast Cancer Update 2004 (1)

DR HAROLD J BURSTEIN: The IBCSG is coordinating a series of three nested trials: SOFT, PERCHE and TEXT. These studies address what is probably the most important conceptual question in premenopausal breast cancer right now: Beyond tamoxifen, does planned ovarian suppression benefit patients? In particular, does it benefit women who receive chemotherapy or who don't receive chemotherapy, and if a woman experiences chemotherapy-related amenorrhea, does she still need ovarian suppression? These are important trials that offer a wonderful opportunity for community oncologists to participate in answering this critical question. Currently, I consider ovarian suppression for two groups of patients. The first group includes patients at high risk — multiple positive nodes, very high-risk tumors — and particularly young women, less than 35 or 40 years of age, who may not go into menopause with chemotherapy.

The other group includes women who are at the opposite end of the spectrum — very low-risk tumors, smaller tumors, node-negative — for whom the benefits of chemotherapy are small. With these women, I present ovarian suppression as an option, not necessarily in addition to chemotherapy but perhaps even instead of it.

Breast Cancer Update 2006 (5)

DR DANIEL F HAYES: I believe an important issue, which has been lost, is that all of the aromatase inhibitor studies enrolled women who were postmenopausal by virtue of not having a period for at least a year prior to enrollment. We have estrogen ablation studies ongoing for premenopausal women, such as SOFT, TEXT and PERCHE. We don't know the answers from those studies yet.

I believe estrogen ablation is a more effective therapy than a SERM, but I also believe it's more toxic. I'm very supportive of those trials. We have enrolled 11 patients on SOFT. They're important studies, almost as much for the toxicity as for the outcomes.

The ovaries can go to sleep and wake back up again. Ian Smith at the Royal Marsden and I discussed this recently. He went back and retrospectively reviewed his institution's experience with women who had received chemotherapy, became amenorrheic and were then placed on an aromatase inhibitor.

About one quarter of those patients had their ovarian function reemerge, either by virtue of developing menses or by having their estrogen levels increased.

FIGURE 9

Postmenopausal patients who have never received an aromatase inhibitor (AI) and who are between five and 10 years from diagnosis of an ER-positive tumor should generally be offered an AI.

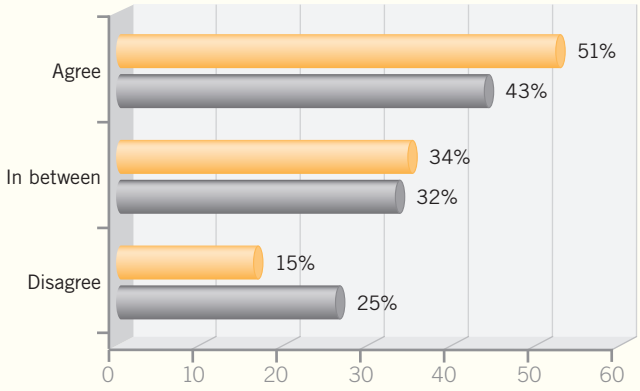
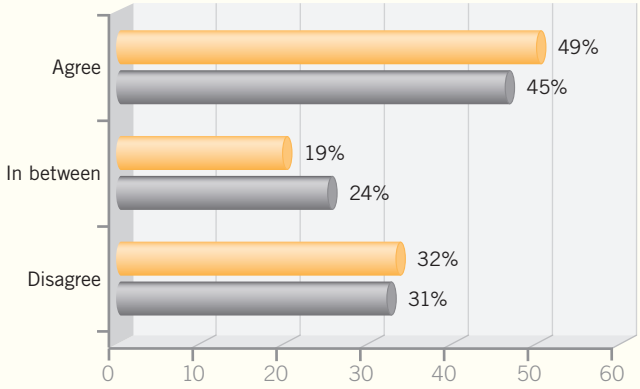


FIGURE 10

In select patients, adjuvant aromatase inhibitors should be continued beyond five years of treatment.



Breast Cancer Update 2006 (7)

DR ROBERT W CARLSON: If I were to treat 100 postmenopausal women with endocrine therapy for early breast cancer, the vast majority would walk out with a prescription for an aromatase inhibitor — usually anastrozole in my practice.

We have to establish a practice pattern, and mine is to lead with an aromatase inhibitor. It is interesting how expert panels interpreted the emerging aromatase inhibitor data differently. Within 10 to 14 days of the initial 2001 ATAC presentation, the NCCN panel had modified the guidelines to allow anastrozole as an alternative to tamoxifen as initial hormonal therapy for postmenopausal patients with ER-positive disease.

The ASCO panel initially believed that tamoxifen should remain the standard hormonal therapy, but that guideline, over time, has also changed. Currently, the NCCN and the ASCO guidelines are essentially identical in terms of up-front hormonal therapy.

The different methods of using aromatase inhibitors or incorporating them — initial aromatase inhibitor therapy versus sequential after two to three years of tamoxifen versus extended after five years — have never truly been studied in a randomized fashion, one against another. The BIG 1-98 trial will give us the first look at that sort of comparison.

The real question is whether tamoxifen does something to prime the breast cancer cells and cause the aromatase inhibitor to be more effective in the switching studies. Or, rather, is it that the population of women and the characteristics of their breast cancer change over time in a way that would make the aromatase inhibitors — or any hormonal therapy — more effective?

I believe a substantial amount of data exists to support the selection bias theory that the population of breast cancer patients over time is changing. You would expect the endocrine-resistant, receptor-positive breast cancer to recur earlier, so those women are removed from the denominator.

If you have a sensitive population and an insensitive population with hormone receptor-positive tumors — even with no difference in efficacy between the hormonal therapies — you should expect to see an increasing effect the later in time you initiate the therapy. However, it's hard to have a drug that's so effective down the road that you are able to regain the loss of two to three absolute percentage points that women may experience when the drug is used in this context.

Breast Cancer Update 2006 (7)

DR VICTOR G VOGEL: How to approach a patient who has received five years of an adjuvant aromatase inhibitor is a challenging question. Up until the 2005 San Antonio meeting, I wasn't certain what the answer was to that question. But I was heartened by the data that were presented, both by Paul Goss and Jim Ingle, on the continued follow-up of the

FIGURE 11

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

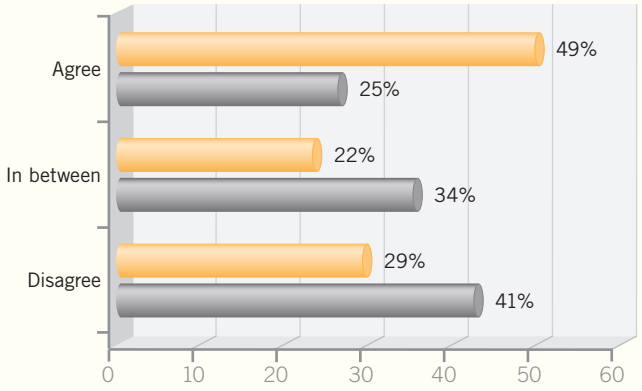
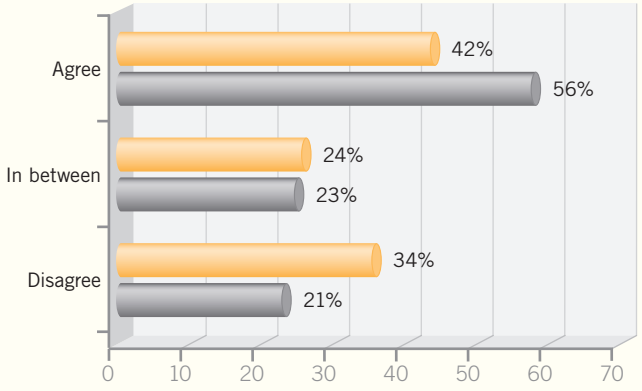


FIGURE 12

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



MA17 trial patients and, particularly, those patients who had initially been assigned to placebo and then crossed over to letrozole.

Two patterns were evident from those data. The first was that the longer a patient received the aromatase inhibitor following five years of tamoxifen, the greater the benefit. It is rare in medical oncology to see a benefit that increases as the duration of therapy increases. But it was clear that the longer the duration of therapy with letrozole was, the greater the benefit was.

Comparing two years to four years, the benefit almost doubled. So for our patients at high risk, especially those with larger tumors and those with positive nodes, based on those data, we're now telling them they should continue to take their aromatase inhibitor because we know they're at risk for a very long time — two decades or longer — for recurrence, and these data now show that longer therapy may improve their outcomes.

The other question those data helped us answer relates to patients who have a gap between the end of their tamoxifen therapy and the initiation of their aromatase inhibitor therapy.

The patients who were initially assigned to placebo after five years of tamoxifen in the MA17 trial crossed over to letrozole. Approximately 1,600 patients made the crossover, and their average duration off therapy — that is, the time between the end of their tamoxifen and the initiation of their letrozole — was about 30 months.

Even with that delay in the initiation of the aromatase inhibitor, a statistically significant benefit was demonstrated with the so-called delayed initiation of the aromatase inhibitor after tamoxifen.

Breast Cancer Update 2006 (5)

DR JULIE R GRALOW: The update of the MA17 trial examined the patients who originally received a placebo after five years of tamoxifen as opposed to letrozole and then at about 30 months, when the study was unblinded, were offered letrozole. Approximately two thirds of those patients chose letrozole, and they tended to be a higher-risk group.

Those patients had an average gap of 30 months without any endocrine therapy. Despite that and the fact that they were a good eight years out from their diagnosis, a reduction appeared across the board in every type of breast cancer recurrence — contralateral, in-breast and distant. It's impressive.

We saw the updated analysis for the MA17 trial at the San Antonio meeting in 2005, and at that point I began to at least offer patients the option of going back on an endocrine agent if they'd been off everything for a couple of years, especially if they were at high risk.

Although it might offer some benefit 10 years later, the duration off therapy in the MA17 trial was approximately 30 months, so I consider restarting endocrine therapy for patients up to three years off treatment. That's arbitrary, but you have to pick some time period.

Cancer Conference Update, San Antonio Breast Cancer Symposium 2005

DR PETER M RAVDIN: The problem with the extended letrozole trial (NCIC-

FIGURE 13

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

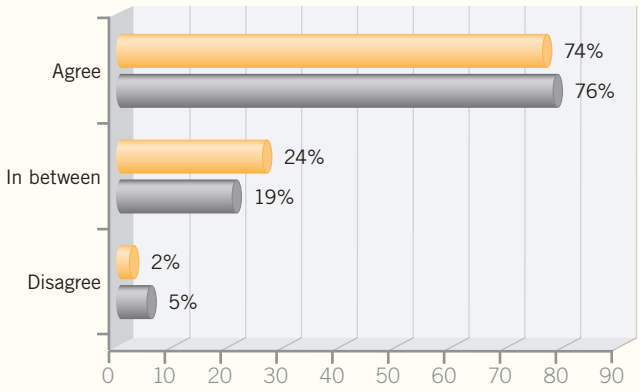
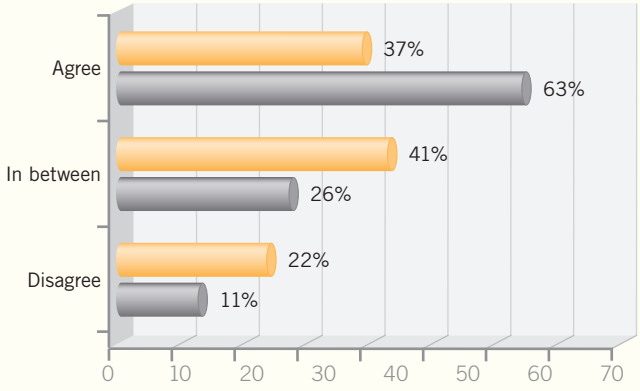


FIGURE 14

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



CTG-MA17) was that the patients were unblinded at 2.4 years, and because most patients then switched over to the active agent, we will never know with any certainty what would have happened had they been unblinded at five years. That is a shame because we are going to be treating these patients for five years, so it would have been nice to know the differences in toxicity and efficacy between the two arms. The data for one or two years are complete because most of the patients had gone through those years. There were a lot of data in year three, a modest amount in year four and almost no data for the fifth year.

An analysis of relapse risk within each year could then be performed. This was possible not only for years one and two but also for year three, when it seems that the relative benefit was greater, which is interesting and reassuring. That was also the case in year four. That analysis used year-by-year hazards to determine whether benefit was attenuating, staying as strong or becoming stronger. Although we will never know what it would have been if the trial had been unblinded at five years, we are somewhat reassured by the results of this analysis that going beyond 2.4 years of treatment is reasonable.

Breast Cancer Update 2006 (8)

DR HARRY D BEAR: In my practice, by and large, the postmenopausal patients who do not have osteoporosis are receiving aromatase inhibitors up front. The ATAC results are difficult to dispute. For patients who have been on tamoxifen for a year, I haven't jumped to switch them to an aromatase inhibitor.

I will probably follow the paradigm of some of the other trials and leave them on tamoxifen for a couple or three years. Then I'll switch them over. I believe they will obtain some bone-density benefit by staying on tamoxifen for a while and start out at a better baseline when we switch them over to an aromatase inhibitor.

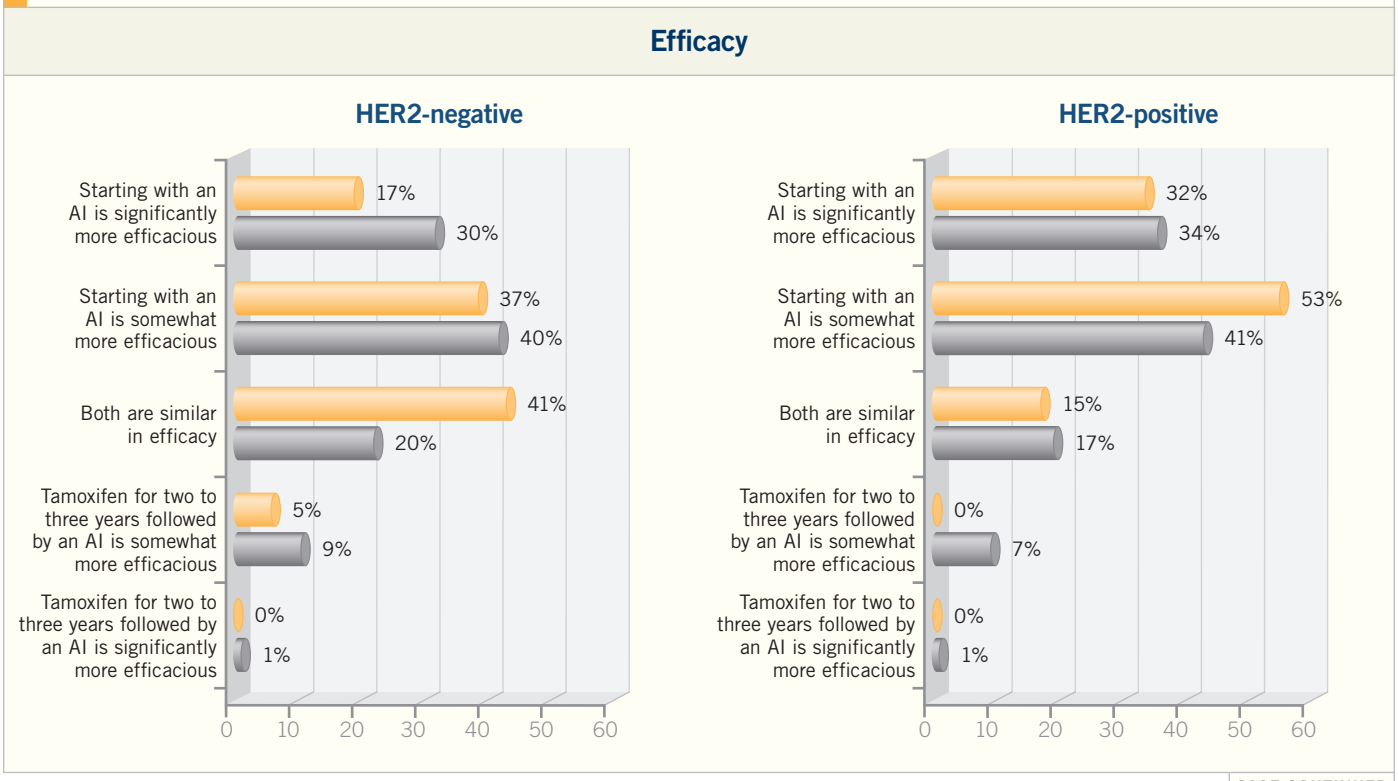
NSABP-B-42 will address the question of duration of therapy. It will look at the group of patients who have been on five years of either a combination of tamoxifen and an aromatase inhibitor or an aromatase inhibitor alone. The trial will determine whether those patients should receive an aromatase inhibitor for another five years. It's a five- versus 10-year question, reminiscent of the NSABP-B-14 rerandomization.

Interview, September 2006

DR NORMAN WOLMARK: The NSABP-B-42 trial just opened. It has a sample size of about 3,800, and of course one of the questions that remains unanswered is the duration of an aromatase inhibitor. We went through this process and it

FIGURE 15

*How would you generally compare the **efficacy** of an aromatase inhibitor (AI) up front **versus** tamoxifen for two to three years followed by an AI for a woman in average health with a 1.2-cm, Grade II tumor, ER 90%, PR 60% and three positive nodes?*



CASE CONTINUED

took us years to determine the optimum duration of tamoxifen therapy, and at the end of the day there was enormous surprise from the B-14 data that not only is 10 years not as good as five, but it is also somewhat detrimental. We believe it's important to address the duration of an aromatase inhibitor, and this is what NSABP protocol B-42 will be doing.

The data with aromatase inhibitors from the multiple trials have all been positive. The duration question remains relatively unaddressed.

We have seen trials that have introduced aromatase inhibitors after a period of tamoxifen and have shown an advantage. We've seen direct head-on comparisons between aromatase inhibitors and tamoxifen up front also showing an advantage, and we're waiting to see the results of a trial that starts with an aromatase inhibitor and sequences it with tamoxifen.

NSABP-B-42 Protocol July 2006; nsabp.pitt.edu.

In the adjuvant setting, AIs have demonstrated activity in three distinct clinical situations. In the first situation, an AI was compared to tamoxifen as initial adjuvant hormonal therapy in patients with resected operable breast cancer. The ATAC trial demonstrated that 5 years of anastrozole significantly improved disease-free survival (DFS) when compared to 5 years of tamoxifen. More recently, the BIG 1-98 trial also demonstrated improved DFS as well as distant DFS for 5 years of letrozole compared to 5 years of tamoxifen.

In the second situation, an AI was compared to tamoxifen in patients who had already received 2-3 years of adjuvant tamoxifen. In three randomized trials (the IES trial [International Exemestane Study], the ABCSG-8/ARNO 95 trial, and the ITA trial [Italian Tamoxifen vs Anastrozole]), 2-3 years of an AI (exemestane or anastrozole) improved disease-free survival compared to 2-3 years of tamoxifen in patients who had already completed 2-3 years of tamoxifen therapy.

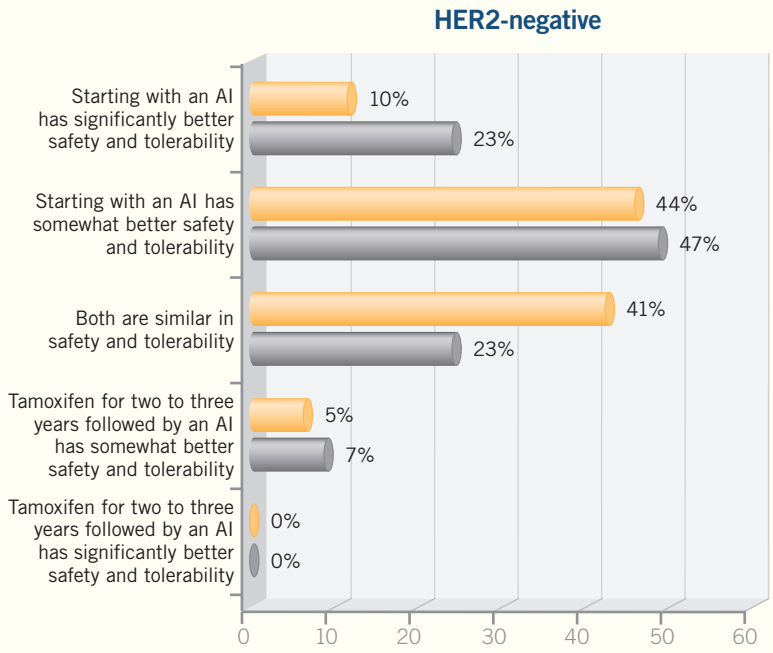
In the third clinical situation, an AI was evaluated as extended adjuvant hormonal therapy following completion of 5 years of adjuvant tamoxifen. The NCIC-MA17 trial compared 5 years of letrozole with 5 years of placebo in patients who had already completed 5 years of adjuvant tamoxifen and demonstrated significant improvement in disease-free survival in favor of the group that received the AI.

Based on the results from these trials, AIs are increasingly utilized as adjuvant therapy in these three clinical situations. At this time, there are no available results from trials that directly compare these different approaches for using AIs. Thus, the best setting for the adjuvant

FIGURE 16

*How would you generally compare the **safety and tolerability** of an aromatase inhibitor (AI) up front **versus** tamoxifen for two to three years followed by an AI for a woman in average health with a 1.2-cm, Grade II tumor, ER 90%, PR 60% and three positive nodes?*

Safety and tolerability



CASE CONTINUED

use of AIs cannot be readily determined at present.

Breast Cancer Update 2006 (1)

DR PAUL E GOSS: We don't know what the appropriate approach is to selecting one of the three aromatase inhibitors in the up-front setting. I have the good fortune of chairing a key study in this regard. The MA27 study will complete accrual in 2006, and it is addressing precisely that question of whether there is an optimal aromatase inhibitor. The randomization is between the steroidal exemestane and the nonsteroidal anastrozole.

In the meantime, there are ample data to say these compounds are different in terms of their biochemical and preclinical effects. But in the clinic, with the present data, there is no evidence of a wide difference between these drugs. So I think that one has to restrict one's choices to the approved therapies by the regulatory agencies and the published evidence-based data.

John W Berry. ***Are all aromatase inhibitors the same? A review of controlled clinical trials in breast cancer.*** *Clin Ther* 2005;27(11):1671-84.

There may be important clinical differences between the AIs. However, data from direct comparative clinical trials are limited, and making comparisons across trials is difficult given differences in design, methodology, patients, and endpoints. At the present time, the choice of an AI for clinical use should be based on the strength of the data within the distinct clinical scenarios: neoadjuvant therapy, adjuvant therapy, or advanced/metastatic disease.

Breast Cancer Update 2006 (1)

DR AMAN U BUZDAR: As the safety data for the three aromatase inhibitors are emerging, we see that they are quite different. In the package insert for exemestane, a small but definite increased risk of cardiac dysfunction is noted. If you consider the letrozole data from the BIG trial, at 25 months a small but definite increased risk of cerebrovascular accident and myocardial infarct is evident. However, in the 68-month follow-up data for the ATAC trial, we see none of those risks with anastrozole. If you examine the cardiac deaths, it is 49 with anastrozole versus 46 with tamoxifen, and cerebrovascular accidents are substantially reduced with anastrozole compared to tamoxifen.

An interesting study presented at the 2005 San Antonio Breast Cancer Symposium evaluated 90 healthy, postmenopausal volunteers who received, in a blinded fashion, up to 24 weeks of anastrozole, letrozole or exemestane. When the effects on the lipids were examined, they were found to be totally different. We have to be aware of the different effects and realize that not all aromatase inhibitors are alike and that it does matter which one we select.

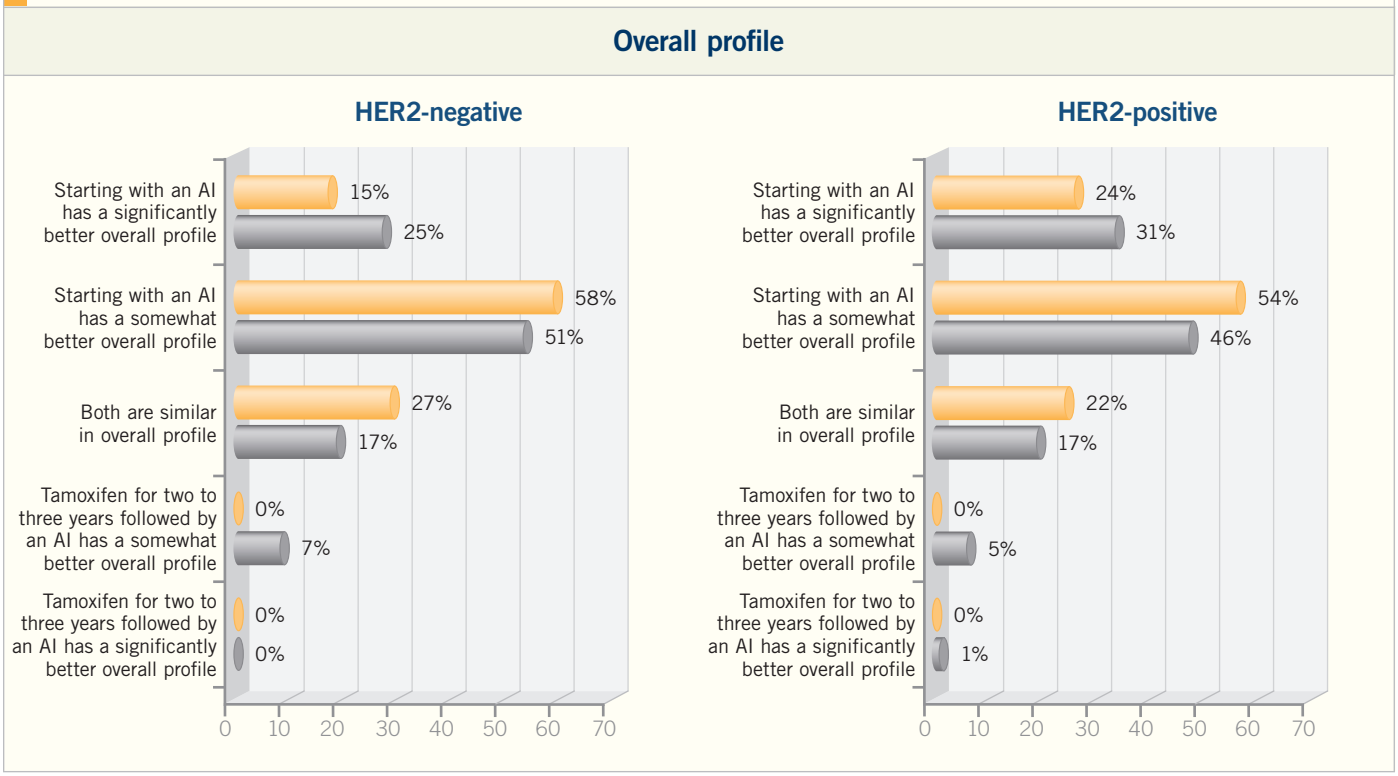
Jean Marc Nabholtz, Joseph Gligorov. ***Cardiovascular safety profiles of aromatase inhibitors: A comparative review.*** *Drug Saf* 2006;29(9):785-801.

A significantly reduced risk of thrombo-embolic disease was observed for all three AIs compared with tamoxifen. Anastrozole is, at this point, the only AI with a detailed benefit-risk profile from over 5 years' follow-up in the adjuvant setting.

Thus far, no apparent CV-safety concerns have emerged. Preliminary data on letrozole and exemestane suggest that longer follow-up is needed for these two AIs before being able to fully assess their respective long-term CV toxicity profile. The present differences in CV-safety profiles suggest that third-generation AIs should not be considered as equivalents in clinical practice.

FIGURE 17

*How would you generally compare the **overall profile** of an aromatase inhibitor (AI) up front **versus** tamoxifen for two to three years followed by an AI for a woman in average health with a 1.2-cm, Grade II tumor, ER 90%, PR 60% and three positive nodes?*



Meet The Professors 2006 (3)

DR DEBU TRIPATHY: As time goes on, less and less of a distinction can be made between the aromatase inhibitors. Up front, I don't have a strong preference. We certainly have data for anastrozole and letrozole. I tend to use anastrozole simply because it has longer safety data. There we have the largest number of patients that have been followed, so in my mind, there's more confidence in the safety profile.

BONE AND AROMATASE INHIBITORS

Breast Cancer Update 2006 (5)

DR GRALOW: The five-year bone density substudy of the ATAC trial was very interesting. The fracture rates on that trial were approximately 11 percent in the anastrozole arm and about 7.5 percent in the tamoxifen arm at 68 months of follow-up.

However, we were trying to determine who should receive bisphosphonates up front and how often we should follow bone density studies. I believe the ATAC data that Rob Coleman presented at ASCO showed that not everyone needs a DEXA scan every year or a bisphosphonate up front.

What was surprising to me but very reassuring was that none of the patients who started the ATAC trial with a normal bone mineral density — a T-score better than minus one — were osteoporotic after five years of treatment, although approximately 50 percent had become osteopenic.

We expect about a two to three percent bone loss during the five years simply based on aging, but in the tamoxifen arm, approximately 15 to 20 percent of the patients went from normal to osteopenic, and the rate was 50 percent for patients who received anastrozole.

Aging happens even to the best of us, but I believe these data show us that if the patient started with a normal bone mineral density, her chance of becoming osteoporotic after five years as a result of receiving an aromatase inhibitor in that study was zero.

ADHERENCE TO LONG-TERM ORAL ENDOCRINE THERAPY

Interview, August 2006

DR VICTOR VOGEL: In terms of patients stopping long-term medications, published data show that the decay over time is very high.

There are more data published on tamoxifen than on the aromatase inhibitors, but even some aromatase inhibitor data show that as many as one third of patients stop their medication within the first year and by the second year, as many as half of patients have stopped taking their aromatase inhibitor. This should be distressing to all of us.

FIGURE 18

Consider a breast cancer patient receiving oral adjuvant endocrine therapy. For what percentage of the time do you think the patient would take her medication as prescribed? (mean)

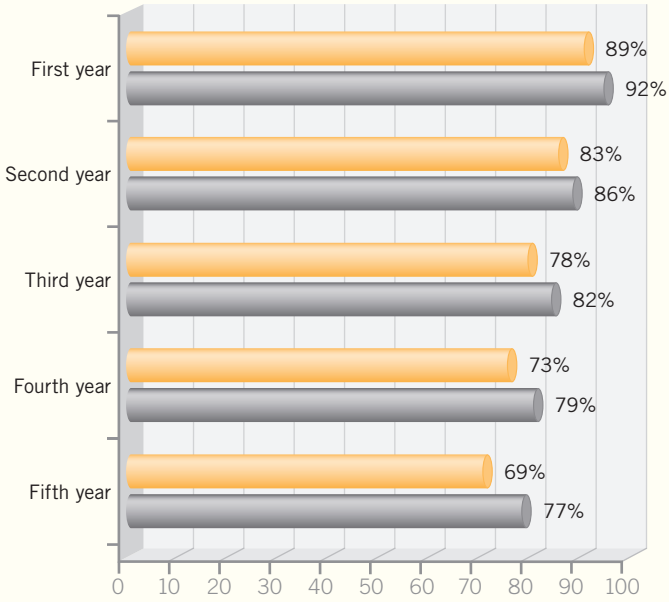
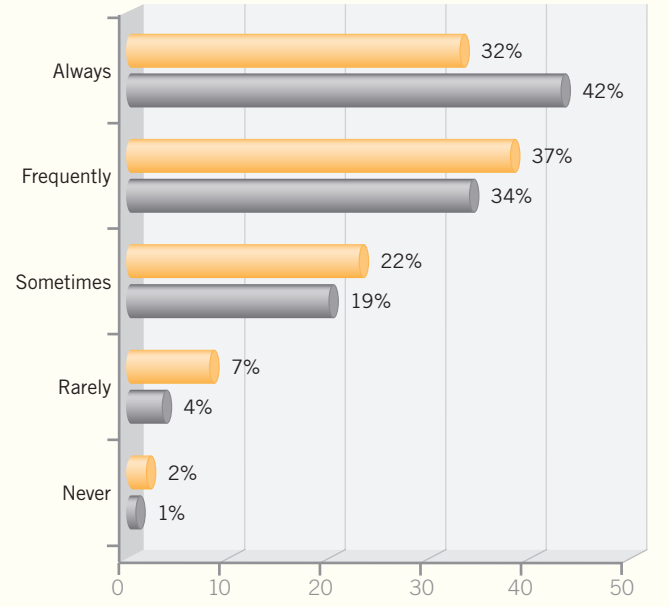


FIGURE 19

How often during routine follow-up visits with patients on long-term adjuvant endocrine therapy do you ask your patients how regularly they take their medication?



A number of barriers exist, such as cost and side effects. An equally important barrier is patients' misperception that if time has transpired and they're doing well — they're coming back for their second and third annual visits and their mammograms are fine, their physical exams are normal and they're asymptomatic — that their risk has passed and, therefore, it's not necessary to continue the medications.

It's important for oncologists to be aware that patients are stopping their medication and that we need to regularly ask patients whether they're taking the medications daily and determine whether there are any barriers to doing so — be it cost or symptoms or perceptions about the risk of recurrence.

I don't think it was well recognized in our treatment community that patients were stopping their medications. We are not in tune with the reality, and when you actually examine prescription refills and availability of medications over time, in fact, patients are not being compliant.

I think the first step is for us to recognize that patients aren't compliant and to stop pretending that they simply follow our directions because we told them this is what they need to do.

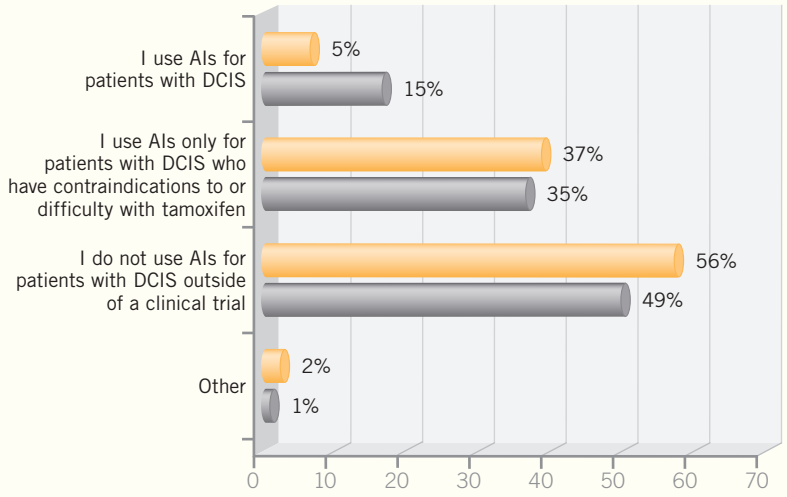
We need to ascertain if the patient is compliant, and there are many strategies we can use to do this, be it pill counts, pharmacy records or simply asking patients. We need to constantly ensure that what we believe the patient is doing is what they're actually doing. The data would suggest that, in fact, patients are not following our advice.

Interview, June 2006

DR D LAWRENCE WICKERHAM: We spend a fair amount of time and energy educating our physicians, nurses and coordinators about the importance of compliance and adherence. Within the context of a clinical trial, you can pick your patients a little, so we try to identify those individuals most likely to be compliant with the regimen — not only taking their pills but also receiving their follow-up exams, mammograms and so forth. Then we institute

FIGURE 20

*Which one of the following best describes how you have used an aromatase inhibitor **outside of a clinical trial** for a breast cancer patient with DCIS (ductal carcinoma in situ)?*



a number of strategies to help maintain that level of compliance during the course of the trial.

We design our trials with a built-in level of noncompliance. Clearly, you want patients to take their medications so they can obtain the maximum benefit and so that the study results, both benefit and toxicity data, are as accurate as possible.

Applying that information to the general population of patients who are not in clinical trials has recently become an area of interest in both the treatment and the prevention settings. As we have more oral agents in oncology, it becomes increasingly important for us to be thinking about how to keep our patients on these therapies.

The most important thing is to ask the patient in an open fashion whether they're having any difficulties taking their medication. Without making it sound threatening, that should be asked at each follow-up visit, and the importance of taking their medication as prescribed should be reinforced. Patients should be told to announce any difficulties in taking their medications, be it side effects, toxicities or economic issues. These can all be addressed, but only if they are described.

Interview, June 2006

DR ROWAN T CHLEBOWSKI: Adherence to oral hormonal therapy has received minimal attention, but it's an area of increasing interest.

I believe that because chemotherapy is perceived as being a burden and difficult, the concept is that when you are done with the chemotherapy, you are done with the heavy lifting. Indeed, some practices provide diplomas, like graduation, after chemotherapy.

When oncologists see patients three and four years out in a 12-minute slot, when we reassure them that they are doing fine and give them a six-month prescription for aromatase inhibitors, it's easy to understand how patients might perceive that they are done with their cancer.

If you're taking pills, you're admitting that you have a problem. And if you can stop the pills, mentally, in a certain sense, you are putting the problem behind you. When women get three or four years out after a breast cancer diagnosis, they'd like to think the problem is behind them.

The other issue is cost, and when a woman says, "That's too expensive," I ask her, "Do you have the money to pay for the medication?" Some women don't, but many women, in effect, are spending the money on something else. Then I'll ask them, "If you don't want to spend the money on the aromatase inhibitor, what do you plan to spend the money on?"

That lets them know that I think it's important that they're making this choice. And then I remind them that this is quite different than considering a decision to get dial-up or cable internet, where, at the end of two years, you have saved $2,000, and you were willing to put up with the slowness of the internet speed.

Here, you're doing something more than that. You're making a bet. Because I tell the women that there's appreciable cost to themselves and their family for a breast cancer recurrence. If the patient develops a recurrence, that could cost thousands and thousands of dollars and jeopardize their entire financial bearing. You have to judge very carefully a decision that may effect the risk of a recurrence.

Breast Cancer Update 2004 (7); 2006 (3)

DR PATRICK I BORGEN: NSABP-B-35 and IBIS-II are important trials, both comparing anastrozole and tamoxifen in postmenopausal patients with DCIS. Aromatase inhibitors have already proved to have a significant effect in invasive cancer, and it's highly likely they will affect DCIS as well.

We know that the majority of DCIS lesions are likely to be ER-positive. Craig Allred has shown that age per age, tumor for tumor, DCIS is even more likely to be ER-positive than invasive cancer. If that's true, then we have even more reason to be optimistic about the studies of aromatase inhibitors in DCIS.

We have viewed tamoxifen as a highly appropriate option for treating a patient with ER-positive DCIS since the NSABP-B-24 trial. However, when we consider risks, benefits and quality-of-life issues, it's common for our New York patients to demur, so we probably have one of the lowest percentages

of patients with ER-positive DCIS on tamoxifen in the country.

The same can be seen in our prevention setting, in which we've not been successful in getting patients to take tamoxifen.

The two most obvious concerns about tamoxifen in these settings are endometrial cancer and gynecological events. Even when we provide the raw numbers on how infrequent those events are, because we are talking about minimal, if any, impact on long-term survivorship and moderate impact on local control, it simply is not an attractive option.

We'd like more information about DCIS and aromatase inhibitors, but since the initial publication of the ATAC data, aromatase inhibitors have become our endocrine therapy of choice for postmenopausal patients with ER-positive, invasive cancers. That literally happened overnight, like gangbusters, and so a "bleed over" to postmenopausal patients with DCIS is natural.

In my clinical practice, it's clear that the aromatase inhibitors are vastly better tolerated than tamoxifen in postmenopausal patients.

Our surgeons are beginning to give first-line endocrine therapy without a mandatory consult from medical oncology. We perform bone density tests before we start our patients on aromatase inhibitors, and treating these patients has been satisfying.

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

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

Adjuvant Chemotherapy

FIGURE 21

A 77-year-old woman in good health with an ER-negative, PR-negative, HER2-negative tumor and three positive nodes wishes to receive chemotherapy. What would you likely recommend?

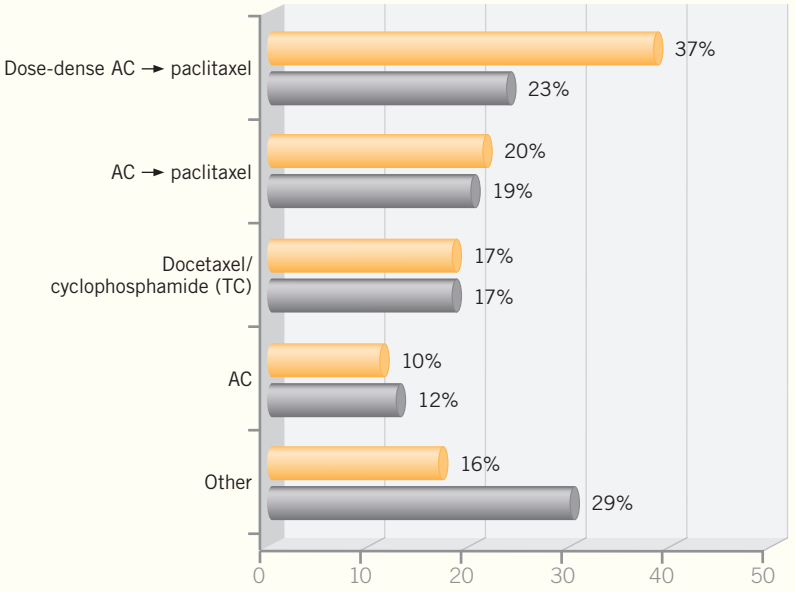
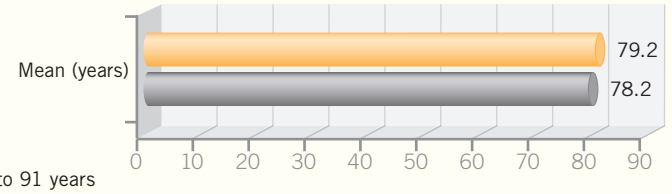


FIGURE 22

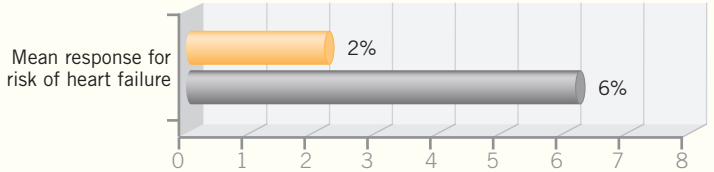
What is the age of the oldest breast cancer patient you have treated with adjuvant chemotherapy?



Range: 60 to 91 years

FIGURE 23

A 60-year-old woman has well-controlled hypertension. What would you tell her is the risk of heart failure for four courses of AC (240 mg/m^2)?



CLINICAL INVESTIGATORS (CI)
PRACTICING ONCOLOGISTS (PO)

Breast Cancer Update 2006 (5)

DR HAYES: For older women, I believe the jury is out regarding the potential benefits of chemotherapy. The issue has two components. One is whether — for some mysterious reason — chemotherapy doesn't work as well in older women as in younger women. The second is whether the toxicities are greater for older women and, therefore, the benefit-to-toxicity ratio is smaller.

Another component is whether the number of life-years saved will be lower for older women and therefore not acceptable. An 80-year old woman on average has another 10 years to live, but the number of life-years saved for her will be lower than for a 50-year-old woman for the same potential reduction in recurrences. Peter Ravdin has begun to build that into Adjuvant! Online. It's not something we normally talk to patients about, but I believe it is part of the equation.

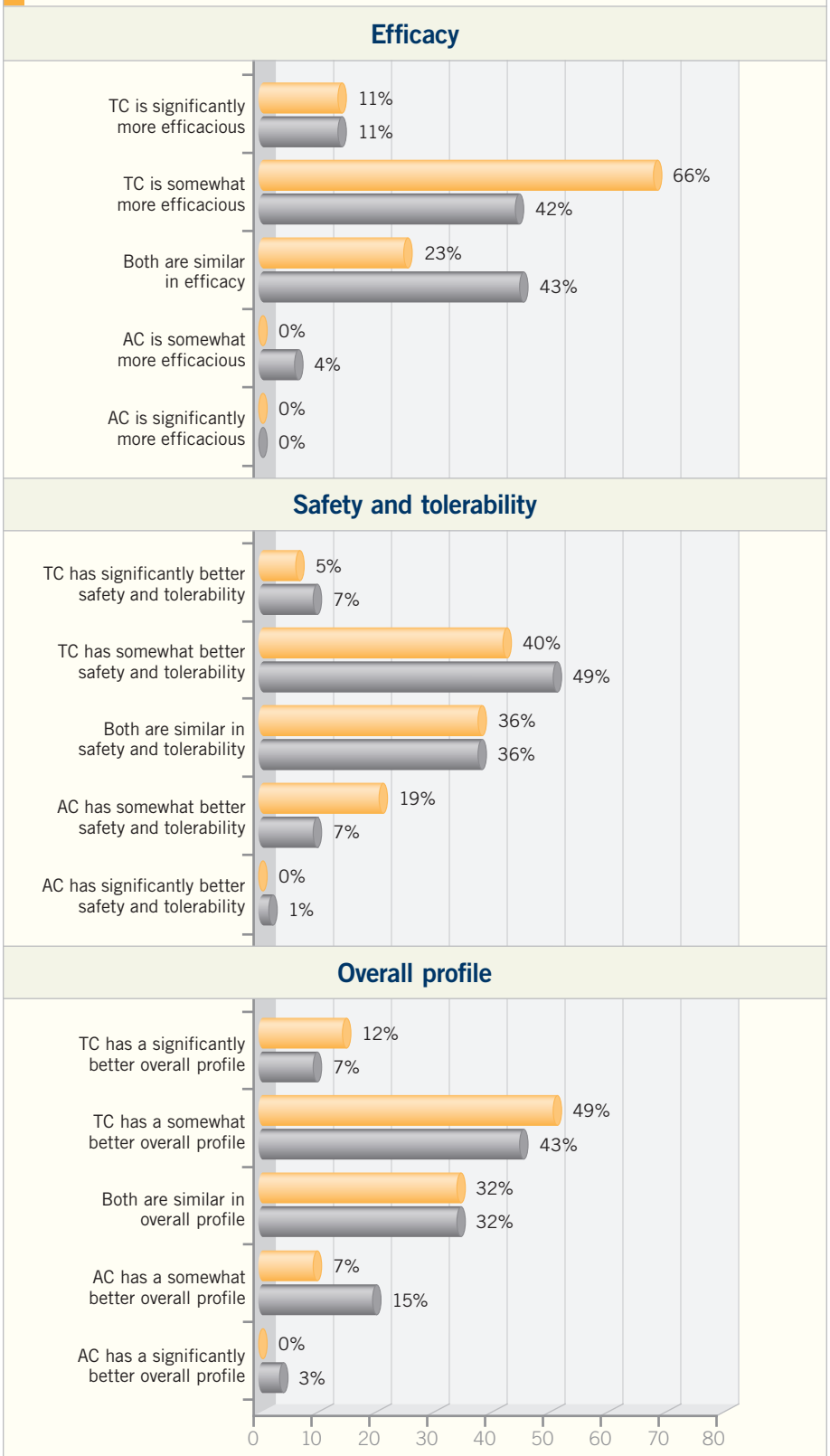
The CALGB-49907 study, which is restricted to patients over age 65, assumes that chemotherapy is beneficial. It is not a trial of chemotherapy versus none. The question is whether in this older age group one type of chemotherapy might be more acceptable by being less toxic. Patients either receive one of the standard regimens — AC or CMF — or capecitabine. A critical part of the study is to determine whether capecitabine is a more acceptable regimen.

Breast Cancer Update — Think Tank Issue 2, 2006

DR HOPE S RUGO: I would consider adjuvant chemotherapy for an otherwise healthy woman in her eighties with triple-negative disease, but even more so for the patient with an ER-negative, PR-negative and HER2-positive tumor, for whom we know that recurrence is heavily weighted in the first two or three

FIGURE 24

How would you compare docetaxel/cyclophosphamide (TC) to AC?



Data on efficacy and tolerability are from Patterns of Care, August 2006

years. As the survival of our population increases, these 81- and 82-year-old women who don't have major medical problems are reasonable candidates for limited approaches to chemotherapy.

This must be within the limits that we all know to be important, such as understanding morbidities. That's one of the reasons Adjuvant! Online can be very useful in directing physicians who are treating older patients. First, in this older population, the patients with hormone receptor-negative disease are the ones for whom we are going to be thinking about chemotherapy.

Then, in regard to morbidity, if a patient has a major morbidity, such as heart failure, and is not going to be alive in three years, that is not the patient we should be treating with chemotherapy.

Breast Cancer Update — Think Tank Issue 2, 2006

DR CLIFFORD HUDIS: In the quantifiable, objective ways in which we assess toxicity, you cannot support the argument that dose-dense therapy is more toxic. In CALGB-9741, it appears to be equivalent or perhaps less toxic in many ways. The one toxicity that stood out in the original Citron paper was the high rate of packed red blood cell transfusions, which appears to be abrogated with the use of erythropoietin or darbepoetin as prophylaxis. It's my subjective opinion that patients stay on schedule more easily when they receive every two-week therapy with growth factor support than when they are treated with an every three-week schedule. When patients can't plan their therapy, it is an annoyance, and it can reduce quality of life.

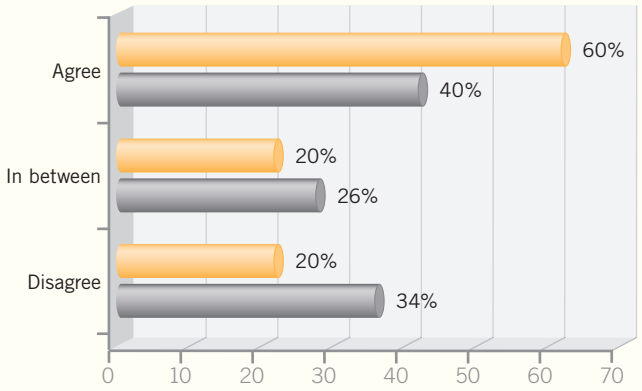
Also, completing therapy faster is always worthwhile. We've taken the position that unless we have a compelling reason not to administer a growth factor, we use every two-week therapy for everybody who receives AC and a taxane.

Breast Cancer Update 2006 (7)

DR CARLSON: Docetaxel administered every three weeks at 100 mg/m^2 is a reasonable taxane to use following AC chemotherapy. I have no difficulty with

FIGURE 25

All other factors being the same and with the same risk of relapse, I am less likely to use adjuvant chemotherapy for women with ER-positive tumors than for women with ER-negative tumors.



that. ECOG trial E1199 suggested equal efficacy to paclitaxel in that setting. Perhaps a little more toxicity, especially febrile neutropenia, occurred with the every three-week regimen. Given the increased frequency of febrile neutropenia, growth factors would be reasonable to use with that dose and schedule.

TAC certainly causes febrile neutropenia with a high enough frequency that growth factors should be used. The NCCN Breast Cancer Treatment Guideline specifies the use of growth factors with two of the adjuvant chemotherapy regimens. One is TAC and the other is a dose-dense chemotherapy regimen.

Breast Cancer Update 2006 (6)

DR I CRAIG HENDERSON: I see dose-dense AC without paclitaxel being administered off protocol in my own clinic. I started a couple of patients in the last few weeks on dose-dense adjuvant chemotherapy and discussed it with some of my colleagues, and in fact, they are doing this in the university setting. In CALGB-9741, which compared sequential doxorubicin, paclitaxel and cyclophosphamide versus concurrent AC followed by paclitaxel at 14- and 21-day intervals, we can't separate which is the critical factor — the AC or the taxane. We will have to wait and see what the science says.

Breast Cancer Update 2006 (7)

DR CARLSON: I believe that every two-week AC without a taxane with only growth factor support is a reasonable regimen, and I use it for the patients for whom I do not consider a taxane necessary. It's based on the belief — and it's just a belief, it's not yet proven — that if dose-dense AC followed by paclitaxel, or the ATC dose-dense regimen, is superior, it's likely that every two-week AC should be superior or at least equal to every three-week AC.

I'm impressed at how nontoxic this regimen is when you use growth factors. I believe women like to get through these therapies quickly, and you shorten the duration of treatment with the dose-dense regimens.

Breast Cancer Update 2006 (7)

DR MARK D PEGRAM: The presentation by Steve Jones at San Antonio 2005 of the US Oncology adjuvant trial of docetaxel/cyclophosphamide versus AC was an exciting presentation, and I'm not surprised at all by the data. Steve presented a randomized trial for patients with early-stage breast cancer, approximately 40 to 50 percent of whom had node-negative disease. They were randomly assigned to four cycles of AC versus four cycles of TC.

They showed a significant relapse-free survival advantage with the TC compared to the AC arm, and a numeric trend even appeared in the survival analysis, although it hasn't reached statistical significance yet. Steve Jones concluded — and probably rightly so — that this constitutes a new regimen that replaces AC. If you were going to use a four-cycle regimen, you probably wouldn't want to use AC anymore, based on this data set.

I was also favorably surprised by the toxicity and safety data. The TC was well tolerated compared to AC. It goes to show that we probably underestimate the toxicity of AC routinely because we're so used to prescribing it.

I saw a young woman recently in my clinic with newly diagnosed doxorubicin cardiotoxicity after adjuvant therapy for what will probably be curable breast cancer. It's sobering and scary when you see cases like this.

Breast Cancer Update 2006 (6)

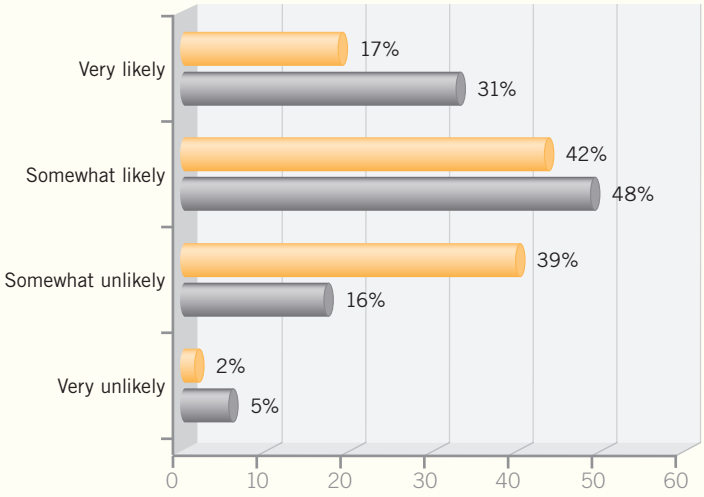
DR MARC E LIPPMAN: Almost 30 years ago, we published, in *The New England Journal of Medicine*, that patients with ER-negative disease responded more frequently to chemotherapy than patients with ER-positive disease.

Those data have been replicated in the meta-analyses conducted in England by Sir Richard Peto and his collaborators. The clue as to why that occurs is obtained if you observe recurrence rates for women with breast cancer as a function of whether their disease is ER-positive or ER-negative. It is commonly said, but that doesn't necessarily make it the truth, that having ER-positive disease is a good prognostic factor. The data show — and this has now been shown several times — that early on, if your disease is ER-positive, your relapse rates are lower.

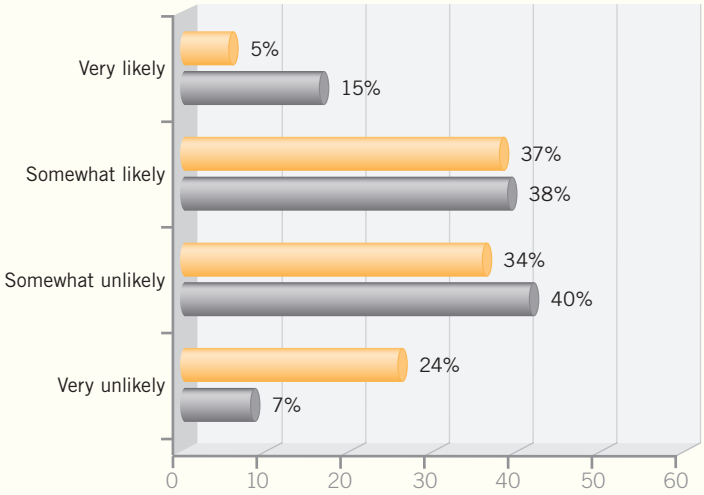
Over time, the patients with ER-negative disease, who relapse at a higher rate, initially stop relapsing, perhaps because most of the ones with bad prognoses have already died, whereas the patients with ER-positive disease continue to relapse, and those lines actually cross. At about 10 to 15 years, you're worse off having ER-positive than ER-negative disease.

FIGURE 26

*You estimate a 10 percent risk of recurrence for a 65-year-old woman with an **ER-negative**, HER2-negative tumor. How likely would you be to recommend chemotherapy for this patient?*



*You estimate a 10 percent residual risk of recurrence for a 65-year-old woman with an **ER-positive**, HER2-negative tumor **after receiving adjuvant hormonal therapy**. How likely would you be to recommend chemotherapy for this patient?*



Breast Cancer Update 2006 (7)

DR CARLSON: The analyses of dose-dense chemotherapy and TAC in hormone receptor-positive patients are provocative. Dose-dense chemotherapy showed very little benefit in receptor-positive breast cancer, whereas not much difference in efficacy appeared between the patients with ER-negative and ER-positive disease in the TAC study. Those are indirect comparisons, so I'm not sure we can make much of that specific finding. It'll be interesting to see, as ECOG-E1199 unfolds, if a differential responsiveness appears with docetaxel versus paclitaxel based on ER status, because that's what you'd have to hypothesize.

Breast Cancer Update 2006 (7)

DR PEGRAM: Determining a chemotherapy regimen for patients with ER-positive disease depends on their age, et cetera. If they're getting on in years, I'm more likely to use AC followed by weekly paclitaxel, for example, because that's so well tolerated. If they are young, fit, in their thirties, have no comorbid medical illnesses and have a number of positive nodes, I would have no hesitation using TAC because we participated in some of those TAC trials and we're comfortable with the regimen when we use pegfilgrastim.

Breast Cancer Update 2006 (8)

DR RAVDIN: In the most recent Oxford Overview chemotherapy data, the correlation between estrogen receptor status and impact on outcome was hotly debated and complicated by the fact that age has to be taken into account in evaluating the first-generation trials. Overall, it looks as if ER status did not make a difference.

In contrast, ER status appears to make a difference in older patients. Patients with ER-positive tumors benefited, although the benefit was smaller than in those with ER-negative disease — approximately a 2:1 difference. So ER status is important in therapy, but its importance is more obvious among older patients.

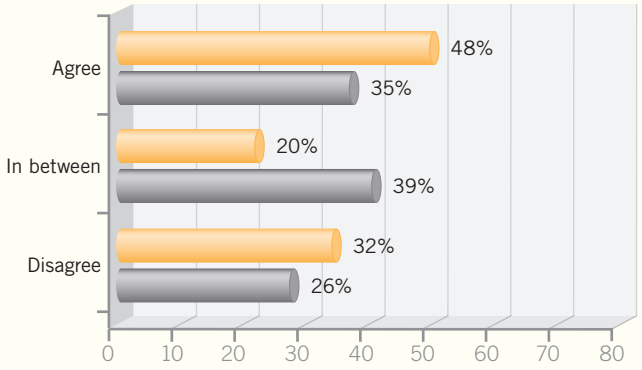
Breast Cancer Update 2006 (7)

DR VOGEL: Using archival tissue blocks from past trials, Genomic Health and Dr Soon Paik from the NSABP analyzed about 200 genes that were reported to possibly relate to outcome in breast cancer. They narrowed that set down to just 16 genes that could be sorted into logical groups based on the estrogen receptor, the HER2 protein and proliferation and invasion characteristics of the cells.

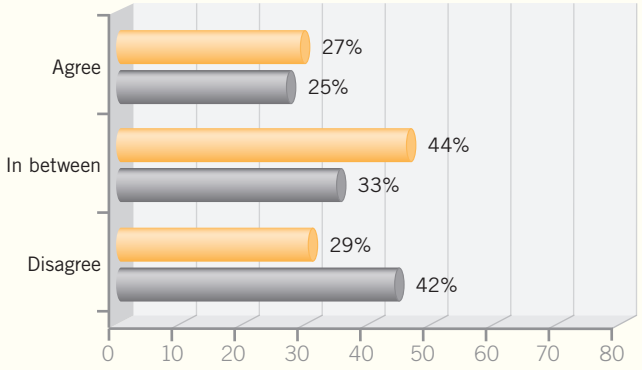
That set of 16 genes plus five reference genes were used to see if breast cancer patients could be sorted into prognostic and predictive groups. When I

FIGURE 27

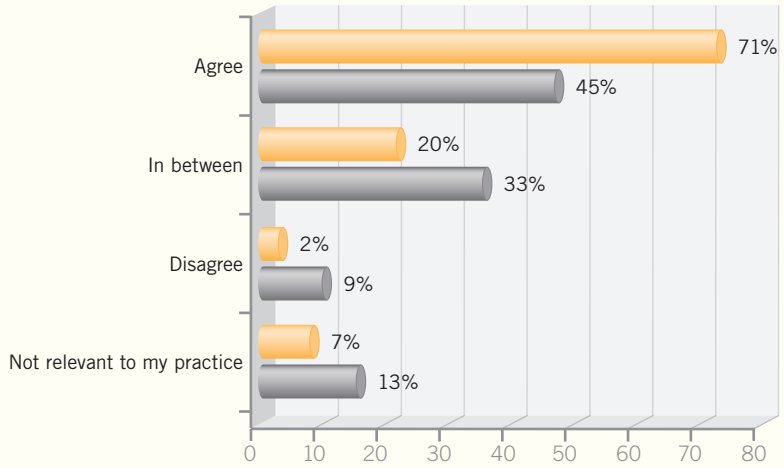
There is essentially no role for the Oncotype DX™ assay in the management of HER2-positive tumors.



Assays like Oncotype DX will eventually replace IHC and FISH for evaluating HER2 and ER.



The way I integrate Oncotype DX into my practice is cost effective for the healthcare system.



say "prognostic" I mean to predict the likelihood of recurrence, and when I say "predictive" I mean to predict patients who would benefit from chemotherapy. So the investigators examined the archival subsets and were able to determine that those 16 genes and five reference genes could be used to sort patients along a continuum they called the recurrence score, which varies from zero to 100. Using simple mathematic regression procedures, that recurrence score could then be translated into a probability of recurrence over 10 years.

The investigators were also able to determine that patients who had low recurrence scores — that is, scores lower than 18 — benefited from hormonal therapy but derived no additional benefit from the addition of chemotherapy to their hormonal therapy regimens.

Conversely, patients with high recurrence scores — scores of 31 or higher — showed a clear, statistically significant and large benefit when cytotoxic chemotherapy was added to hormonal therapy — that is, tamoxifen. In the intermediate group, the group with scores between 18 and 30, no benefit was apparent from the addition of chemotherapy, but the confidence intervals — the statistical certainty of no benefit — were not established.

What came out of that work was the Oncotype DX assay from Genomic Health. It is commercially available and essentially allows selection of patients for hormonal therapy alone or hormonal therapy with chemotherapy in the high-risk group.

In the intermediate-risk group, we're left with some uncertainty. An Intergroup clinical trial, known as the TAILORx study, is for patients with ER-positive, node-negative, early-stage — Stage I, small Stage II — breast cancer. Patients with intermediate recurrence scores will be randomly assigned to chemotherapy or no chemotherapy, in addition to their hormonal therapy.

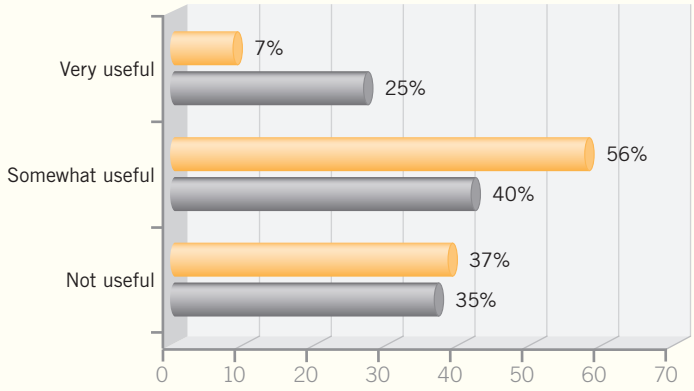
Breast Cancer Update 2006 (6)

DR C KENT OSBORNE: I believe the Oncotype DX is well done — well standardized and well validated. It produces

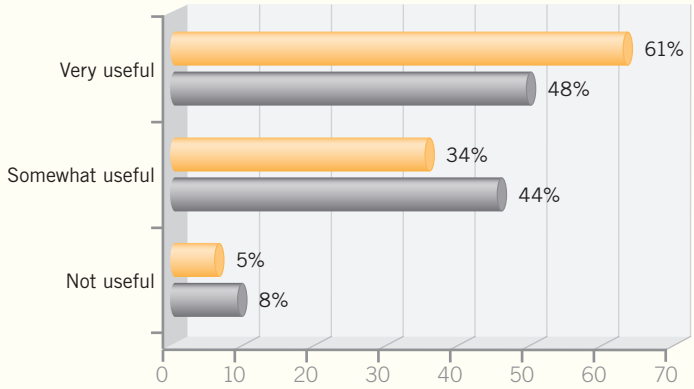
FIGURE 28

How useful is the Oncotype DX assay for a patient with a node-negative, ER-positive tumor which is:

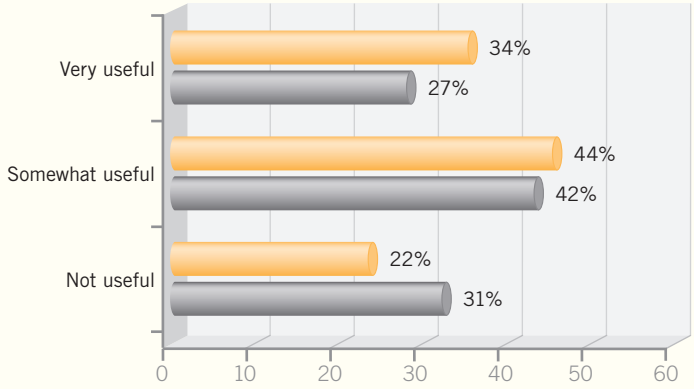
Less than one centimeter?



One to two centimeters?



Two to three centimeters?



good results. For laboratories that don't perform a high volume of assays, where estrogen receptor and HER2 assays are not reliable, the Oncotype DX would provide a much more reliable estrogen receptor test, because the estrogen receptor is such an important part of the generating signal.

So for institutions that don't measure these things very well, I believe they should use Oncotype DX. In terms of trying to decide who has a worse prognosis and who might need to have adjuvant chemotherapy for a small, node-negative tumor, I believe the Oncotype DX can be helpful.

Breast Cancer Update — Think Tank Issue 1, 2006

DR HAYES: The reason we are conducting the TAILORx trial is that we are in enormous equipoise about the addition of chemotherapy for the Oncotype DX intermediate recurrence score group. I believe we all agree that the addition of chemotherapy for the low recurrence score group is below our radar screen in terms of benefit, and most of us also agree that patients with high recurrence scores have at least a five to six percent or higher absolute reduction in recurrence rates. Those are the patients for whom we would probably recommend chemotherapy.

But for the intermediate group, whether we define it by a recurrence score of 11 or 18, we are in great equipoise. That is especially true because the aromatase inhibitors may be more effective than tamoxifen so patients have a better prognosis than the patients in the NSABP study. I also believe that doxorubicin and the taxanes will be more effective in patients with lower ER and higher HER2 levels.

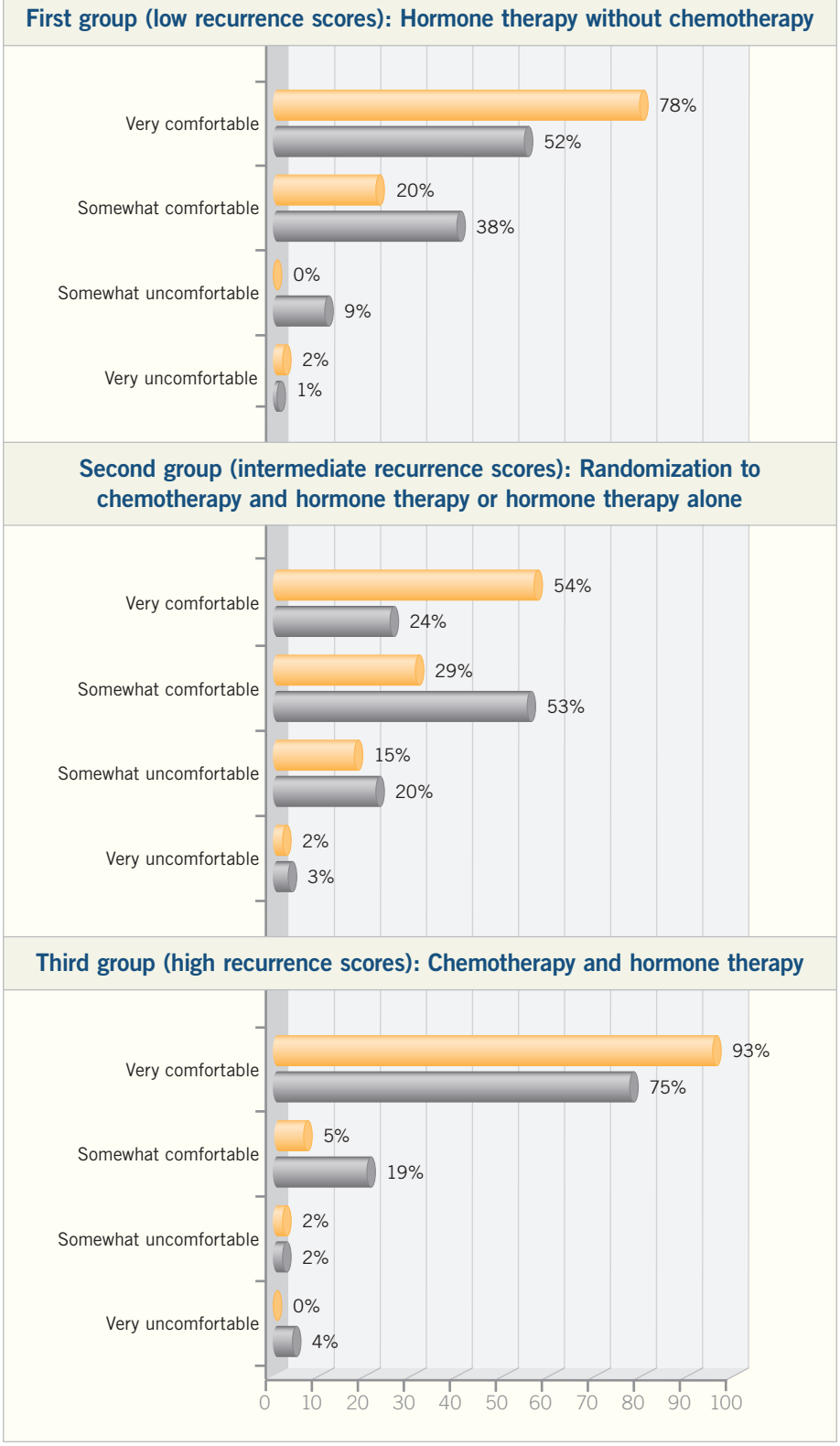
So depending on where you are in that intermediate group, you may have a better prognosis than we think you have, but you may have a higher proportional reduction than that achieved with CMF. The randomized portion of that trial is critical.

Interview, September 2006

DR WOLMARK: The TAILORx trial is following up on the findings of the value

FIGURE 29

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



of the Oncotype DX assay in assessing the risk of recurrence and predicting the benefit from chemotherapy. It's an interesting and ambitious trial that is scientifically compelling and that we would like to see completed.

SELECT PUBLICATIONS

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

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

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

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

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

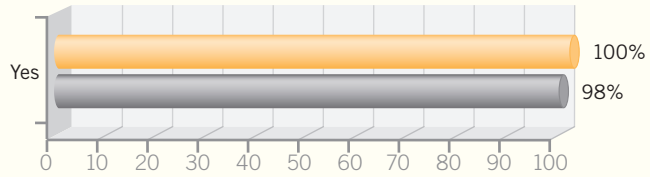
Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26. **Abstract**

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.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 48**.

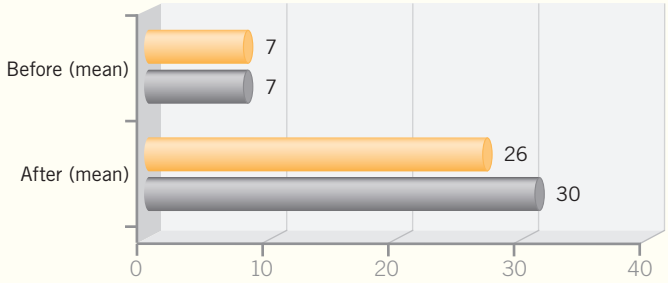
Vogel CL et al. **First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study.** *J Clin Oncol* 2005;23(6):1178-84. **Abstract**

FIGURE 30

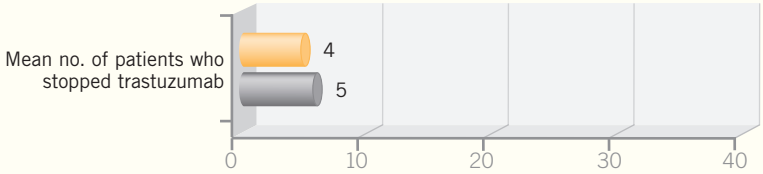
Have you used adjuvant trastuzumab?



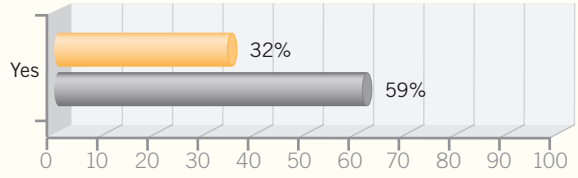
If yes, in approximately how many patients have you used adjuvant trastuzumab before and after the 2005 ASCO meeting?



In approximately how many patients have you stopped using adjuvant trastuzumab because of a decrease in EF or other cardiac concerns?



Have you used adjuvant trastuzumab without chemotherapy?



Breast Cancer Update 2006 (6)

DR CHARLES E GEYER JR: The exciting thing about the adjuvant trastuzumab data has been that no matter how you use it, patients derive a substantial benefit. Small differences probably occur among the different ways of using trastuzumab, which we can't definitively address because the trials weren't designed that way, but it's clear that trastuzumab is the most important element of therapy for a patient with HER2-positive breast cancer.

TCH (docetaxel/carboplatin/trastuzumab) certainly has low cardiac toxicity, but TCH is not a gentle regimen for an elderly woman.

I believe the weekly carboplatin/paclitaxel/trastuzumab that we use for metastatic disease is active and well tolerated. Those are the substitutions I believe would be reasonable to consider for an elderly patient, if you felt you needed to use chemotherapy.

Can you use trastuzumab alone or with hormone therapy? I'm sure you can. You have to use your clinical judgment. Trastuzumab is active without chemotherapy; there is no question about that, but if I were going to use trastuzumab, I would like to use some kind of chemotherapy, maybe just four cycles á la the HERA trial.

Breast Cancer Update 2006 (7)

DR TRIPATHY: Theoretically, adjuvant trastuzumab monotherapy may be a reasonable approach. Remember that in the HERA study, a 50 percent reduction in recurrence was seen in all patient groups, which included all comers. But keep in mind that as a requirement of the HERA study, all patients received prior chemotherapy. We know that synergy exists between chemotherapy and trastuzumab, so we could argue that trastuzumab works best in the context of chemotherapy. Although I would guess that trastuzumab monotherapy would reduce recurrence, we don't have any data to support that. Sometimes extrapolations require too much speculation, and I believe the leap to trastuzumab monotherapy is one of those situations.

Trastuzumab monotherapy would be good to include in a trial if we could identify an appropriate patient population. We currently have options for chemotherapy regimens that are nontoxic, like some of those used in the HERA

FIGURE 31

Have you utilized dose-dense AC → paclitaxel/trastuzumab in a nonprotocol setting?

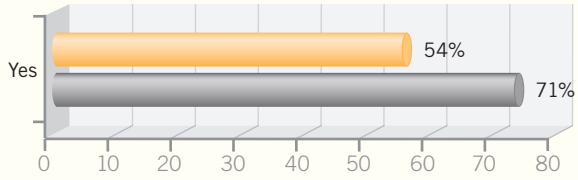
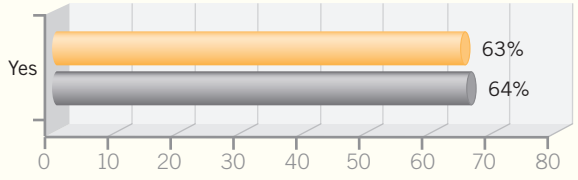
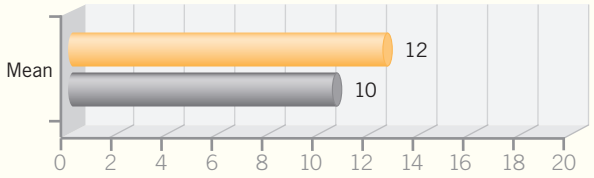


FIGURE 32

Have you used TCH as nonprotocol adjuvant therapy in patients with HER2-positive tumors?



If yes, in how many patients?



CI n = 26; PO n = 96

trial. Dr Heikki Joensuu has studied vinorelbine followed by FEC, opening the door to studies of agents with preclinical synergy and great activity in the advanced setting. I would advocate a trial, maybe with vinorelbine and trastuzumab in one arm and trastuzumab alone in another arm.

Combining a taxane alone with trastuzumab is a little more reasonable, although again, we do not have the data. Technically, the HERA study would have allowed that, but I don't think there were any patients who received paclitaxel alone. In talking about where one would draw the line, a taxane alone with trastuzumab, in my mind, would be reasonable.

Breast Cancer Update 2006 (7)

DR PEGRAM: If you're going to consider an anthracycline-based adjuvant regimen followed by trastuzumab with taxanes, you need to tell patients that it carries a defined risk of cardiotoxicity. In particular, in the NSABP-B-31 adjuvant trastuzumab trial, after four cycles of AC approximately four to five percent of the patients were ineligible for adjuvant trastuzumab at all. In clinical practice, it is important to measure the ejection fraction before and after the AC to make sure that your patient would have met the eligibility for the study and you could draw on that safety database.

Moreover, during the year of adjuvant trastuzumab for the patients who received the drug, an additional approximately 15 percent of the patients had to drop out because of decreases in ejection fraction, which I find alarming. My fear is that in the community, busy practitioners will forget to obtain those ECHOs and MUGAs every three months, which was done on all of the adjuvant trastuzumab trials.

I'm fearful of what might happen for patients who have marked decreases in ejection fraction but may not be having symptoms from heart failure yet, and because they didn't get their ECHO or MUGA they are simply continued on more trastuzumab. Clinicians need to know that if they're going to prescribe adjuvant trastuzumab, they should do so following the same guidelines that were used in those protocols, which was an ejection fraction assessment every three months during the one year of trastuzumab.

If the ejection fraction decreased to less than institutional norms, patients had to drop out. If it dropped 15 points and was above institutional norms, they had to hold the trastuzumab, at least temporarily, and wait for recovery. If recovery was evident on a follow-up one month later, then they were allowed to attempt to reinstitute it, as long as they were not symptomatic or at lower than institutional norms. These protocol guidelines are available, and they should be strictly followed if you're going to use anthracyclines.

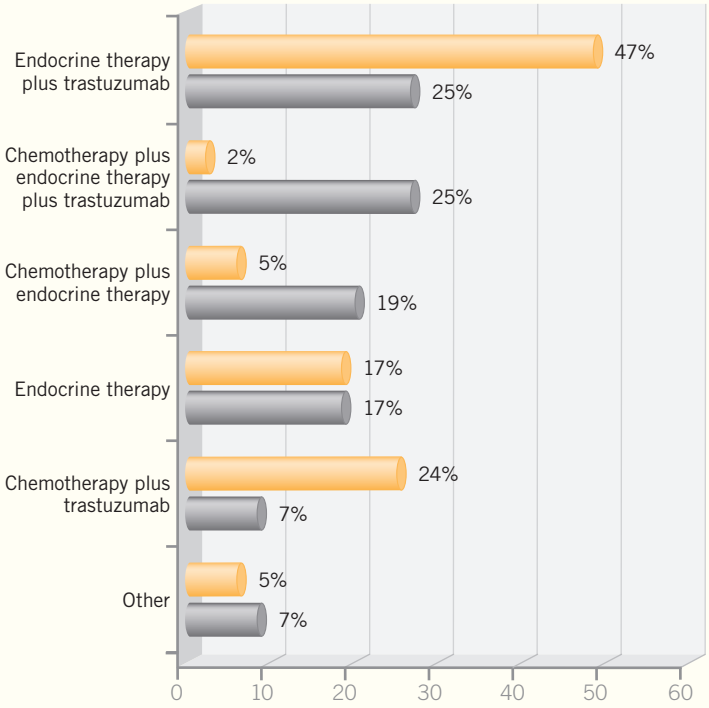
Breast Cancer Update 2006 (6)

DR GEYER: For me, the precedent for cardiac monitoring of a patient receiving trastuzumab has been set by the adjuvant trials. The plan was a reasonable one: Check imaging halfway through the chemotherapy, check it at the end of chemotherapy and then check it three months later. It made sense for the trial, and I believe it makes sense for the clinic.

In NSABP-B-31 and NCCTG-N9831, we stopped the drug in a significant number of patients — about 15 percent of the patients had asymptomatic declines in LVEF. We don't know that we

FIGURE 33

*A **60-year-old woman** was diagnosed **three years earlier** with **node-positive,** ER-positive, PR-positive, **HER2-positive** breast cancer and received AC → paclitaxel, trastuzumab and anastrozole. While receiving anastrozole, she now has moderately symptomatic bone metastases and no other sites of disease on staging. Which therapy would you recommend to this patient?*



Above groups may include combination with other biologic agents

would have seen a higher rate of clinical heart failure if we had continued to treat them, but it's a reasonable assumption.

Breast Cancer Update 2006 (8)

DR BURSTEIN: The biggest question I get at tumor boards right now is how to approach patients who have small HER2-positive tumors — patients who wouldn't have been eligible for the adjuvant trials, such as the patient with the 7-mm, ER-negative, HER2-positive tumor or the 1.2-cm, ER-positive, HER2-positive tumor.

We don't have great data on the outcomes for these women. We have proposed, and I believe we'll put forward, a multicenter trial evaluating trastuzumab with paclitaxel as a treatment regimen for patients at low risk. We will treat something in the order of 300-400 patients in what will essentially be a feasibility study to show that if you carefully select the patients at low risk and administer a paclitaxel/trastuzumab combination that should be well tolerated, you have a low risk of recurrence.

We would love to see a huge randomized trial for these women, but that is impractical given the resources and the generally low risk for patients with node-negative disease.

Breast Cancer Update 2006 (8)

DR RAVDIN: Currently, the Adjuvant! program doesn't make projections for trastuzumab outcomes at 10 years because we have data with follow-up of only two to three years. In general, many of the patients with ER-positive disease will experience recurrence later. If we don't know that part of the story, we could give wildly inaccurate estimates. Instead, the program provides a separate output for trastuzumab, projecting benefit at five years, which is reasonable to talk about.

Some patients have been followed for five years in the trastuzumab trials.

The program also provides information about some of the toxicities and uncertainties about toxicity. Version 9 of the breast cancer program is about to be released. For the first time, it includes HER2 status as one of the program parameters.

Breast Cancer Update 2006 (7)

DR PEGRAM: Fulvestrant, rather than tamoxifen or the aromatase inhibitors, makes the most sense to combine with trastuzumab because in HER2-positive breast tumor cells there is ligand-independent activation of the estrogen receptor. That is, the cross talk between HER2 signaling and the estrogen receptor can activate estrogen-dependent genes in the absence of estradiol.

The aromatase inhibitors remove the ligand for the ER, but the ER can still be turned on by HER2 signaling. So that's a strike against aromatase inhibitors. Tamoxifen can also be more agonistic as a result of this cross talk mechanism.

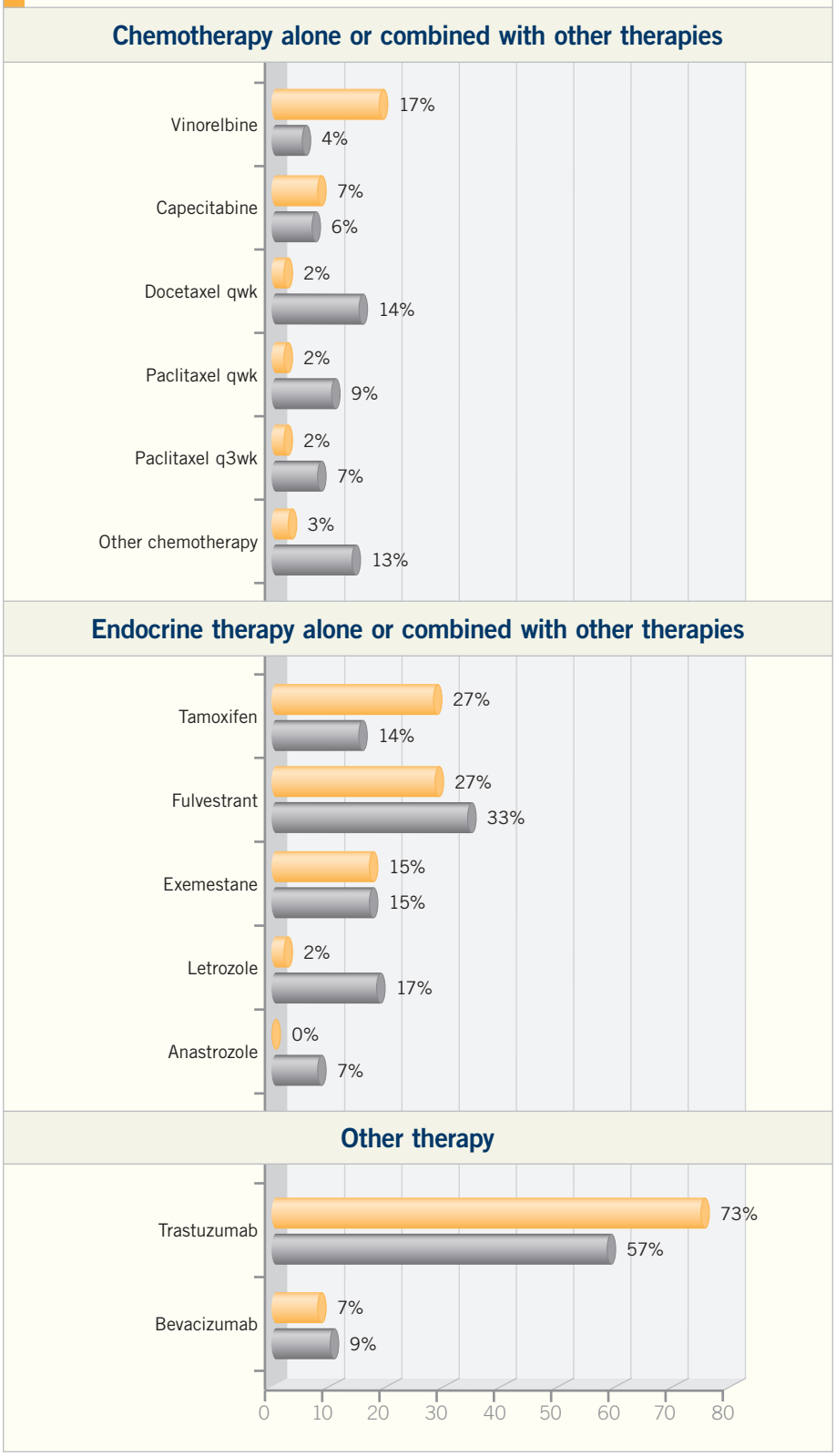
The question is, how can you tackle such a complex issue? It would be ideal to eliminate the estrogen receptor, and that's exactly what fulvestrant does.

Therefore, it is appealing from a theoretical point of view to incorporate HER2-directed therapy with fulvestrant, and we have a randomized Phase II trial under way in the metastatic setting comparing fulvestrant alone to trastuzumab alone to the combination. It's accruing slowly, unfortunately, and may have to be pared down to get some point estimate on the activity of the combination in the future.

I have a number of patients on fulvestrant and trastuzumab who are doing well, although they were started on the treatment off protocol because our protocol wasn't open when they started.

FIGURE 34

Same case (60-year-old woman with moderately symptomatic, ER-positive, PR-positive, HER2-positive bone metastases). Responses by specific therapy



I've had some nice anecdotal responders on that combination. Remember that many of these patients have already received adjuvant aromatase inhibitors anyway. So fulvestrant is a reasonable consideration when they relapse.

Breast Cancer Update 2006 (7)

DR TRIPATHY: The patient with HER2-positive disease who was treated six months or a couple of years ago poses a dilemma. You have to decide one way or the other — if the patient comes to you, then you can't just throw up your arms and say you don't know. My approach is to individualize therapy.

We know that in both the HERA study and the North American studies, the hazard rate in the entire population was still pretty high at two and three years — around 10 percent per year. Now, the question is, does the risk reduction still apply two years out? That we don't know.

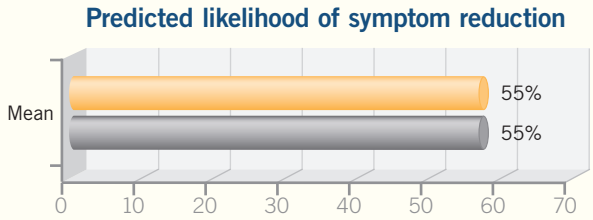
I can make an analogy with hormonal therapy. I was surprised when the data came out for patients who had been on tamoxifen for five years and were then randomly assigned to placebo versus letrozole. Even when initiating hormonal therapy after five years, approximately a 40 percent reduction was still evident, which is about what we expect of hormonal therapy anyway. So at least in the case of hormonal therapy, it looks as though the odds reduction is preserved whether treatment is given up front or much later.

Extending that to trastuzumab, patients at average risk would still have an annual reduction in hazard ratio of about five percent per year. So that would be 10 percent over two years and maybe even more as time goes on. We have to realize that even two or three years out, an odds reduction is likely. Again, this is where you need to tailor treatment. For a patient with node-negative disease who is a borderline candidate, I would use trastuzumab up front or maybe six months out. For patients with two or three nodes, I believe it's appropriate to consider trastuzumab even two years out. I know that's a stretch, but at least it

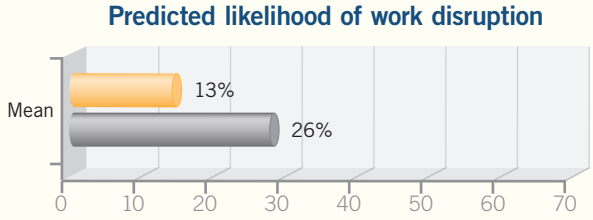
FIGURE 35

Same case (60-year-old woman with moderately symptomatic, ER-positive, PR-positive, HER2-positive bone metastases). How would you respond if:

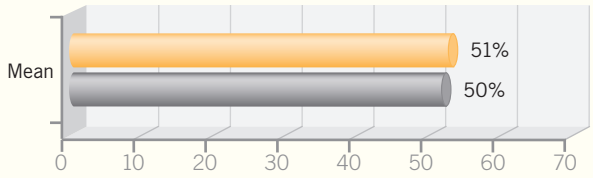
The patient asks what the chances are that the bone pain will be controlled, at least for a while, with the systemic first-line therapy you are recommending?



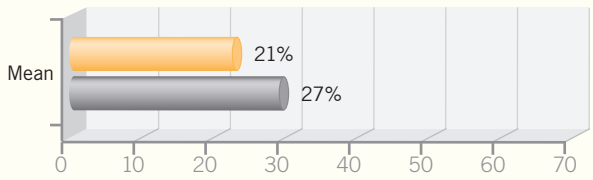
The patient asks what the chances are that the systemic first-line therapy you are recommending will cause significant disruption of her daily life — for example, completely preventing her from working at her present job?



*The patient asks what the chances are that she will be alive with the cancer controlled and without major symptoms in **two** years with your first-line therapy?*



*The patient asks what the chances are that she will be alive with the cancer controlled and without major symptoms in **five** years with your first-line therapy?*



is based on data on annual hazards and some extrapolations of the activities of other drugs.

I believe it's reasonable even when the patient was treated more than two years ago. We don't have hazard rates that far out. Right now, we have them as far as three years on the longest-running NSABP study. Keep in mind that every year we will have more data on the annual hazards. Currently I would say two, two and a half years is my limit. But a year from now, when we will have more data, I believe we can feel more comfortable. So it's a moving target, and we have to stay tuned.

Breast Cancer Update 2006 (8)

DR BURSTEIN: With the tremendous outpouring of the major adjuvant trastuzumab trials in 2005, a lot of retrospective clean-up work has begun. People want to see if they can figure out which tumors benefited most markedly from trastuzumab. Is there a marker — whether it's cMYC or TOPO II — or do we have something else that will predict which patients do or don't need trastuzumab? Which patients who receive trastuzumab have such a fabulous prognosis that they don't need anything else?

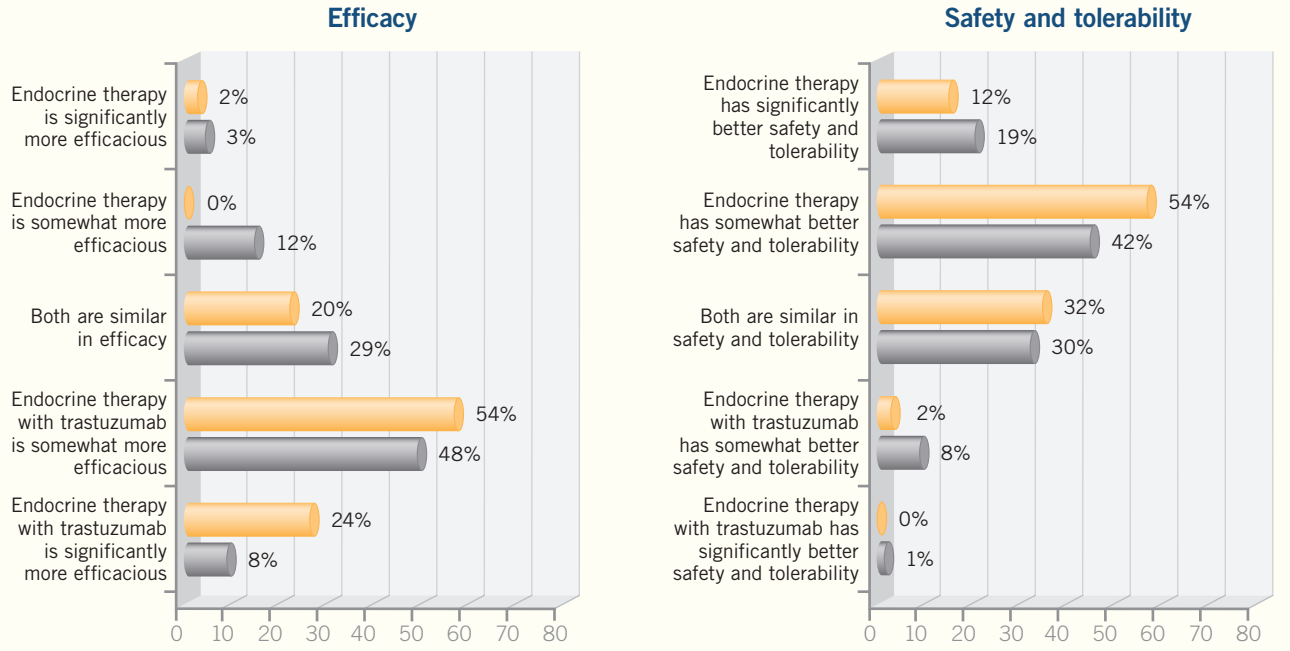
In terms of treatment, the next big trial will be from the Breast International Group (BIG). This will be a four-arm randomized trial of trastuzumab (BIG 2-06) for patients who have HER2-positive breast cancer and have received chemotherapy. Patients will receive trastuzumab versus lapatinib versus a combination of the two versus a sequential treatment program of trastuzumab followed by lapatinib. Some patients will receive only lapatinib.

Another controversy is that this study follows the HERA treatment program, in which patients would, for the most part, receive chemotherapy first and then receive the biological therapy with the option of receiving the biological therapy concurrently with taxane therapy. I have been impressed that the best results seen with trastuzumab in the adjuvant setting and with trastuzumab and lapatinib in

FIGURE 36

Same case (60-year-old woman with moderately symptomatic, ER-positive, PR-positive, HER2-positive bone metastases). How would you compare the following agents/regimens ***for this particular case****?*

Endocrine therapy versus endocrine therapy with trastuzumab



Trastuzumab versus trastuzumab with endocrine therapy

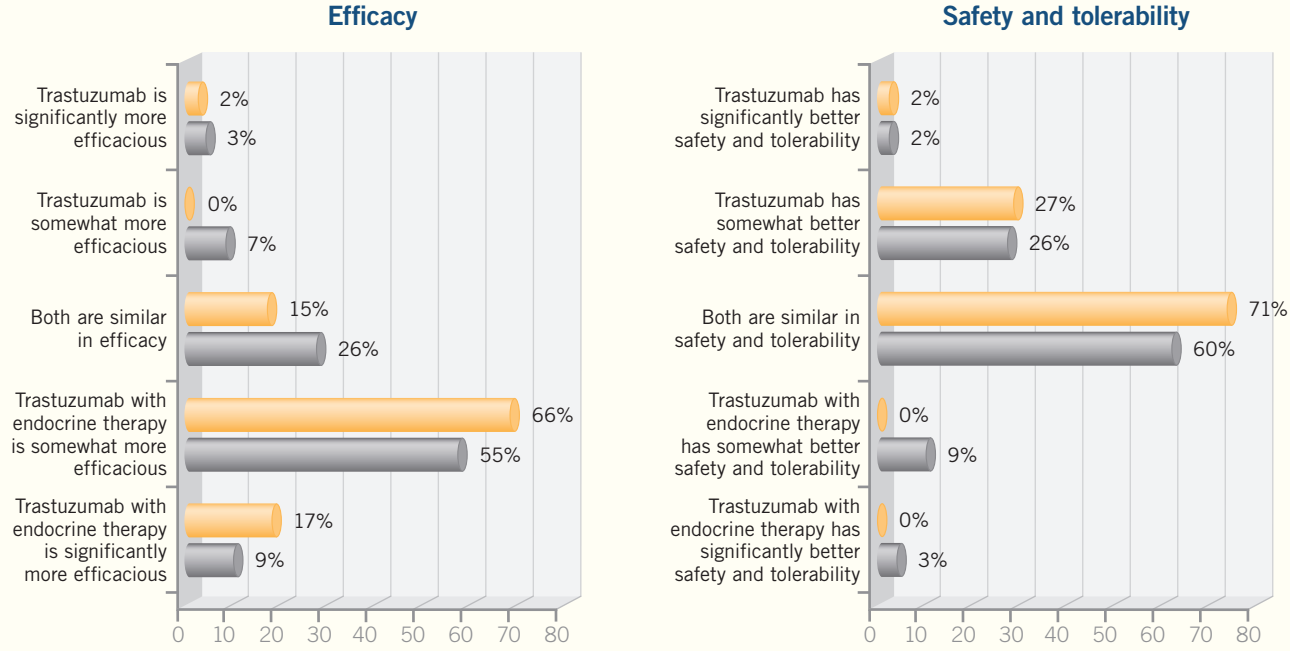
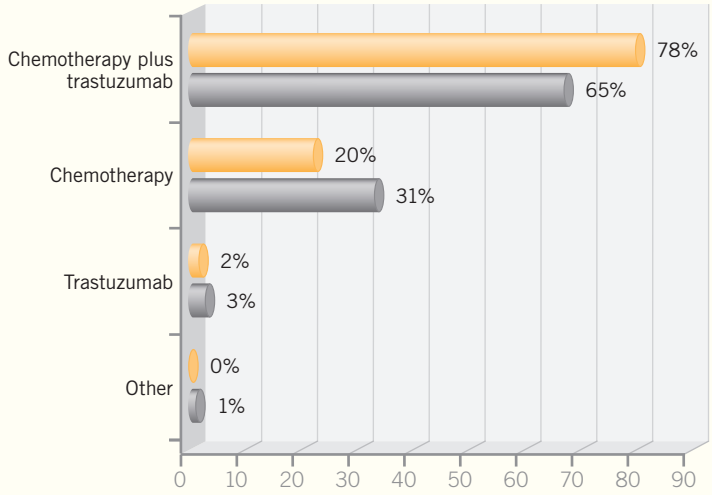


FIGURE 37

*A **60-year-old woman** was diagnosed **three years earlier** with **node-positive,** ER-negative, PR-negative, **HER2-positive** breast cancer and received AC → paclitaxel and trastuzumab. She now has moderately symptomatic bone metastases and no other sites of disease on staging. Which therapy would you recommend to this patient?*



Above groups may include combination with other biologic agents

the metastatic setting occur when you pair these products with chemotherapy. By not insisting on administering these drugs with chemotherapy, you probably do not optimize the beneficial effects of these drugs, and that is a substantial criticism of the study.

Additionally, we have an awful lot of good-quality data on trastuzumab but not every patient will receive trastuzumab, and that will affect accrual in some quarters. A lot of excitement has arisen about lapatinib, but I believe that is a potential weakness of the study design. You have to bring new agents forward and you need corporate sponsorship for trials, so hard choices have to be made, but I believe that this will affect some patients' and doctors' willingness to contribute to that study.

Breast Cancer Update 2006 (6)

DR HENDERSON: TOPO II makes sense scientifically. We began talking about it more than a decade ago. It's particularly interesting because TOPO II is on the same chromosome as HER2, and in the early papers we thought there was a correlation between the impact of doxorubicin and HER2.

I don't believe that has really held up. Certainly, when Dan Hayes presented the data from CALGB-9344 at ASCO 2006 we didn't see a correlation between HER2 expression and doxorubicin dose.

I believe anthracyclines are so powerful and so valuable in the treatment of breast cancer that I would be hesitant to leave out doxorubicin until we had compelling data that a particular group of patients received no benefit from it.

It's similar to the way we view estrogen receptor status and chemotherapy. We know that patients with ER-positive disease derive less benefit from chemotherapy than those with ER-negative breast cancer, but it's not an all-or-none phenomenon.

I believe the same principle applies here. When will you be comfortable enough to leave out a powerful drug? As good as the taxanes are — and I am enthusiastic about them — I don't believe they are any better than the anthracyclines in the treatment of breast cancer.

Breast Cancer Update 2006 (6)

DR LIPPMAN: The data on TOPO II that were presented at the San Antonio Breast Cancer Symposium were very exciting, and I hope they are substantiated. It makes biological sense — TOPO II is a target for doxorubicin. That would potentially explain which subsets of patients gained particular advantage from the doxorubicin combinations compared to the platinum combinations.

I'm not ready to draw the conclusion that Professor Slamon seemed to want to draw, which is that in those patients who did not overexpress TOPO II, the use of a nondoxorubicin-containing combination was as efficacious.

That may be true, but I'm not there yet. I believe we need more analysis. Given the additional cardiac risks of using trastuzumab with doxorubicin, particularly in older women, it would be nice to have a less cardiotoxic regimen to use.

In that same regard, I found the data Soonmyung Paik presented from the NSABP on cMYC overexpression extremely exciting and, once again, biologically plausible.

cMYC is an oncogene that is generally upregulated when cells are stimulated to grow; it is part of the growth response, and it is clearly overexpressed in about 20 to 25 percent of human breast cancer cases.

The question is, why is it that many patients with tumors that unquestionably overexpress HER2 do not respond to trastuzumab? Even in previously untreated patients, the response rates are only about 35 percent.

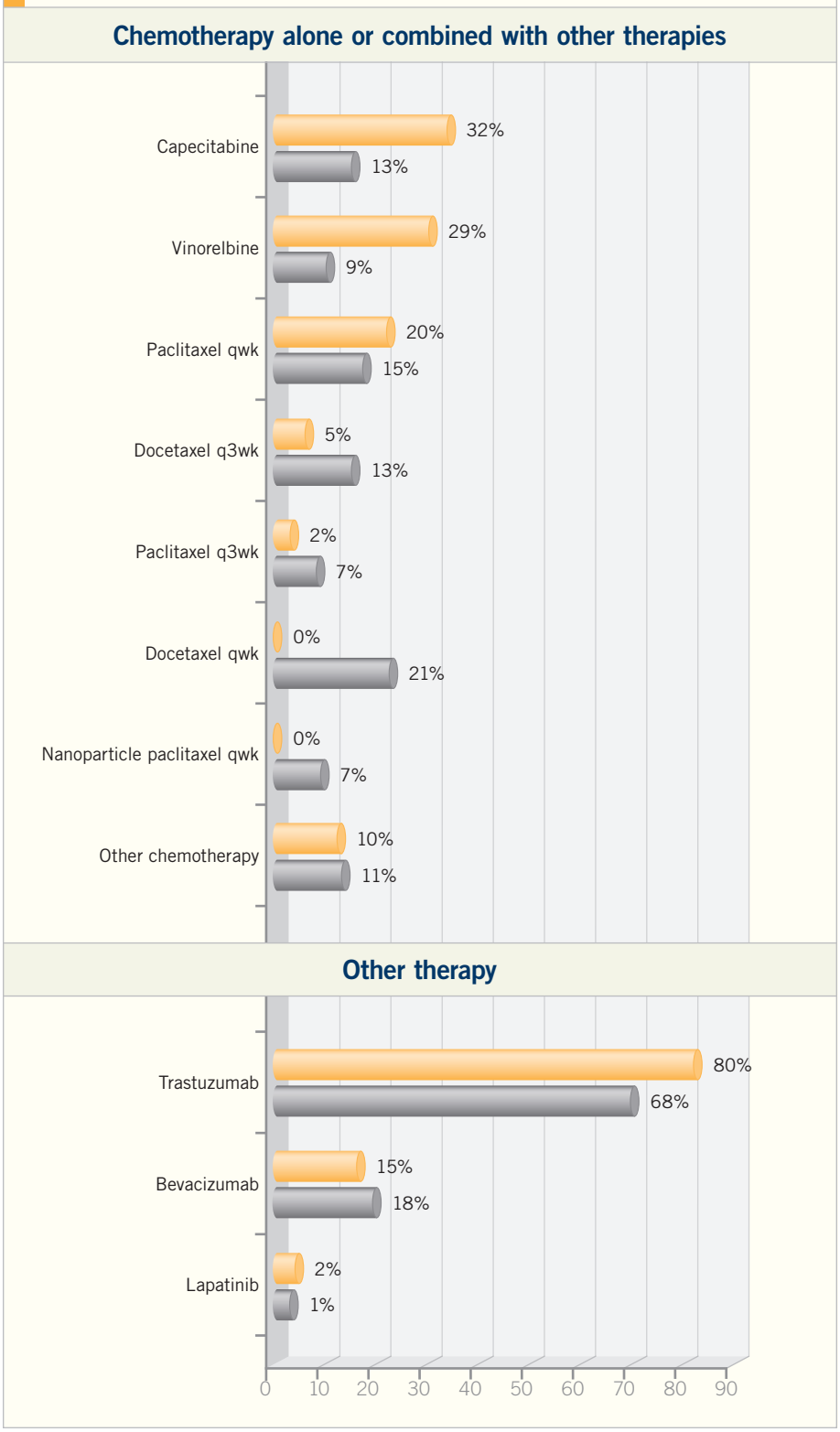
Dr Paik's data showed rather conclusively that only in those patients whose tumors coexpressed cMYC and HER2 was a response to trastuzumab seen. Those data must be replicated, but if that were the case, this observation would be tremendously insightful.

Breast Cancer Update 2006 (8)

DR JENNY C CHANG: The bottom-line, take-home message from Soon Paik's data was that if you have HER2-positive and cMYC-positive disease, you do very well with trastuzumab-based thera-

FIGURE 38

Same case (60-year-old woman with node-positive, ER-negative, PR-negative, HER2-positive breast cancer with prior AC → paclitaxel/trastuzumab): Responses by specific therapy



pies. cMYC is an oncogene, and it was expected that if you had cMYC-positive disease, you would do badly.

In the adjuvant trastuzumab study, however, patients with cMYC-positive disease who received trastuzumab did extremely well. Their chance of relapsing was low — less than 10 percent, which was counterintuitive.

TOPO II is a different story. TOPO II is the target for anthracyclines. We also know trastuzumab in combination with anthracyclines adversely affects cardiac function and increases cardiotoxicity. The BCIRG wanted to determine whether any subpopulations of patients receiving trastuzumab could be spared therapy with anthracyclines.

As presented at the 2005 San Antonio Breast Cancer Symposium, the study demonstrated that, across the board, the nonanthracycline-containing trastuzumab-based regimen was not superior to anthracycline-containing trastuzumab-based therapy. The subset of patients with TOPO II nonamplified disease who received a nonanthracycline-containing regimen, however, did as well as the patients who received anthracyclines.

Breast Cancer Update 2006 (7)

DR TRIPATHY: In the next generation of clinical trials in HER2-positive disease, we'd like to improve the odds reduction. We would also like to use drugs that target other aspects of the HER2 pathway. A leading candidate is lapatinib, a dual HER1 and HER2 kinase inhibitor that also inhibits the same target, HER2, but in a different way.

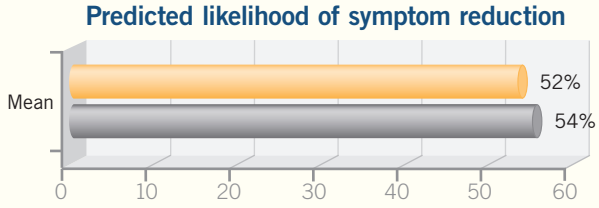
It works on the cytoplasmic kinase domain, which is part of the signaling initiator. Some early data show a higher response rate when you combine lapatinib and trastuzumab. We already know from early pilot trials that previously untreated patients with HER2-positive disease show good response rates with lapatinib.

Bevacizumab with trastuzumab is also a reasonable combination to study. I would prefer to try to isolate the patients who will benefit, but without that, I do believe it's reasonable. Some pilot stud-

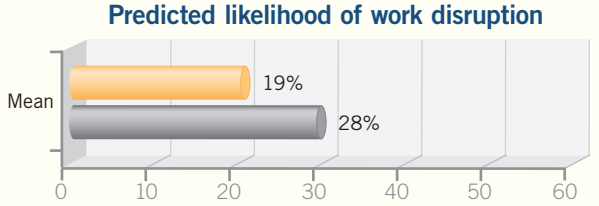
FIGURE 39

*Continued from previous case: A **60-year-old woman** was diagnosed **three years earlier** with **node-positive, ER-negative, PR-negative, HER2-positive** breast cancer and received AC → paclitaxel and trastuzumab. She now has moderately symptomatic bone metastases and no other sites of disease on staging. How would you respond if:*

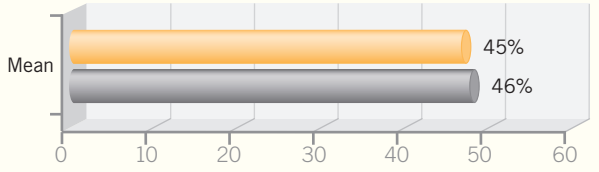
The patient asks what the chances are that the bone pain will be controlled, at least for a while, with the systemic first-line therapy you are recommending?



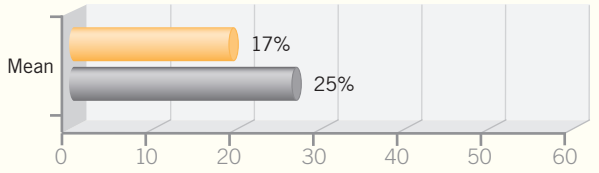
The patient asks what the chances are that the systemic first-line therapy you are recommending will cause significant disruption of her daily life — for example, completely preventing her from working at her present job?



*The patient asks what the chances are that she will be alive with the cancer controlled and without major symptoms in **two** years with your first-line therapy?*



*The patient asks what the chances are that she will be alive with the cancer controlled and without major symptoms in **five** years with your first-line therapy?*



ies also show that the bevacizumab/trastuzumab combination is safe and active. We have no randomized studies yet, but I believe that would be a reasonable place to look.

Breast Cancer Update 2006 (8)

DR LISA A CAREY: I consider HER2-driven breast cancer, in a biologic sense, as being at least two different groups. The HER2-positive, hormone receptor-negative group is different from the HER2-positive, hormone receptor-positive group. They both benefit from HER2-targeted treatments, but they are different.

In terms of how HER2 functions, we're obtaining a lot of information from the emerging studies of trastuzumab resistance and the pathways that are important in trastuzumab resistance. The first issue — and I believe lapatinib speaks to this — is whether HER1 is important in acquired HER2 resistance.

The studies of HER1 expression in de novo trastuzumab resistance have not been particularly compelling. They're also not very big. The fact that lapatinib shows efficacy in patients with acquired trastuzumab resistance, I believe, provides a strong suggestion that the HER1 pathway may be implicated in getting around HER2 signaling. Tumor cells are smart, and they figure out ways to go around our therapeutic interventions. They co-opt nearby pathways.

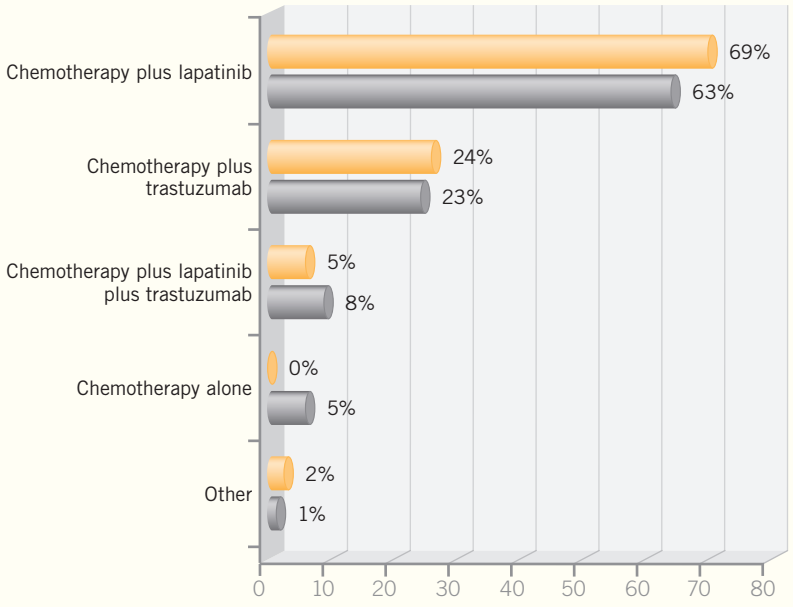
One of the ways they co-opt is by using HER1. Similarly, instead of borrowing a neighbor to stimulate the same pathway, they can use a neighboring pathway that stimulates the same downstream molecules. That's where the IGF1R data fit in, which do not so much indicate co-opting as simply a redundant pathway. Fortunately, several IGF1R, largely antibody-based therapies are entering clinical trials.

Breast Cancer Update 2006 (6)

DR GEYER: We are committed to collaborating with Dennis Slamon and the BCIRG jointly on the concept of adding bevacizumab to adjuvant trastuzumab. We have been waiting for their pilot data evaluating the combination of

FIGURE 40

Cost and reimbursement issues aside and assuming lapatinib were available for clinical use, how would you generally treat a patient with ER-negative, HER2-positive breast cancer who developed metastatic disease nine months after completing one year of adjuvant therapy with AC → paclitaxel/trastuzumab?



bevacizumab and trastuzumab as front-line therapy for patients with HER2-positive disease. The trial is progressing well, and from what they have been able to share, it looks as if this is something we definitely will be pursuing.

When patients' tumors have HER2 amplification, a high percentage — about three quarters of the patients — also have upregulation of VEGF. Those patients do not do well when treated with chemotherapy alone — they have a strikingly poor outcome.

The assumption is that something is mechanistically driving the cancer, and if you shut down both of those pathways, you will improve outcomes. Preclinical models look very strong, and they were the justification for taking this into a clinical trial.

We are currently working on a straightforward concept evaluating trastuzumab versus lapatinib versus the combination using an AC followed by weekly paclitaxel template as neoadjuvant therapy. All the patients will receive that basic chemotherapy regimen, and the HER2 blockade will start with paclitaxel.

Then the patients will have surgery to determine the pathologic complete response rate. After surgery, all the patients will receive trastuzumab for one year. They will be receiving standard therapy with trastuzumab, but we will obtain baseline tissue and do the correlative work to see if we can determine which patients might do better with each of the drugs individually or in combination.

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

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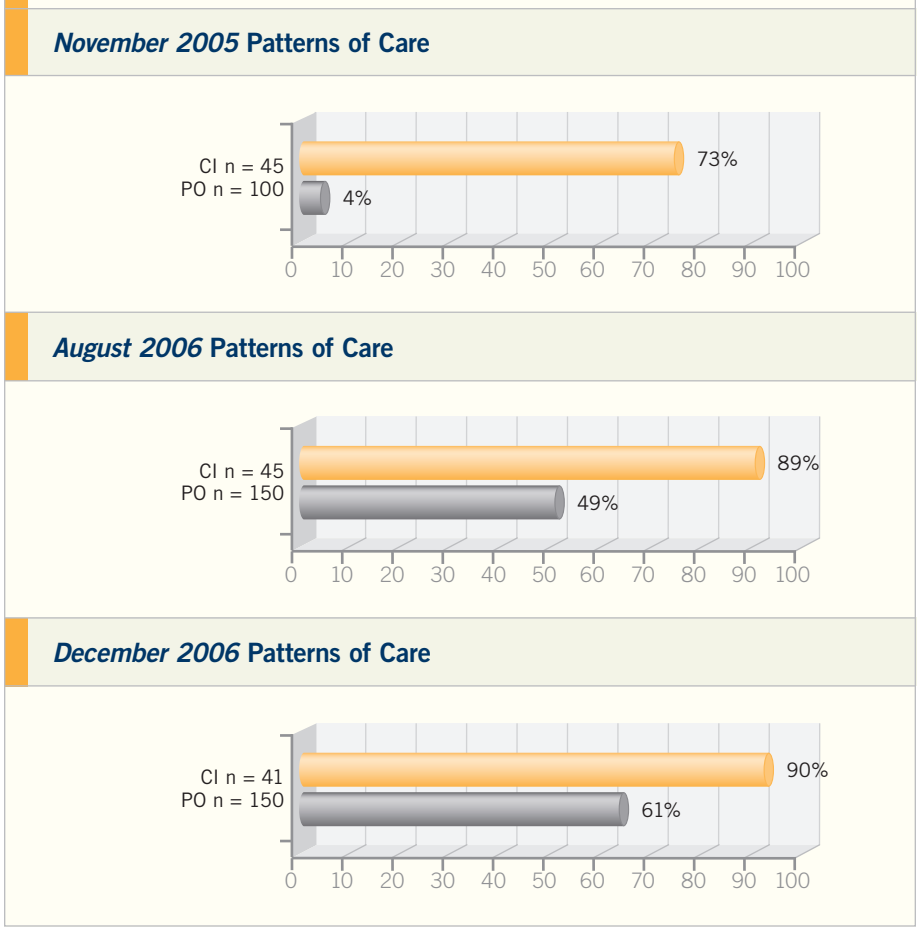
FIGURE 41

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



Breast Cancer Update 2006 (7)

DR TRIPATHY: The main endpoint of ECOG-E2100, progression-free survival, was significantly prolonged with the combination of bevacizumab and paclitaxel compared to paclitaxel alone. The hazard rates indicate a more robust improvement than we've seen with single chemotherapy compared to chemotherapy doublets.

Much attention has been given to the survival difference, which was statistically significant when initially presented at ASCO but was not significant at the next two presentations at ECCO and San Antonio. It's important to remember that the number of events was nowhere near what was projected for that analysis. So although survival is an important endpoint, I don't believe the trial had enough power to demonstrate whether a survival advantage exists. In the end, data on overall survival will be important in deciding whether to use bevacizumab. But right now, you have to go with the data on progression-free survival.

I have tried to practice the way the trial was designed, using bevacizumab for patients only as first-line therapy. I use it with paclitaxel, and I tend to reserve it either for patients who are symptomatic or for those who may not be symptomatic but whose disease trajectory is such that I would predict they might become symptomatic soon. It's a judgment call.

In terms of whether or not we might want to generalize this and combine it with other chemotherapeutic drugs, I believe that's a reasonable consideration. For patients who have already received a taxane in the adjuvant setting, should we use a drug like capecitabine? I believe it would be reasonable.

Breast Cancer Update — Think Tank Issue 2, 2006

DR RUGO: In addition to evaluating the combination of capecitabine/bevacizumab, another research strategy is to combine endocrine therapy with bevacizumab. Some interesting data indicate that estrogen may directly modulate angiogenesis through effects on endothelial cells in both physiologic and pathologic conditions. We also have data indicating that antiestrogen therapy blocks VEGF expression and estrogen-induced angiogenesis may be blocked by antiestrogen therapy.

Rakesh Jain's group in Boston has observed an androgen-dependent tumor model and shown that castration, interestingly, leads to initial vascular regression, and then a second wave of angiogenesis occurs with vascular regrowth in this murine tumor model.

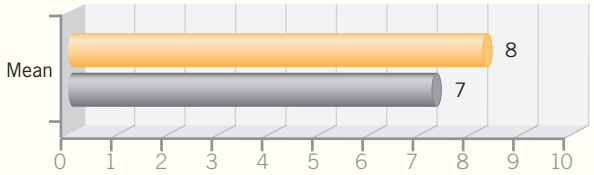
So a hypothesis was generated that anti-VEGF therapy may overcome this resistance of the second wave of angiogenesis seen with endocrine therapy in animal models and could improve the efficacy of standard hormone therapy in hormone receptor-positive metastatic breast cancer.

In the study presented by Dr Traina at ASCO this year, 43 patients received bevacizumab at 15 mg/kg every three weeks and letrozole at 2.5 mg per day. The combination appeared to be well tolerated. The drug-related toxicities were expected and only seen in a small number of patients. The efficacy analy-

FIGURE 42

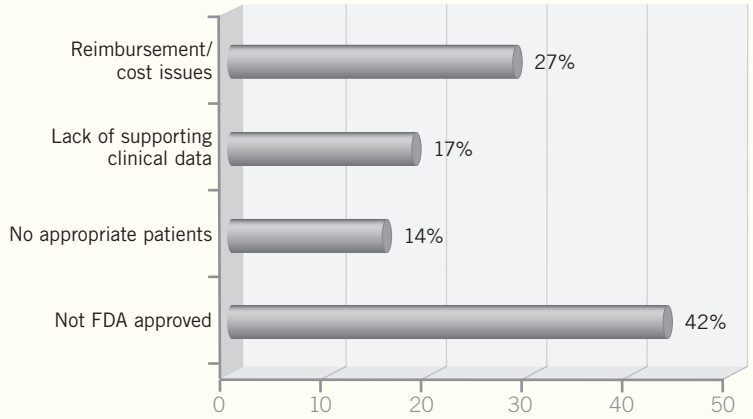
Have you used bevacizumab for metastatic breast cancer off protocol?

If yes, in how many patients?



CI n = 37; PO n = 91

If no, which of the following best explains the main reason you have not yet used bevacizumab for metastatic breast cancer off protocol?



CI n = 4; PO n = 59
Clinical investigator responses: Reimbursement/cost issues = 2; lack of supporting clinical data = 1; no appropriate patients = 1

sis, which wasn't the primary goal, was confounded by the long duration of prestudy aromatase inhibitor therapy in most patients, although it did appear that a number might have benefited from the therapy.

We have planned a Phase III study within CALGB and the Intergroup in patients with hormone receptor-positive disease. The patients will be randomly assigned to endocrine therapy with placebo or bevacizumab (administered every three weeks) as first-line therapy.

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DR WILLIAM J GRADISHAR: Right now, we have positive data from ECOG-E2100. By that, I'm emphasizing the fact that it's used in the first-line setting. I have no reason to believe bevacizumab in conjunction with other agents, as first-line therapy, wouldn't have a similar benefit. I don't believe we will see people restricting themselves to the use of bevacizumab with paclitaxel alone, but we don't have a lot of Phase II data for combining bevacizumab with a variety of different agents.

That said, the experience with trastuzumab is similar — we had preclinical models that guided us and then the Phase II trials followed. They all were consistent in that they demonstrated an incremental improvement when you combined the given agent with trastuzumab. I believe that when bevacizumab is combined with other chemotherapy agents, we will see the same improvement in outcome that we've seen in ECOG-E2100.

Breast Cancer Update 2005 (9)

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

The challenge is how to treat patients in the second- and third-line settings. At present, there really are only minimal data to indicate that bevacizumab is beneficial for such patients. Another challenge is what to do for those women who received anthracyclines and taxanes in the adjuvant setting.

Do you rechallenge them with paclitaxel and bevacizumab? There are two halves to that question. The first is, does bevacizumab actually help these women? We haven't seen the data as yet broken out as a function of prior taxane therapy. The second half of the question is should you give the taxane again? Again, we don't have good answers. If it's been more than a year, it's probably reasonable to give the paclitaxel again.

Occasionally, we recommend our vinorelbine regimen, because of our Phase II experience with vinorelbine plus bevacizumab.

Some people administer capecitabine plus bevacizumab, because, of course, there are safety data for that. On the other hand, those data don't really suggest that particular combination does all that much compared to capecitabine alone. We're all looking forward to more studies, more Phase II trials, to really try and understand how best to utilize this drug for metastatic disease.

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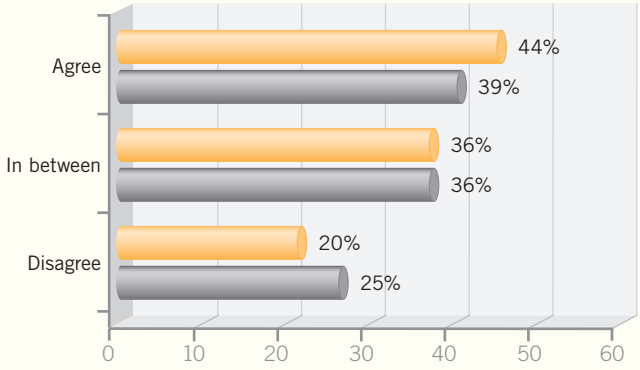
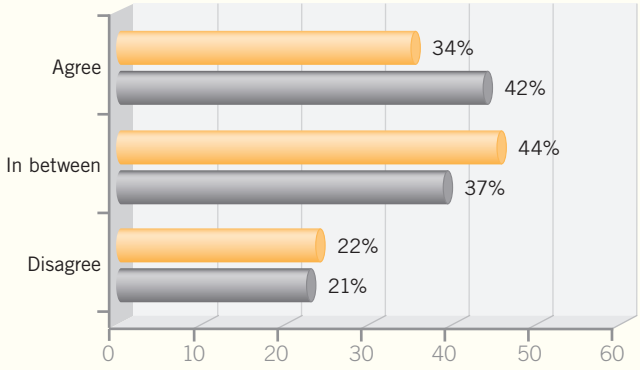
DR RUGO: ECOG-E2100 is a significant advance. Having participated in the initial capecitabine/bevacizumab trial

FIGURE 43

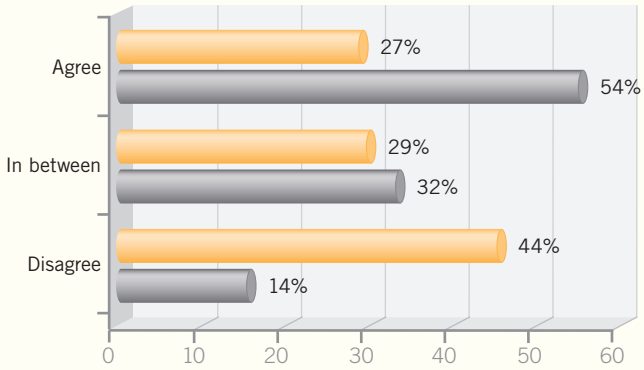
Cost and reimbursement issues aside, bevacizumab should generally be used in a clinical setting only when initiating first-line paclitaxel for metastatic disease.



Cost and reimbursement issues aside, bevacizumab should generally be used in a clinical setting only when first-line chemotherapy is being initiated for metastatic disease.



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.



and also having used bevacizumab in a variety of clinical research settings, we've been convinced for a long time that it has clinical benefit.

ECOG-E2100 produced two important implications. One is that we can, potentially, help patients in the metastatic setting with first-line therapy in combination with a taxane. The second is that it allowed us to move bevacizumab into trials in the early adjuvant setting, as well as into the neoadjuvant setting, which potentially allows us to identify the patient population most likely to benefit from bevacizumab.

Breast Cancer Update 2006 (7)

DR CARLSON: It's reasonable to offer patients with triple-negative disease chemotherapy and bevacizumab as first-line therapy. The best evidence we have is with paclitaxel/bevacizumab. Kathy Miller's ECOG study that evaluated capecitabine with or without bevacizumab showed a slightly higher response rate using the combination but no advantage in terms of relapse-free survival and overall survival.

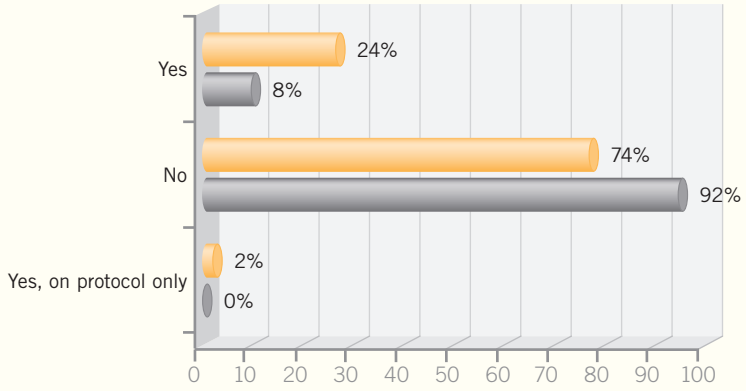
We may be seeing specific drug effects and different drug interactions between bevacizumab and chemotherapy. It may be a result of different patient populations. The patients in the capecitabine study were treated in the second-line setting, not the first-line setting, as with paclitaxel and bevacizumab.

Breast Cancer Update 2006 (8)

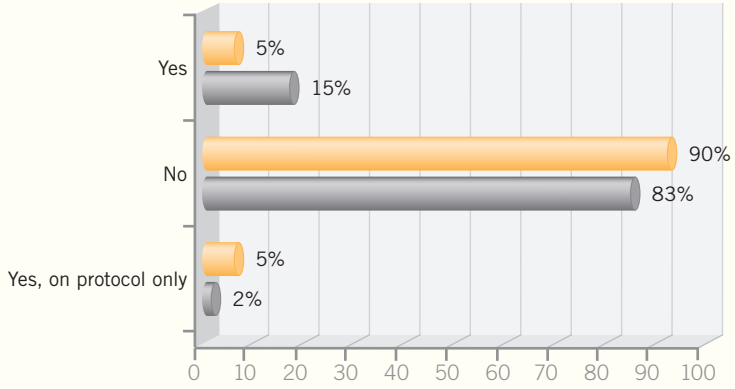
DR BURSTEIN: For patients with triple-negative tumors we don't have a target, so the work focused on optimizing chemotherapy. Some trials are evaluating adding products like capecitabine, and some are evaluating platinum-based chemotherapy. Additionally, there is interest in other biological approaches, and probably the one that is furthest along has been to add bevacizumab to the treatment of these patients. ECOG-E2100 indicated that the patients with ER-negative, HER2-negative disease did handsomely with paclitaxel and bevacizumab. So that is a reasonable patient

FIGURE 44

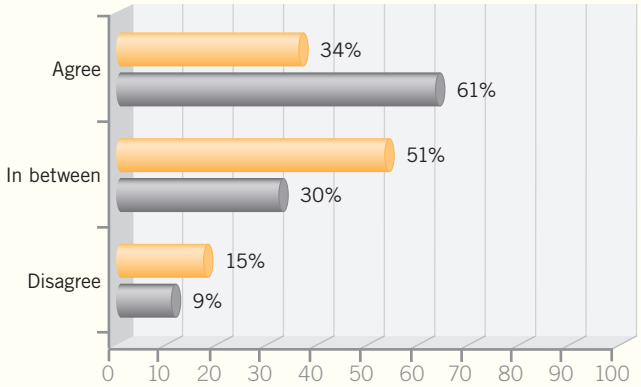
Have you used Harold Burstein's metronomic regimen of bevacizumab, cyclophosphamide and methotrexate?



Have you used endocrine therapy in combination with bevacizumab?



A significant component of the antitumor effect of bevacizumab in breast cancer is the improved delivery of cytotoxics to tumor cells.



population in which to try optimizing chemotherapy and other biological approaches.

For a woman with visceral, triple-negative metastatic disease that is extensive and symptomatic, obviously, we will administer chemotherapy. Most frequently, I use paclitaxel with bevacizumab for patients like that.

I find the data from ECOG-E2100 compelling — we can do better than using chemotherapy alone by adding bevacizumab treatment. I like the idea of using a relatively exciting biological therapy. The other point is that few women who walk in the door are chemotherapy naïve at that point.

Breast Cancer Update 2006 (8)

DR ROBERT B LIVINGSTON: We do not have hard evidence that one chemotherapy regimen is better than another chemotherapy regimen for the patient with serious, moderately symptomatic triple-negative metastatic disease. I believe most of us would be inclined to use anthracycline-based therapy if the patient hadn't received it previously or if it had been more than a year since completion of her adjuvant treatment.

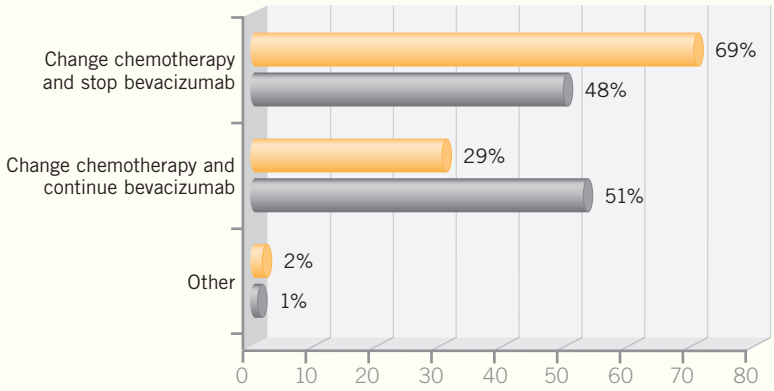
Many of us would be inclined to use a combination rather than a single agent, and I'm one of those because these patients have particularly aggressive disease and tend to experience short times to progression. The delay in time to progression that one sees with combinations may be important for patients with this type of disease.

At both my earlier institutional affiliations in Seattle and in the Southwest Oncology Group, we have been exploring antitubulin combinations, investigating combinations of vinorelbine and a taxane, either docetaxel or paclitaxel. Most recently, I've been involved in a trial with *nab* paclitaxel and vinorelbine. Those combinations are active. What I can honestly tell you is they're probably not more active than somebody else's choice of docetaxel and capecitabine or gemcitabine-based therapy.

The only patient right now, outside of a study, for whom I would probably urge

FIGURE 45

A 60-year-old woman with an ER-negative, PR-negative, HER2-negative tumor experiences relapse after adjuvant AC. She is treated with paclitaxel/bevacizumab and has a near-complete response in her liver and lung, but then her disease progresses at 18 months. What would you recommend?



the use of bevacizumab is this type of individual, because we do have evidence that the taxanes are as active, if not more active, than any other drugs. We do have evidence that weekly paclitaxel, which is the best way to administer the drug, is potentiated by the use of bevacizumab.

And we do have, in the triple negatives, a group of patients for whom, right now, no targeted therapy is available, except bevacizumab, that we can justify on the basis of a randomized trial. So if I were seeing such a patient in the clinic today, I would talk to her about a taxane-based treatment program, in all likelihood, and I would recommend that she also receive bevacizumab.

Interview, September 2006

DR GEORGE W SLEDGE JR: In ECOG-E2100 the progression-free survivals are now approximately a year for the combination of bevacizumab and paclitaxel. If we saw progression-free survivals in the same ballpark in the XCaliBr trial evaluating bevacizumab and capecitabine as first-line therapy, I believe we'd all find that very exciting, and it would certainly suggest that we might be able to combine bevacizumab successfully with other chemotherapeutic agents in a more upfront population.

It becomes important in an era when patients are receiving more and more of their therapy in the adjuvant setting, or more intensive chemotherapy in the adjuvant setting, so that drugs like capecitabine might be a preferential first choice for many patients in the front-line metastatic setting.

Breast Cancer Update — Think Tank Issue 2, 2006

DR HUDIS: I believe any patient with Stage IV breast cancer who is healthy enough to receive bevacizumab deserves a shot at capecitabine. I don't buy the argument that it only works in the first-line setting and that it only works with paclitaxel.

The reasons I say that are, first, the drug has been extensively used with a variety of other chemotherapy agents. I don't have to see safety data for a drug specifically in patients with breast cancer to call it safe. We have a lot of safety data for the 5-FU/bevacizumab combination.

Second, I thought the capecitabine/bevacizumab trial by Dr Miller was a positive signal. It showed a doubling of the response rate, but it did not achieve its primary endpoint of progression-free survival. The third reason is that you can see two patients in a clinic who are both ready to receive first-line therapy but have extraordinarily different prior chemotherapy experiences and exposure. For all these reasons, I offer bevacizumab, essentially, to all eligible patients with a line of therapy at some point in time.

Breast Cancer Update — Think Tank Issue 2, 2006

DR RUGO: We need the data from the ongoing RIBBON 1 and RIBBON 2 trials. The trials randomly assign patients either in the first- or second-line setting to receive chemotherapy with placebo or bevacizumab, and then they allow a crossover. The potential exists to obtain a lot of information. We have a menu of chemotherapy agents to choose from in those settings.

Breast Cancer Update 2006 (7)

DR CARLSON: Capecitabine is often the chemotherapeutic agent that I use as first-line therapy. Capecitabine has efficacy that is in the ballpark of any single agent, and I tend to treat metastatic breast cancer that's not in visceral crisis with single-agent therapy.

The toxicity profile of capecitabine is favorable, and the women appreciate being able to take an oral medication, not having to go to the infusion center and not having to come back as frequently. It's an agent that, at doses that are typically used, is associated with a predictable toxicity experience. I use 1,000 mg/m^2 twice daily — two weeks out of three weeks.

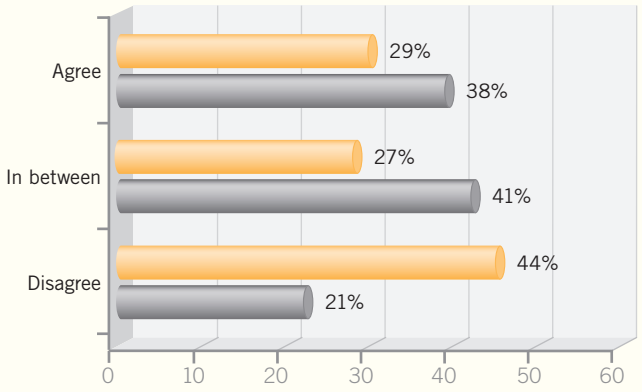
It's very important that capecitabine does not cause alopecia. If you're going to use sequential single agents, it's always nice to start with an agent that doesn't cause alopecia. If the woman already has established alopecia, you don't gain from the nonalopecia properties of the new therapy. That's often an important component of treatment of metastatic disease.

The other reason I often will lead with capecitabine is that many of these women, because it's the first-line therapy, have recently been diagnosed with their metastasis. They will go through all the turmoil and psychic trauma of the new diagnosis, and in that context, often it is easier to start with an agent that has

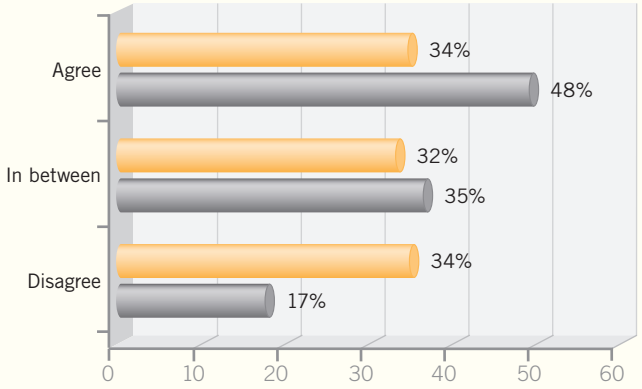
FIGURE 46

For patients with ER-negative, PR-negative, HER2-negative tumors, the following bevacizumab therapy combinations are acceptable in the first-line setting:

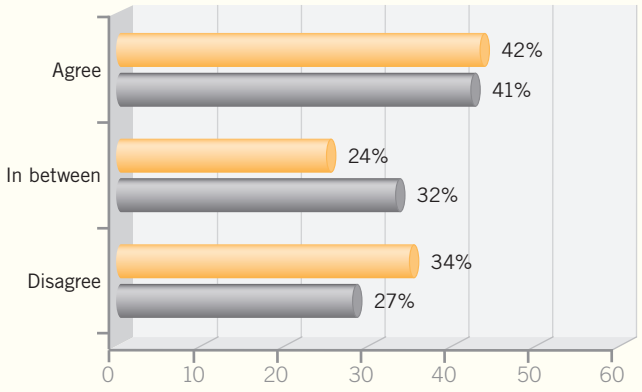
Paclitaxel/capecitabine/bevacizumab



Carboplatin/paclitaxel/bevacizumab



Capecitabine/bevacizumab



acceptable toxicity, so they can become used to the chronic nature of the disease and the need for ongoing chemotherapy with an agent that has good efficacy and doesn't affect their quality of life to a major degree.

Breast Cancer Update 2005 (8)

DR VICENTE VALERO: There are two combination regimens that have proved to be superior to single-agent taxane therapy for metastatic disease. One is gemcitabine with paclitaxel, which was compared to paclitaxel alone. The data were presented at ASCO, showing an improvement in time to progression and preliminary evidence of an increase in overall survival.

The other study compared docetaxel with capecitabine to docetaxel alone and also showed a time to progression and overall survival advantage.

Based on the evidence, both of these combinations are reasonable for first-line chemotherapy of metastatic disease. However, in some patients, sequential chemotherapy is our preference.

I tend to use more sequential single-agent chemotherapy, but I believe the role of combination chemotherapy in some instances is well documented by the two studies I just mentioned.

For women who have symptomatic breast cancer with visceral involvement, it is essential to have a response to alleviate the symptoms and improve their quality of life. For those patients, despite the enhancement of the adverse events, I strongly consider combination chemotherapy.

Breast Cancer Update 2006 (6)

DR OSBORNE: In some ways, I believe nanoparticle albumin-bound (*nab*) paclitaxel is a little safer compared to the other taxanes. I'd also be interested to see how it does, for example, combined with trastuzumab for HER2-positive disease or combined with other chemotherapy regimens to see if the hint that it might be better in the metastatic setting plays out in the adjuvant setting.

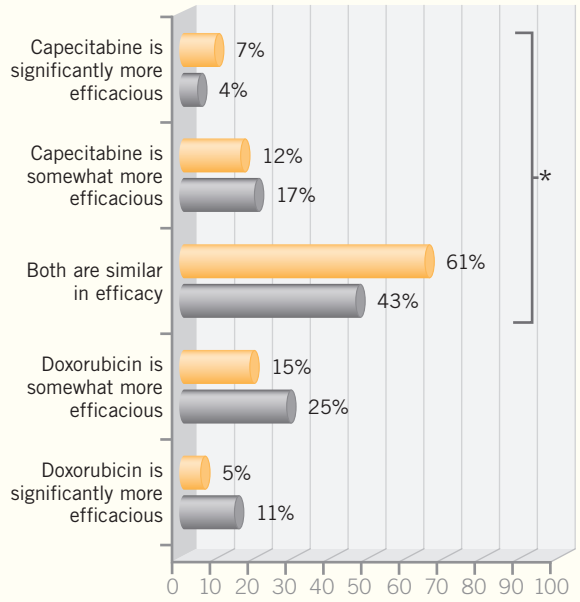
The attractive thing about it is that you don't have to administer premedication.

FIGURE 47

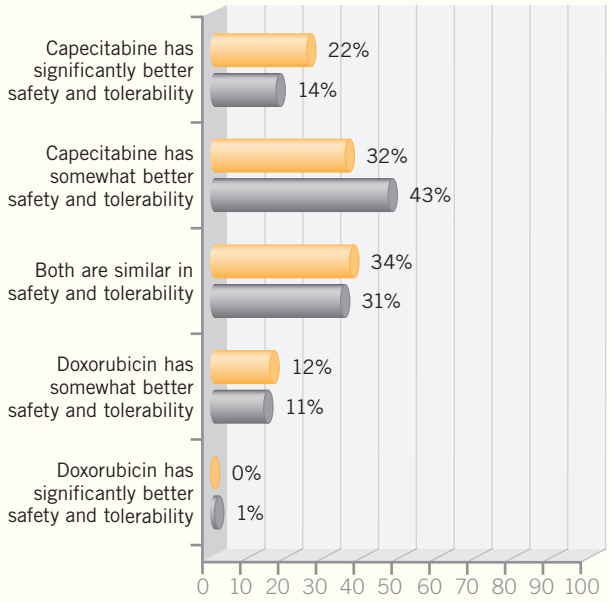
*For a patient who presents with asymptomatic metastatic disease and **no prior systemic therapy**, how would you compare the following agents/regimens?*

Capecitabine versus doxorubicin

Efficacy



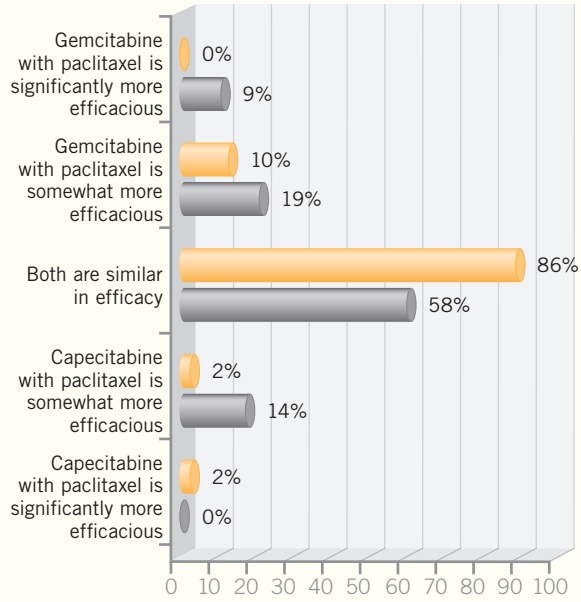
Safety and tolerability



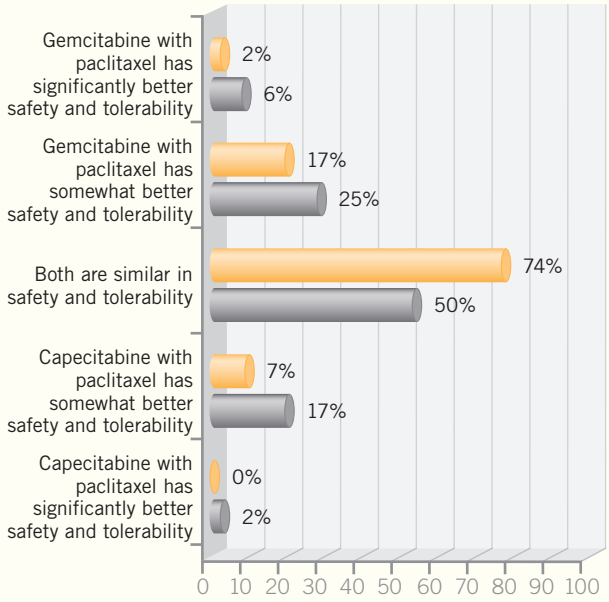
* 80 percent of CIs and 64 percent of POs consider capecitabine to have similar or better efficacy than doxorubicin.

Gemcitabine with paclitaxel versus capecitabine with paclitaxel

Efficacy



Safety and tolerability

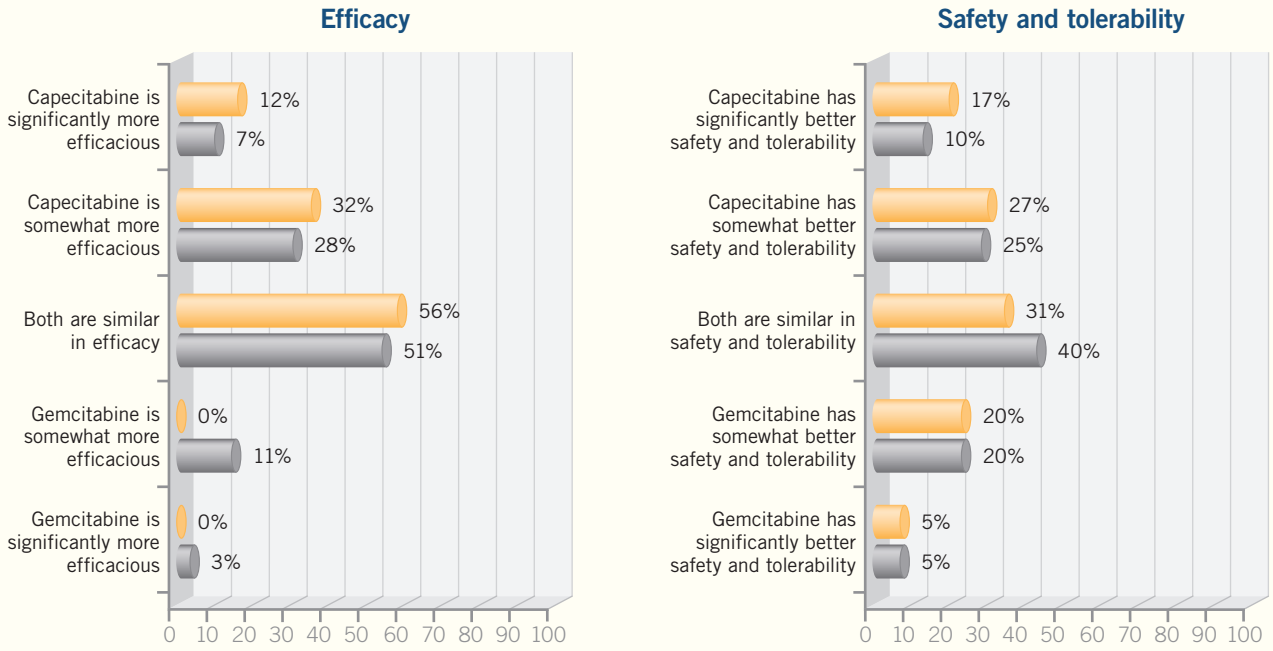


CASE CONTINUED

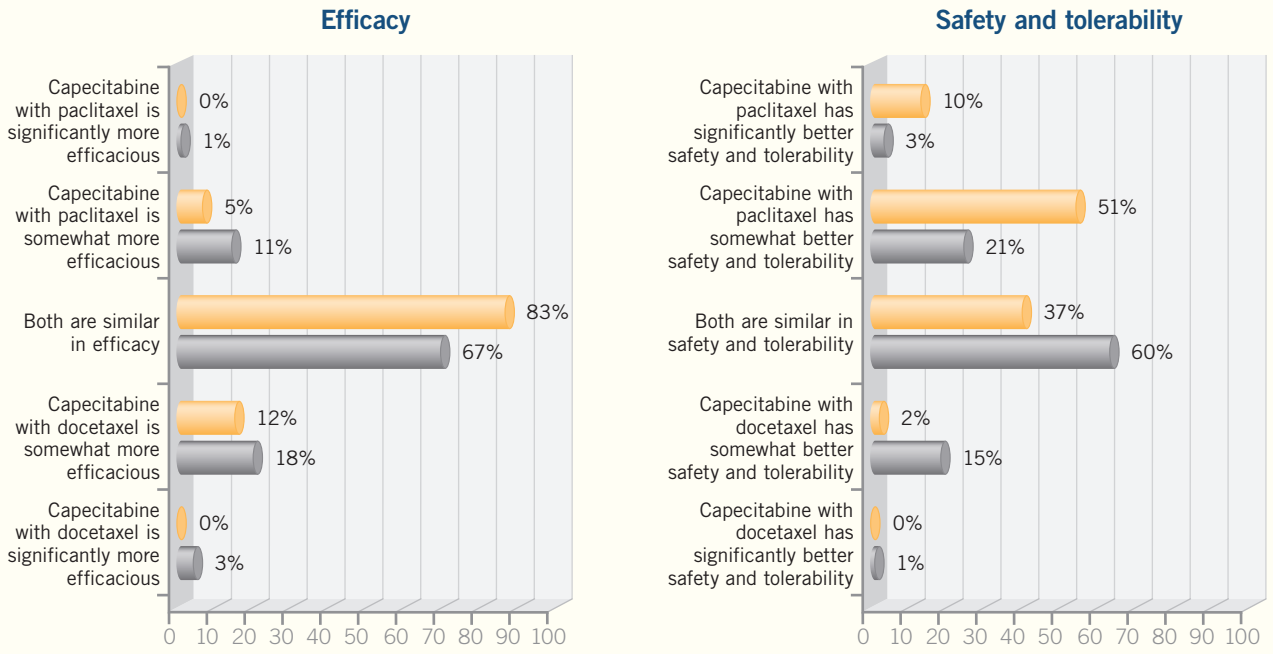
FIGURE 48

*For a patient who presents with asymptomatic metastatic disease and **no prior systemic therapy**, how would you compare the following agents/regimens?*

Capecitabine versus gemcitabine



Capecitabine with paclitaxel versus capecitabine with docetaxel

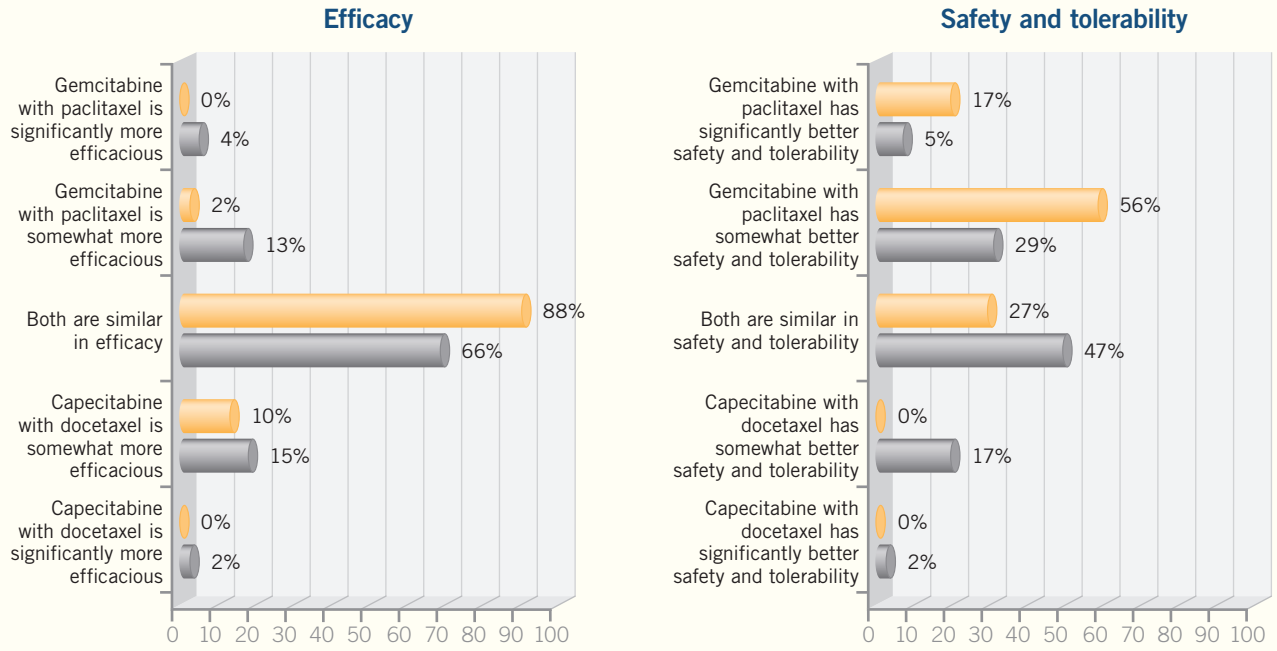


CASE CONTINUED

FIGURE 49

*For a patient who presents with asymptomatic metastatic disease and **no prior systemic therapy**, how would you compare the following agents/regimens?*

Gemcitabine with paclitaxel versus capecitabine with docetaxel



For patients who are on this drug for a long period of time, that's a big advantage.

Dexamethasone premedication can cause its own side effects. I haven't used *nab* paclitaxel all that often yet, but I like it and I'm anxious to see how it's going to be incorporated earlier in the management of the disease.

Breast Cancer Update 2006 (6)

DR HENDERSON: I am enthusiastic about *nab* paclitaxel. I have a bias in that I was very involved in the development of doxorubicin HCL liposome injection and it, like *nab* paclitaxel, has a delivery system that increases the amount of drug that actually reaches the tumor.

The issue of dose of chemotherapy has been a complicated one in cancer. When we examine dose in animal models, we clearly see a dose effect, and in leukemia we see an advantage with higher doses. Almost every oncologist has been taught as part of his or her earliest training that dose is a critical factor.

However, in most dose studies it's difficult to demonstrate that dose makes a lot of difference, high-dose chemotherapy in bone marrow transplant being a case in point. I believe the reason we have been unable to show that dose is so important is that we are examining the dose we administer rather than the dose that reaches the tumor.

With a delivery system, you change the distribution of drug so that less goes to the normal tissue and more — a higher dose — reaches the tumor itself. That's what happens with doxorubicin HCL liposome injection and *nab* paclitaxel. In both cases we can show that elegantly in preclinical models. Showing that in the human, of course, is more difficult because it's not so easy to biopsy a tumor and measure the drug level.

We know that we can administer higher doses. In CALGB-9342, which studied paclitaxel doses of 175 mg/m^2, 210 mg/m^2 and 250 mg/m^2 in patients with metastatic breast cancer, we saw no significant effect from escalating the paclitaxel dose. However, there was some marginal effect from the higher doses and a suggestion of a longer time to tumor progression.

In fact, some of the analyses reached statistical significance as an endpoint. I believe with *nab* paclitaxel we are seeing that we can give higher doses and that patients tolerate higher doses.

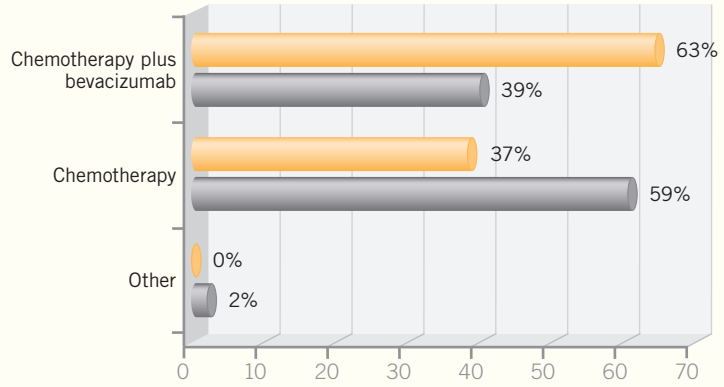
In the preclinical models, mice tolerate higher doses of *nab* paclitaxel than paclitaxel delivered in Cremophor®. In addition, because of the way the albumin interacts with the paclitaxel, higher doses were delivered to the tumor. I believe that's why they were able to show a significantly better outcome with *nab* paclitaxel. It's an interesting step forward.

Breast Cancer Update 2006 (3)

DR GRADISHAR: In terms of first-line

FIGURE 50

*A **60-year-old woman** was diagnosed three years earlier with ER-negative, PR-negative, **HER2-negative** breast cancer and received AC. She now has moderately symptomatic bone metastases and no other sites of disease on staging. Which therapy would you recommend for this patient?*



taxanes in the metastatic setting, the data are still more abundant with both paclitaxel and docetaxel than with *nab* paclitaxel, so if basing a decision on the length of experience, those agents have been around for a longer time.

However, I see no reason to believe that *nab* paclitaxel will prove inferior to those drugs with more data. I believe *nab* paclitaxel will compare favorably, if not prove to be superior.

When you examine clinical trials that have evaluated docetaxel or paclitaxel in similar patient populations with metastatic disease, the indirect evidence shows the activity of *nab* paclitaxel to be comparable to docetaxel. These agents may have similar antitumor effects, so one should consider other factors, including toxicities, patient convenience and cost.

If *nab* paclitaxel can offer the same antitumor effect as docetaxel and paclitaxel along with advantages in terms of lack of premedication and shorter infusion time, whether or not it would become the preferred agent is an important question. When you think of busy office practices, the throughput of patients and convenience to patients are important. An upside to *nab* paclitaxel clearly is the shorter infusion time and the lack of need for premedication.

As for the higher acquisition cost of *nab* paclitaxel, economic analyses suggest that some of the downstream expenses related to administering paclitaxel or docetaxel — specifically the costs of premedications and antibiotics or growth factors to manage the neutropenias or cytopenias — result in a net savings with the use of *nab* paclitaxel.

Although we need more information, I believe we shouldn't necessarily be put off by the up-front cost; we should take into account the whole package of managing the patient's treatment.

Breast Cancer Update 2006 (8)

DR LIVINGSTON: Let's assume *nab* paclitaxel and paclitaxel are equivalent. Should we, therefore, simply substitute *nab* paclitaxel for paclitaxel? We have a fair amount of data, both from preclinical systems and from clinical trials, to suggest that the drug is superior to paclitaxel, independent of its ability to prevent allergic reactions.

A reputable randomized study was published in the *Journal of Clinical Oncology* that compared *nab* paclitaxel to paclitaxel on an every three-week schedule for women with metastatic breast cancer. That study shows a magnitude of difference in terms of response rate and time to progression, which is fairly similar to the magnitude of difference that was demonstrated in ECOG-E2100 between paclitaxel alone and paclitaxel with bevacizumab.

However, the paclitaxel with bevacizumab trial was accepted with great enthusiasm — legitimately — and presented in a fairly frenzied special oral session at ASCO, while the trial involving *nab* paclitaxel versus paclitaxel was basically disregarded.

A plausible hypothesis is that *nab* paclitaxel, in conjunction with other treatment, could produce a higher pathologic complete response rate than standard paclitaxel. This question is worth answering and may be answered more expeditiously in the setting of neoadjuvant therapy, where the pathologic complete response endpoint can be obtained quickly, rather than in an adjuvant trial setting, where it will require many years to obtain an answer.

In my own practice, I'm prescribing patients paclitaxel because of the cost differential. If cost were not an issue, I would stop administering paclitaxel today and substitute it with *nab* paclitaxel.

Interview, September 2006

DR GRALOW: SWOG-S0226 is a randomized, first-line metastatic study in which all patients receive an aromatase inhibitor, and half of them will receive fulvestrant concurrently.

The group that is randomly assigned to receive the aromatase inhibitor alone is asked to switch to fulvestrant at the time of progression, although we know we can't force their next-line therapy.

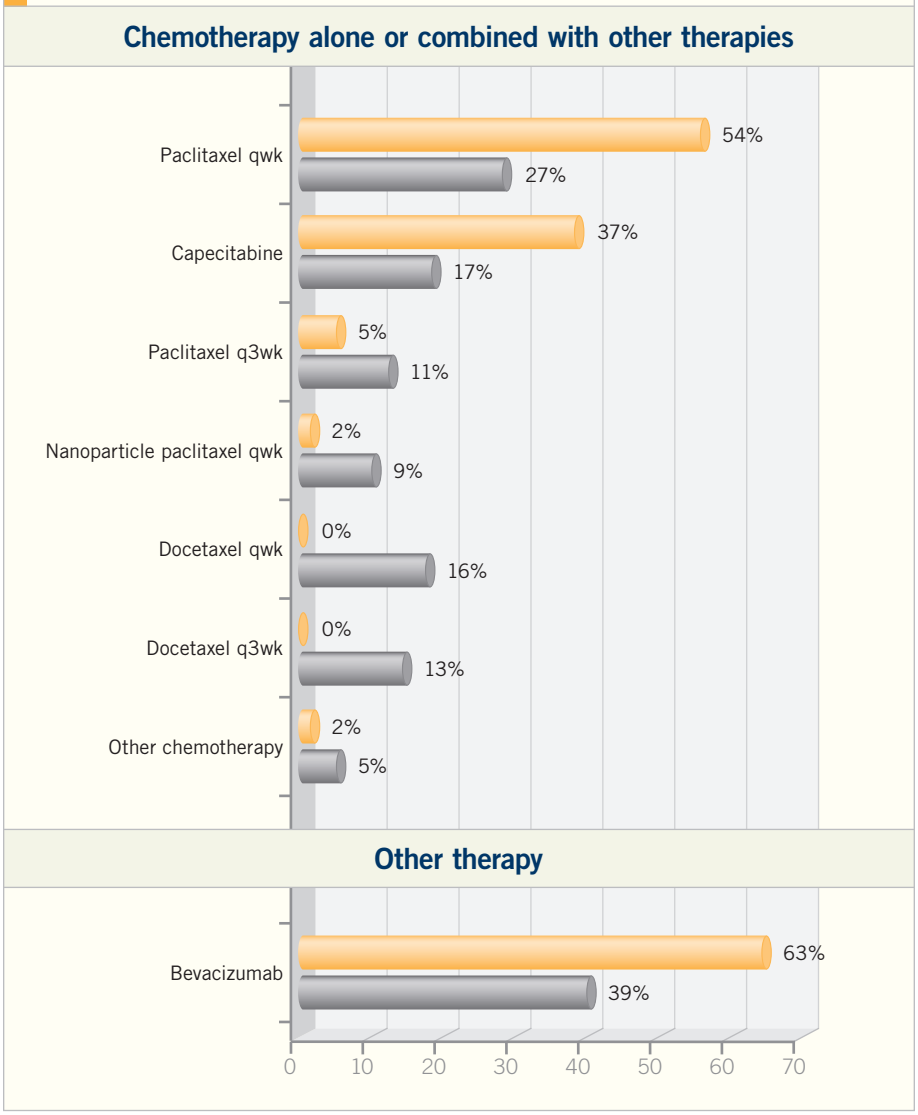
So it's a question of an up-front aromatase inhibitor with a selective estrogen receptor downregulator (SERD), fulvestrant, versus an aromatase inhibitor followed by the SERD. We're hoping that we'll obtain complete estrogen blockade by using this regimen.

We know that in the ATAC trial, the anastrozole/tamoxifen combination arm did not appear to be any better than tamoxifen alone and certainly wasn't going to be the superior arm.

Tamoxifen can have some proestro-

FIGURE 51

Same case (60-year-old woman with ER-negative, PR-negative, HER2-negative breast cancer): Responses by specific therapy



genic properties in an otherwise depleted estrogen state. Fulvestrant shouldn't have these. It's a pure antiestrogen and thus is an interesting concept that is different from considering an aromatase inhibitor with or without tamoxifen. Certainly, preclinical data suggest that this could work. It makes sense, and we have high hopes that it could be better.

Breast Cancer Update CME Meeting June 2005

DR OSBORNE: In the clinical setting, I believe it is a good idea for patients who are progressing on an aromatase inhibitor to continue with an aromatase inhibitor and add fulvestrant, but we have no data. I have done this with a few patients based on two preclinical studies that have evaluated this: my own and Angela Brody's.

Fulvestrant seems to work much better when there's no estrogen around. Even though postmenopausal women have lower estrogen levels in the blood, their tumors don't necessarily have lower estrogen levels, and fulvestrant seems to be more effective when estrogen is low.

In patients progressing on tamoxifen, tamoxifen binds the estrogen receptors and may actually stimulate growth of the tumor — it certainly is no longer inhibiting it. Treating these patients with an aromatase inhibitor will be ineffective until all the tamoxifen is gone, which takes a couple of months. Fulvestrant, on the other hand, competes with tamoxifen for binding, thus the response may be quicker with fulvestrant than with an aromatase inhibitor in that setting.

Breast Cancer Update 2005 (9)

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

In terms of efficacy, fulvestrant seems to be equivalent to anastrozole. Based on data published this year in *Cancer*, there seems to be no difference in overall survival in the randomized trials of anastrozole versus fulvestrant. Fulvestrant is a good drug and a viable alternative to aromatase inhibitors in patients who have disease progression on tamoxifen.

We do have to contend with the randomized trial of fulvestrant versus tamoxifen, where we expected a strongly beneficial effect for fulvestrant over tamoxifen, which was not forthcoming. There were some subsets where fulvestrant appeared to be better, but the overall results were about the same.

Breast Cancer Update 2005 (4)

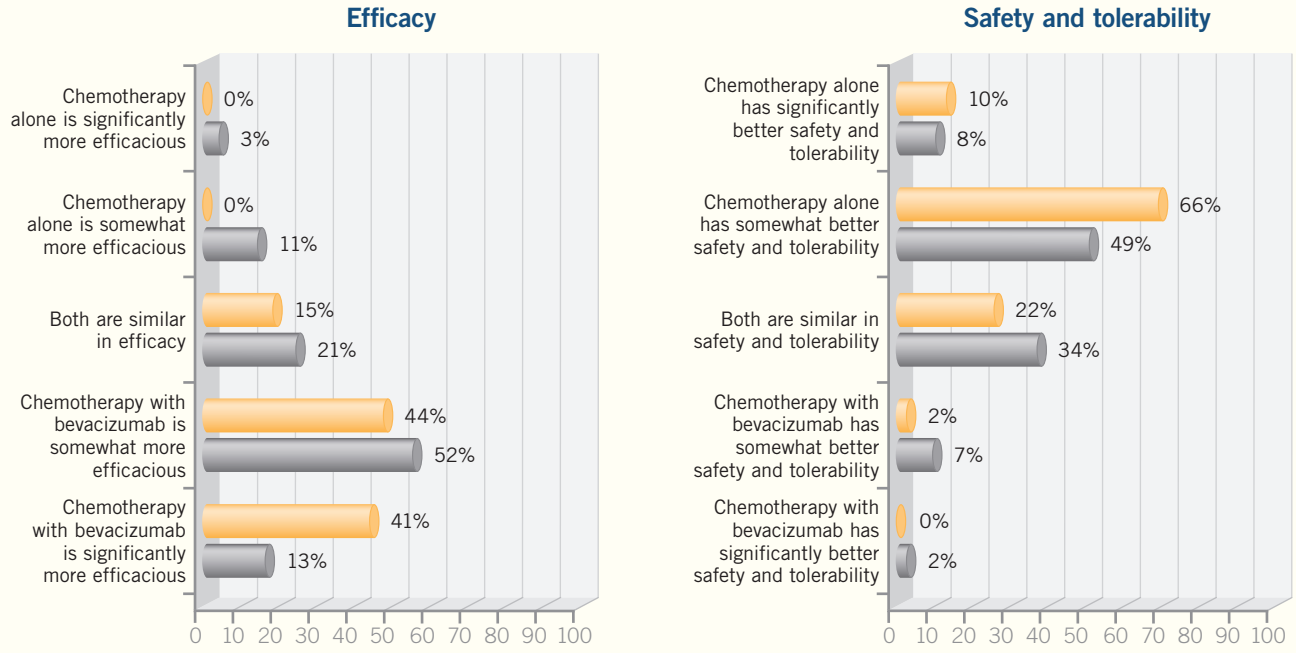
DR GRADISHAR: An important issue is whether fulvestrant at 250 milligrams is optimal, even though that's the approved dose. Some of the data, including preclinical data generated by Kent Osborne and others, suggest that this dose is on the low end of the curve where you might expect the optimal response rate.

Although we may be able to increase the dose, administering 250 milligrams in each buttock, doing that too frequently becomes prohibitive, and patients may not tolerate it.

FIGURE 52

*Continued from previous case: A **60-year-old woman** was diagnosed three years earlier with **ER-negative, PR-negative, HER2-negative** breast cancer and received AC. She now has moderately symptomatic bone metastases and no other sites of disease on staging. How would you compare the following agents/regimens **for this particular case**?*

Chemotherapy (your first choice) alone versus chemotherapy (the same choice) with bevacizumab



Capecitabine versus a taxane

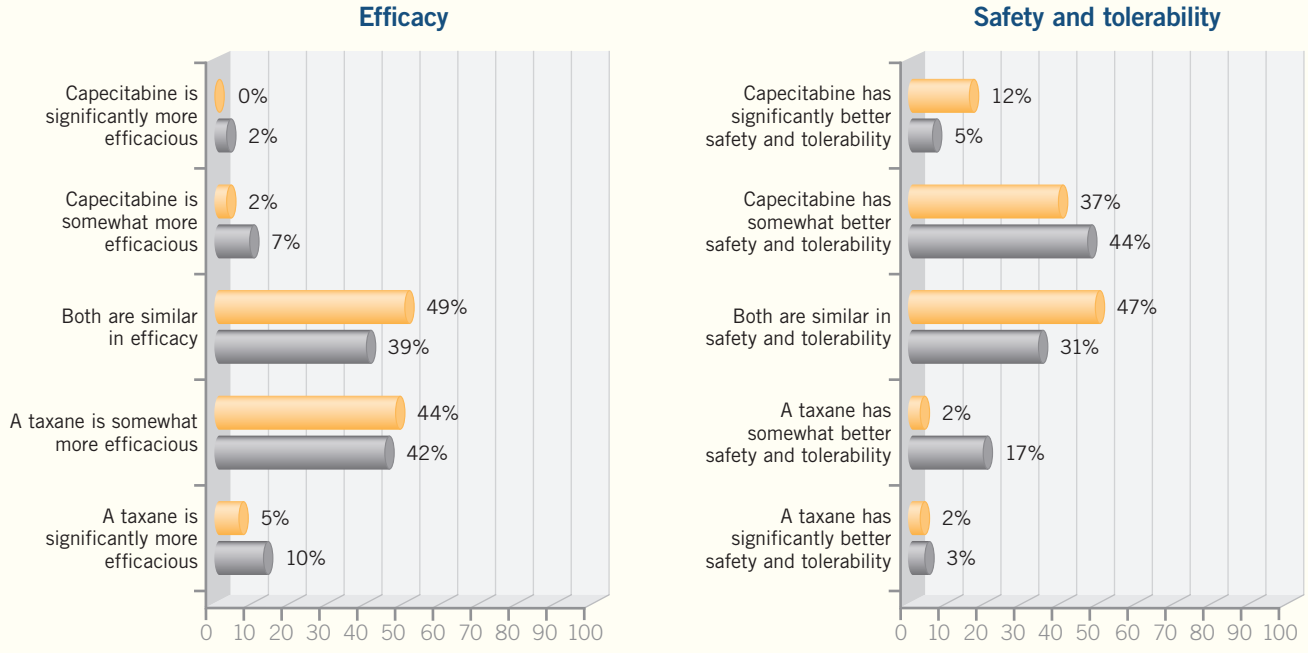
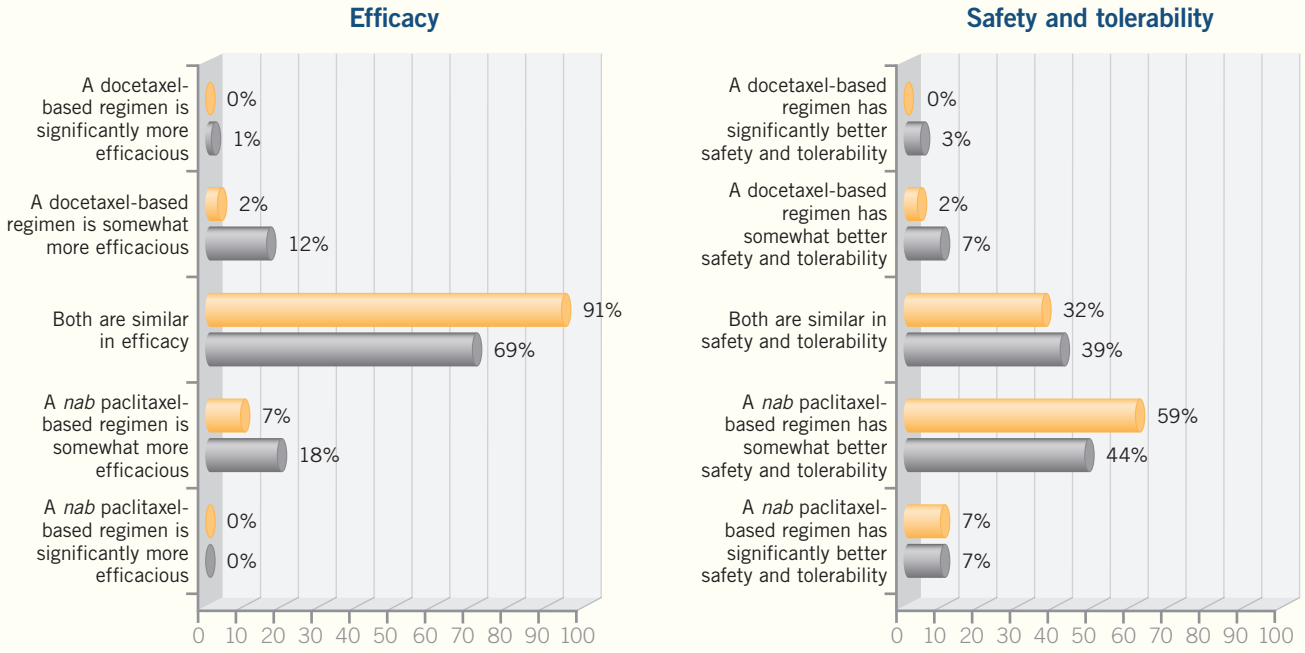


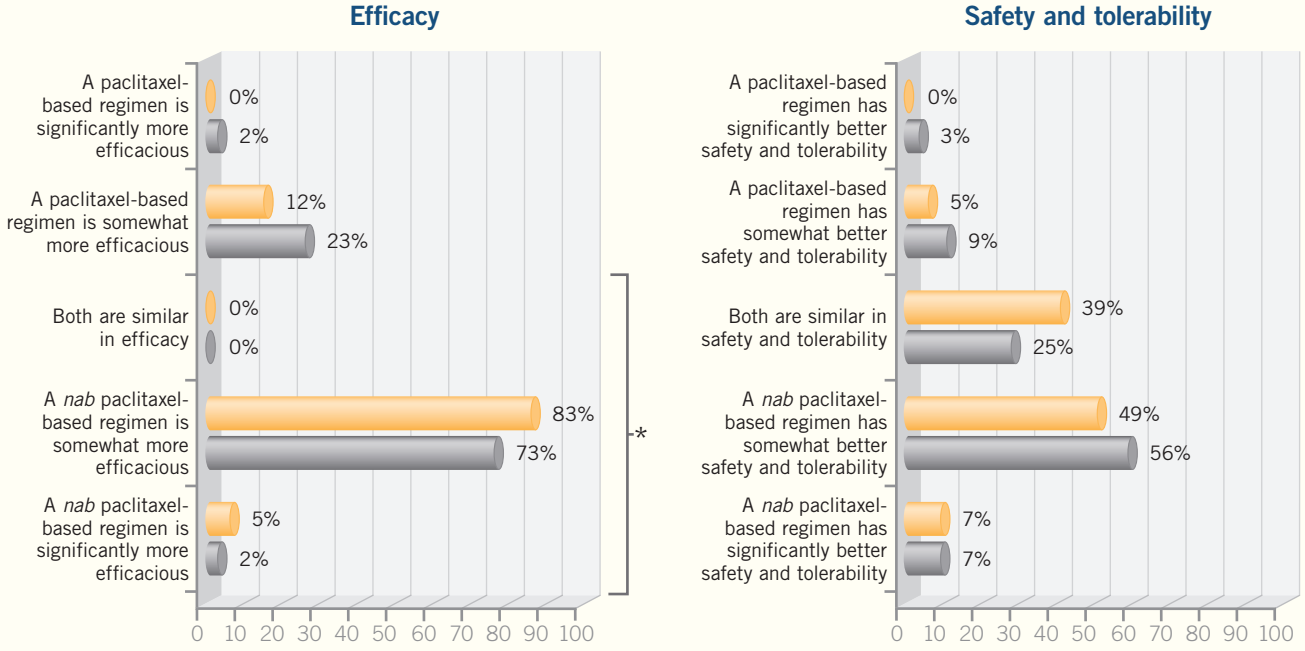
FIGURE 53

*Continued from previous case: A **60-year-old woman** was diagnosed three years earlier with **ER-negative, PR-negative, HER2-negative** breast cancer and received AC. She now has moderately symptomatic bone metastases and no other sites of disease on staging. How would you compare the following agents/regimens **for this particular case**?*

A docetaxel-based regimen versus a nab *paclitaxel-based regimen*



A paclitaxel-based regimen versus a nab *paclitaxel-based regimen*

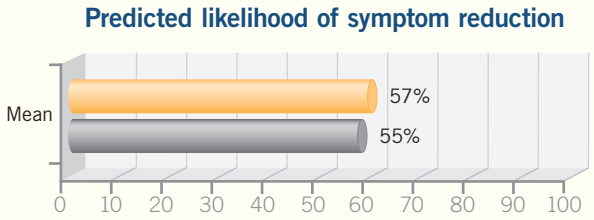


* 88 percent of CIs and 75 percent of POs consider a *nab* paclitaxel-based regimen to have similar or better efficacy than a paclitaxel-based regimen.

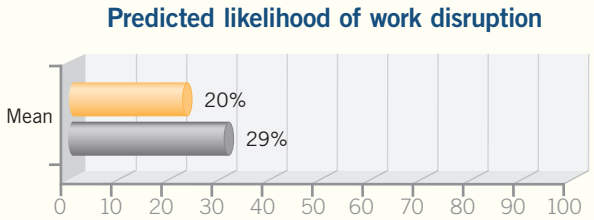
FIGURE 54

*Continued from previous case: A **60-year-old woman** was diagnosed three years earlier with **ER-negative, PR-negative, HER2-negative** breast cancer and received AC. She now has moderately symptomatic bone metastases and no other sites of disease on staging. How would you respond if:*

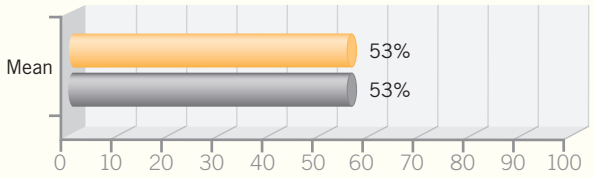
The patient asks what the chances are that the bone pain will be controlled, at least for a while, with the systemic first-line therapy you are recommending?



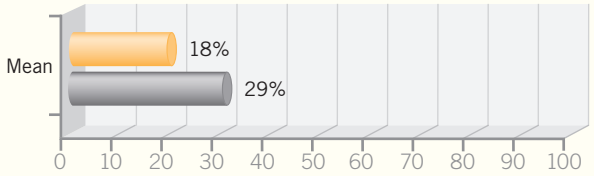
The patient asks what the chances are that the systemic first-line therapy you are recommending will cause significant disruption of her daily life — for example, completely preventing her from working at her present job?



*The patient asks what the chances are that she will be alive with the cancer controlled and without major symptoms in **two** years with your first-line therapy?*



*The patient asks what the chances are that she will be alive with the cancer controlled and without major symptoms in **five** years with your first-line therapy?*



Some strategies have evaluated quickly increasing serum levels of fulvestrant, and those strategies have included administering loading doses of 500 milligrams and then, within two weeks, administering another 250 milligrams and then proceeding to the monthly schedule.

Those strategies are based on mathematical modeling that have shown an ability to achieve steady-state levels much quicker and, consequently, achieve a biologically relevant dose of drug circulating in a given patient much faster.

Breast Cancer Update 2005 (4)

DR OSBORNE: We expected fulvestrant to be superior to tamoxifen, but in the first-line setting it proved to be similar, not better. That's peculiar because second-line trials show fulvestrant to be equal to or better than aromatase inhibitors, and aromatase inhibitors have been shown to be superior to tamoxifen.

It may be that we're not dosing fulvestrant correctly. We know from the randomized trial that half of the currently recommended dose is insufficient, and we know it takes three to six treatments to achieve steady state blood levels with fulvestrant, so perhaps a higher dose or a loading dose (or both) is required. These options are being investigated.

Breast Cancer Update 2004 (3)

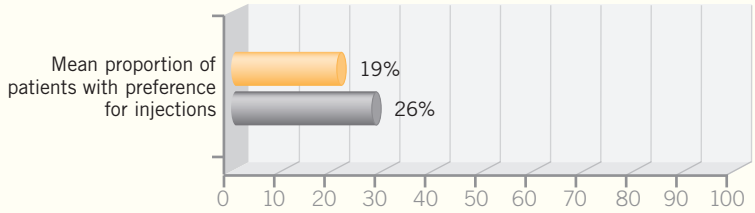
DR JOHN F R ROBERTSON: Fulvestrant at 250 milligrams is an effective dose, as demonstrated by the clinical trials. It is as effective as anastrozole as second-line therapy and equivalent to tamoxifen as first-line therapy in postmenopausal women.

In premenopausal women, data suggest that 250 milligrams of fulvestrant is not effective at down-regulating the estrogen receptor. This raises questions about whether a 250-mg dose of fulvestrant leads to complete down-regulation of the estrogen receptor in postmenopausal women. Could a higher dose of fulvestrant achieve more?

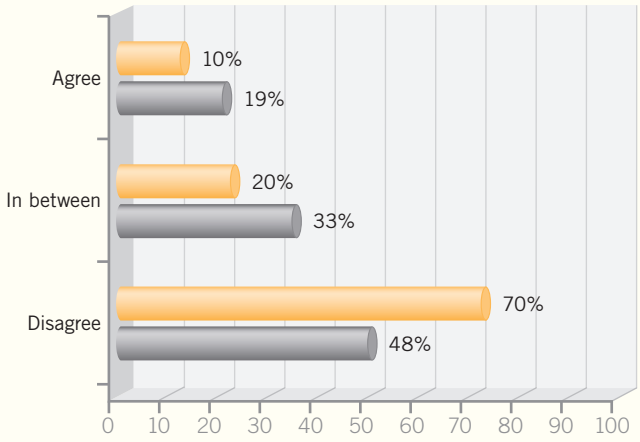
Two strategies exist to increase the dose of fulvestrant. The first is a loading dose sequence. The second is the admin-

FIGURE 55

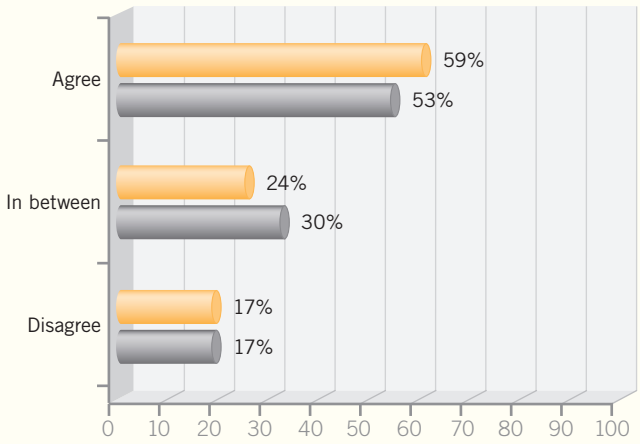
From a convenience perspective, what percentage of your patients with metastatic breast cancer in your practice would prefer to receive a monthly injection of fulvestrant rather than a daily oral endocrine agent such as an aromatase inhibitor or tamoxifen?



One acceptable clinical option for patients with ER-positive tumors who develop progressive metastatic disease on an aromatase inhibitor (AI) is to continue the AI and add fulvestrant.



In a clinical setting, a loading dose of fulvestrant should generally be used if financially feasible.



istration of a higher dose of fulvestrant. For example, instead of administering one 5-mL injection every month in one buttock, one might administer one 5-mL injection in each buttock, for a total of 500 milligrams. Future studies are needed to determine the dose-response curve for fulvestrant.

Breast Cancer Update 2004 (9)

DR GABRIEL N HORTOBAGYI: I believe the trials of fulvestrant underestimate the efficacy of this agent. The dosing schedule used was probably too low because by the time steady state was reached, many patients were off study, presumably because of progression.

In my group, we administer loading doses of 500 milligrams of fulvestrant, followed by 500 milligrams two weeks later and then 250 milligrams monthly.

The pharmacokinetics of fulvestrant suggest a loading dose would be beneficial, so it concerns me that the comparison of fulvestrant to anastrozole in a tamoxifen-resistant population might not have revealed the true efficacy of fulvestrant. It showed fulvestrant to be at least as effective as anastrozole, but I expected it to be superior. We may need to repeat some of these studies with a more appropriate dosing schedule.

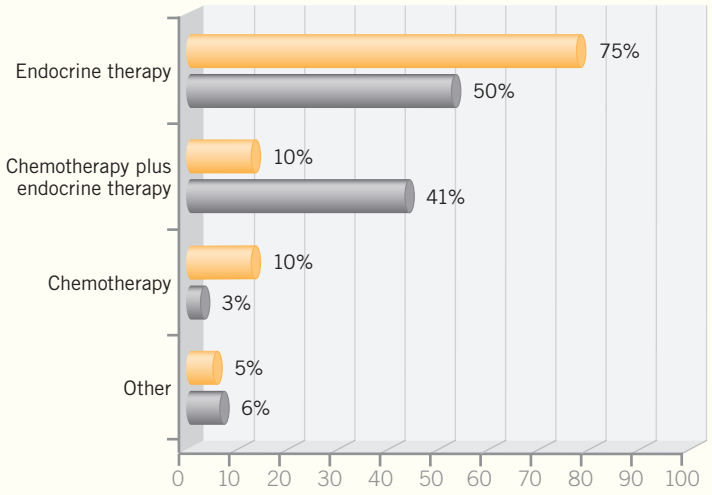
Breast Cancer Update 2003 (6)

DR O'SHAUGHNESSY: I am a little disquieted by the fact that it can take three to five months to reach a steady state with fulvestrant.

A patient with rapidly progressing disease may not benefit from fulvestrant, but fortunately most women with hormone-responsive breast cancer have relatively indolent disease. I'm interested in the clinical trial in which they are loading fulvestrant at 500 milligrams every two weeks for a couple of doses and then reducing it to 250 milligrams monthly. That makes sense to me.

FIGURE 56

*A **60-year-old woman** was diagnosed three years earlier with ER-positive, PR-positive, **HER2-negative** breast cancer and received AC followed by anastrozole. Currently receiving anastrozole, she now has moderately symptomatic bone metastases and no other sites of disease on staging. Which therapy would you recommend to this patient?*



Above groups may include combination with biologic agents

Breast Cancer Update 2005 (8)

DR VALERO: At MD Anderson, we use a loading dose of fulvestrant. We administer 500 milligrams on day one, 250 milligrams on day 15 and day 29 and then monthly.

Many of the key investigators in the early development of the drug believe it is important to attain steady state, but we have no randomized data for the loading approach. Currently, it is FDA approved at 250 milligrams monthly and is reimbursed by Medicare at that dose.

With all of those caveats, I believe — and I don't know if this is my bias — the loading approach is reasonable. However, although we think that may be the best dosing schedule, we won't know unless we do a pharmacokinetic study to show that the doses are equally effective.

Breast Cancer Update 2006 (7)

DR CARLSON: I believe a loading dose of fulvestrant should generally be used in clinical practice, and I continue to see an increase in the number of patients treated with fulvestrant. That's reasonable, and experience has confirmed the tolerability of the drug and the efficacy of the therapy. My expectation is we'll see nothing but increased use of fulvestrant.

In terms of use for the premenopausal woman, I believe that in the metastatic setting, we will see increasing numbers of patients treated with fulvestrant after they are put in a menopausal state.

In part this is because I believe the truly limited number of endocrine agents we have available for the treatment of premenopausal breast cancer means that, functionally, after a premenopausal woman has been treated with tamoxifen, you're obligated to make her postmenopausal.

Once she's postmenopausal, the whole spectrum of endocrine agents, which are effective in the postmenopausal woman, become available.

Because my expectation is that the women will be on hormone therapy for some length of time, I often send those women to the gynecologic oncologist for a laparoscopic oophorectomy.

Dodwell D, Vergote I. ***A comparison of fulvestrant and the third-generation aromatase inhibitors in the second-line treatment of postmenopausal women with advanced breast cancer.*** *Cancer Treat Rev* 2005;31(4):274-82.

Fulvestrant is the first antioestrogen to demonstrate efficacy in tamoxifen-resistant disease, highlighting the difference in mode of action between fulvestrant and the SERMs (which show only limited efficacy in this setting). In phase III studies, fulvestrant was at least as effective as anastrozole in terms of clinical efficacy and was well tolerated.

Furthermore, fulvestrant is associated with significantly fewer joint disorders (arthralgia, arthrosis and arthritis) compared with anastrozole. Indirect comparisons suggest that fulvestrant also offers comparable efficacy to letrozole and exemestane, and may have some tolerability benefits over these agents in the second-line treatment of postmenopausal women with advanced breast cancer.

Breast Cancer Update 2006 (3)

DR GRADISHAR: The SoFEA trial is evaluating the use of endocrine therapy in the metastatic disease setting, comparing exemestane as a single agent to fulvestrant to the combination of anastrozole and fulvestrant. The combined therapy arm may be the most interesting one.

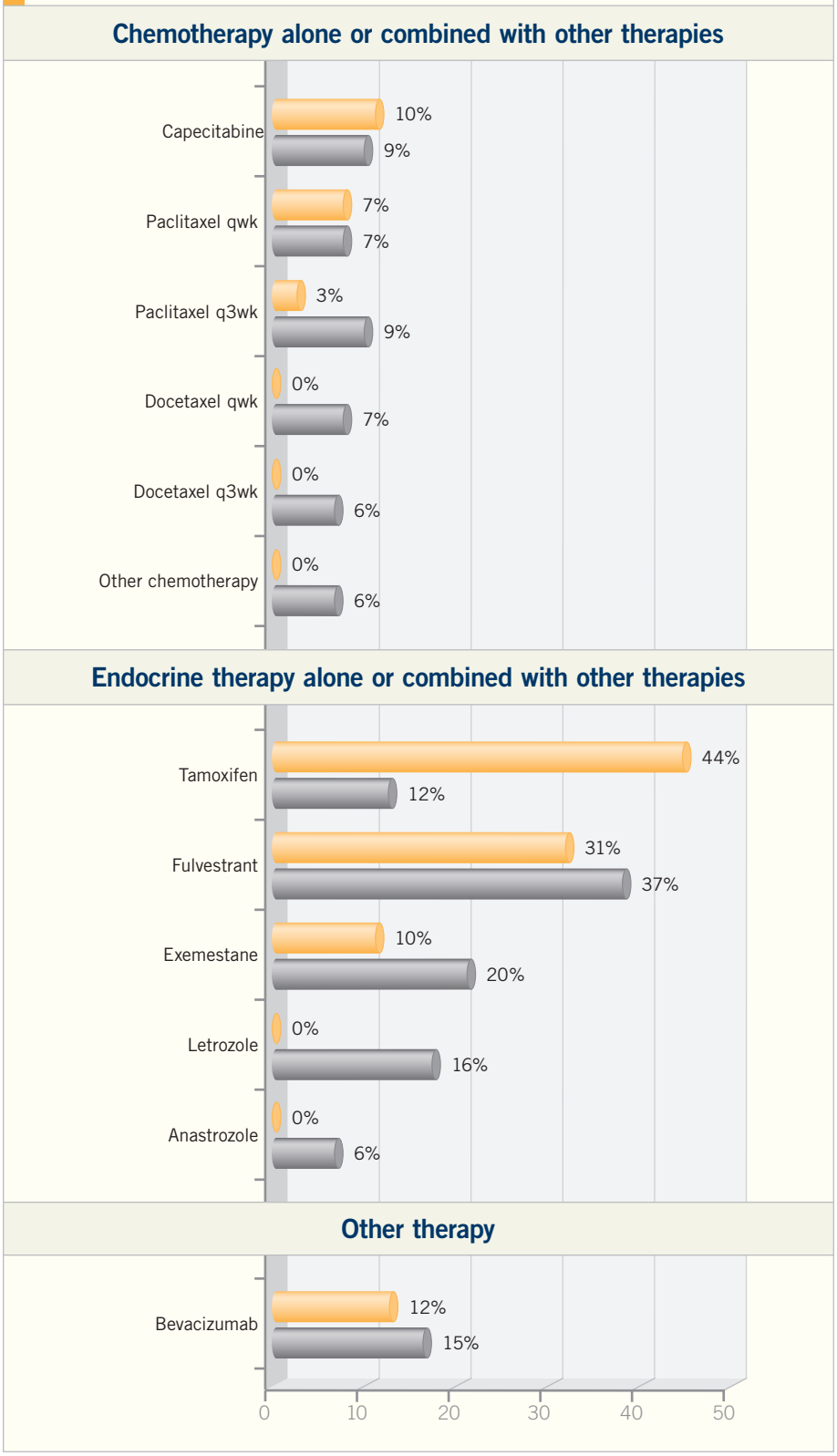
The rationale behind it is not only removing the ligand for the receptor — which is what the aromatase inhibitor would do by decreasing the amount of circulating estrogen — but also eradicating the actual target, which is the receptor. Answering whether absolute removal of those two targets will result in a better outcome is one of the goals of the study.

Breast Cancer Update 2006 (3)

DR ROBERTSON: In cell culture, when MCF7 cells are depleted of estradiol, they become extremely sensitive to low levels of estrogen. The cell line can be inhibited if fulvestrant is then titrated into that long-term estrogen-deprived cell line.

FIGURE 57

Same case (60-year-old woman with ER-positive, PR-positive, HER2-negative breast cancer): Responses by specific therapy



The rationale behind the SoFEA study is that the development of resistance to aromatase inhibitors may result from an increased sensitivity of breast cancer cells to very low levels of estradiol.

Fulvestrant competes with estradiol for the estrogen receptor on a one-to-one basis, so that upon progression while on the aromatase inhibitor, the addition of fulvestrant to the aromatase inhibitor might result in a better blocking effect. I hope the SoFEA trial will show that improvement occurs from the combination of fulvestrant and an aromatase inhibitor.

This will be an interesting study, not only because it will tell us what to do in second- or third-line therapy but because it will also tell us about mechanisms of action and whether they are important in breast cancer.

Stephen R Johnston et al. ***Life following aromatase inhibitors — Where now for endocrine sequencing?*** *Breast Cancer Res Treat* 2005;93(Suppl 1):19-25.

Fulvestrant ('Faslodex') is a new ER antagonist with no agonist effects that binds, blocks and degrades the ER. Due to its unique mode of action and lack of cross-resistance with existing treatments, fulvestrant is an effective therapeutic agent for use in sequential endocrine regimens. Fulvestrant has established efficacy in tamoxifen-resistant disease and there is a growing body of evidence demonstrating its efficacy in patients with AI-resistant disease.

In preclinical models, MCF-7 cells undergoing LTED are refractory to tamoxifen but sensitive to fulvestrant, suggesting fulvestrant is a more appropriate choice following AI resistance.

The steroidal AI, exemestane is also an option in nonsteroidal AI-resistant disease. Clinical trials are underway to compare fulvestrant with exemestane as an appropriate therapy following the onset of AI resistance.

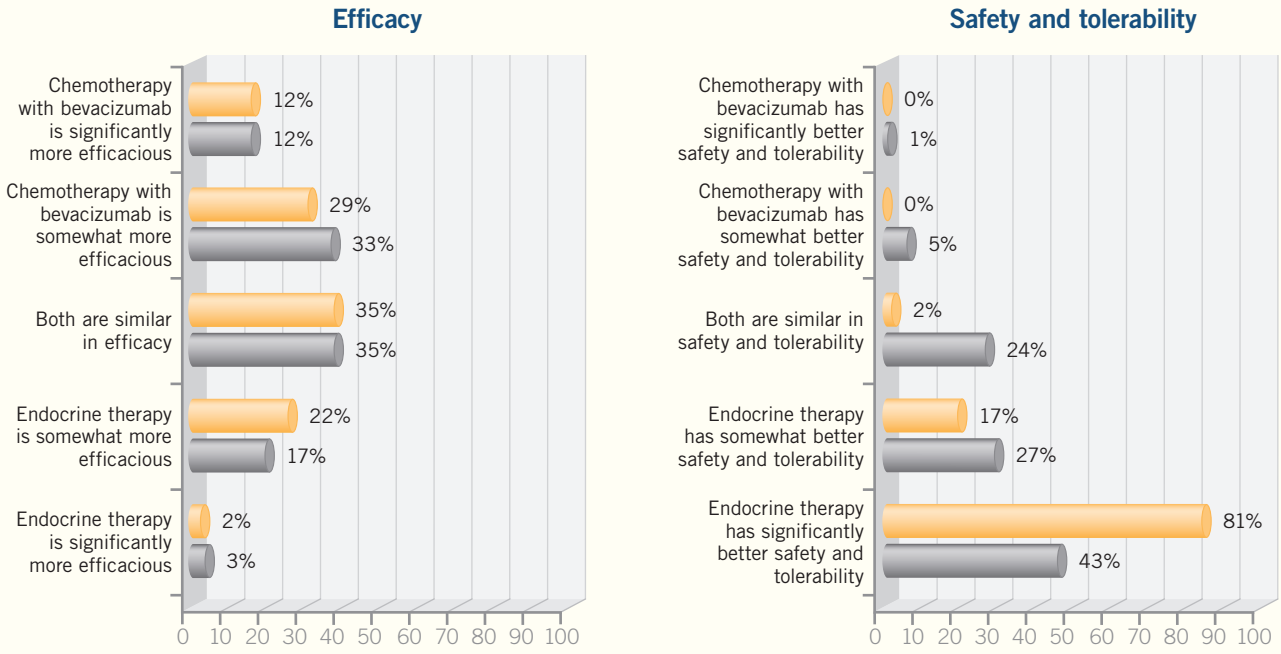
SELECT PUBLICATIONS

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

FIGURE 58

*Continued from previous case: A **60-year-old woman** was diagnosed three years earlier with **ER-positive, PR-positive, HER2-negative** breast cancer and received AC followed by anastrozole. Currently receiving anastrozole, she now has moderately symptomatic bone metastases and no other sites of disease on staging. How would you compare the following agents/regimens **for this particular case**?*

Chemotherapy (your choice) with bevacizumab versus endocrine therapy (your choice)



Tamoxifen versus fulvestrant

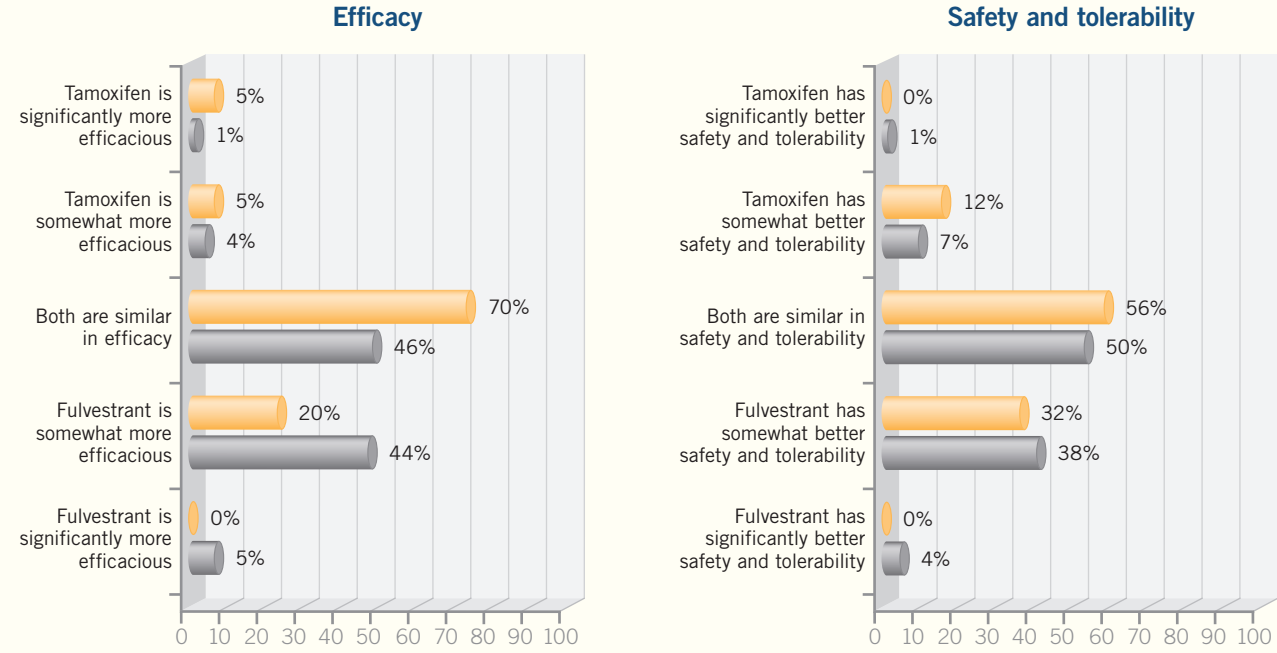
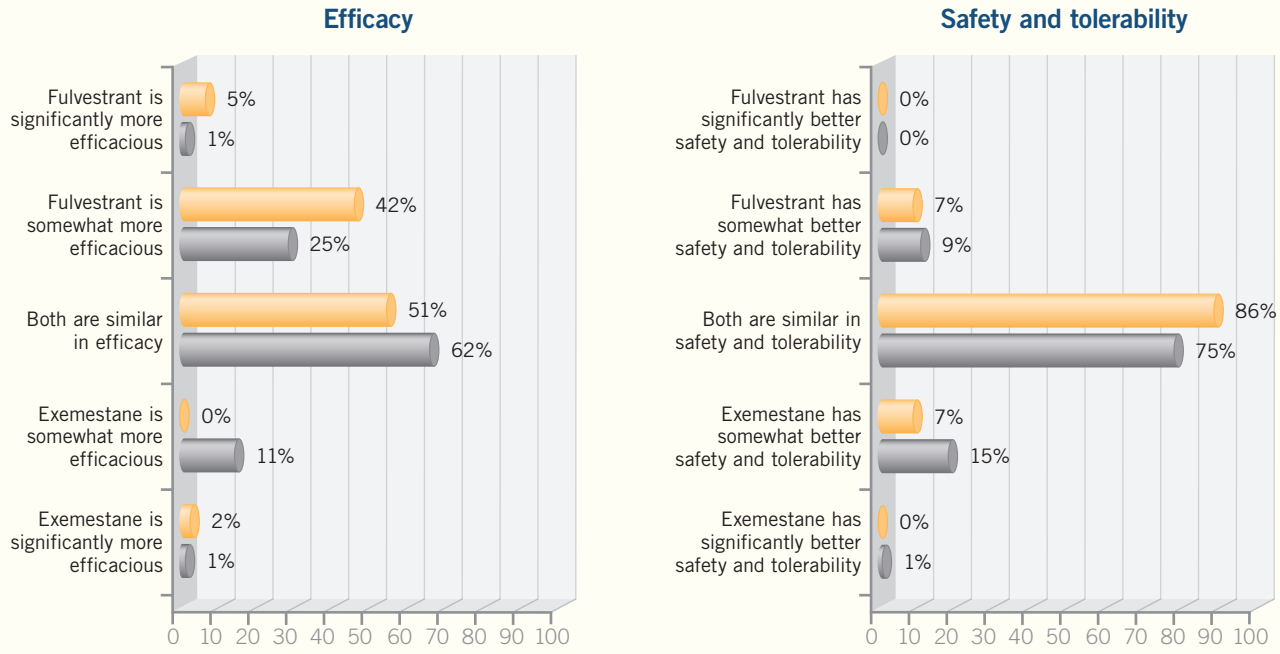


FIGURE 59

*Continued from previous case: A **60-year-old woman** was diagnosed three years earlier with **ER-positive, PR-positive, HER2-negative** breast cancer and received AC followed by anastrozole. Currently receiving anastrozole, she now has moderately symptomatic bone metastases and no other sites of disease on staging. How would you compare the following agents/regimens **for this particular case**?*

Fulvestrant versus exemestane



Dodwell D, Vergote I. **A comparison of fulvestrant and the third-generation aromatase inhibitors in the second-line treatment of postmenopausal women with advanced breast cancer.** *Cancer Treat Rev* 2005;31(4):274-82. **Abstract**

Ershler WB. **Capecitabine monotherapy: Safe and effective treatment for metastatic breast cancer.** *Oncologist* 2006;11(4):325-35. **Abstract**

Forward DP et al. **Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer.** *Br J Cancer* 2004;90(3):590-4. **Abstract**

Franco S et al. **Response to fulvestrant in heavily pretreated postmenopausal women: A single-center experience.** *Breast Cancer Res Treat* 2004;88(2):103-8. **Abstract**

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

Gradishar WJ et al. **Capecitabine plus paclitaxel as front-line combination therapy for metastatic breast cancer: A multicenter phase II study.** *J Clin Oncol* 2004;22(12):2321-7. **Abstract**

Howell A. **Fulvestrant ('Faslodex'): Current and future role in breast cancer management.** *Crit Rev Oncol Hematol* 2006;57(3):265-73. **Abstract**

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

Howell A et al. **A review of the efficacy of anastrozole in postmenopausal women with advanced breast cancer with visceral metastases.** *Breast Cancer Res Treat* 2003;82(3):215-22. **Abstract**

Howell A et al. **Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.** *J Clin Oncol* 2002;20(16):3396-403. **Abstract**

Ibrahim NK et al. **Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer.** *J Clin Oncol* 2005;23(25):6019-26. **Abstract**

Ingle JN et al. **Fulvestrant in women with advanced breast cancer after progression on prior aromatase inhibitor therapy: North Central Cancer Treatment Group Trial N0032.** *J Clin Oncol* 2006;24(7):1052-6. **Abstract**

Jain RK et al. **Lessons from phase III clinical trials on anti-VEGF therapy for cancer.** *Nat Clin Pract Oncol* 2006;3(1):24-40. **Abstract**

Johnson DH et al. **Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer.** *J Clin Oncol* 2004;22(11):2184-91. **Abstract**

Love NH et al. **Preferences for oral versus parenteral antitumor therapy: A survey of patients with metastatic breast cancer.** Oncology Nursing Society Congress 2005;**Abstract 243**.

Mauriac L et al. **Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and nonvisceral metastases: Combined results from two multicentre trials.** *Eur J Cancer* 2003;39(9):1228-33. **Abstract**

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

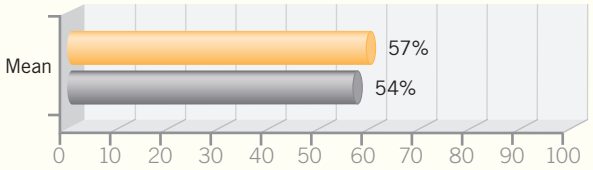
Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.** Presentation. ASCO 2005. No abstract available

FIGURE 60

*Continued from previous case: A **60-year-old woman** was diagnosed three years earlier with **ER-positive, PR-positive, HER2-negative** breast cancer and received AC followed by anastrozole. Currently receiving anastrozole, she now has moderately symptomatic bone metastases and no other sites of disease on staging. How would you respond if:*

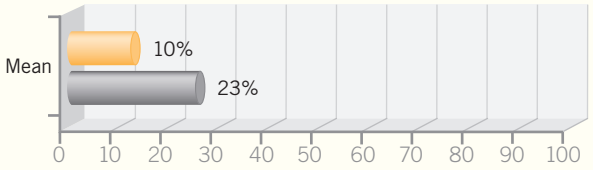
The patient asks what the chances are that the bone pain will be controlled, at least for a while, with the systemic first-line therapy you are recommending?

Predicted likelihood of symptom reduction

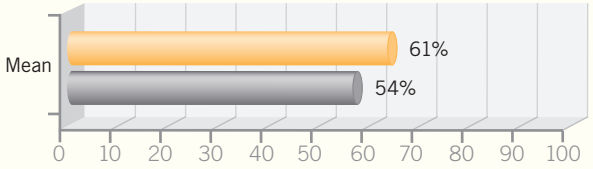


The patient asks what the chances are that the systemic first-line therapy you are recommending will cause significant disruption of her daily life — for example, completely preventing her from working at her present job?

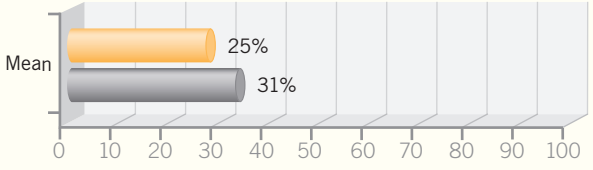
Predicted likelihood of work disruption



*The patient asks what the chances are that she will be alive with the cancer controlled and without major symptoms in **two** years with your first-line therapy?*



*The patient asks what the chances are that she will be alive with the cancer controlled and without major symptoms in **five** years with your first-line therapy?*



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5	4	3	2	1
Outstanding	Good	Satisfactory	Fair	Poor

GLOBAL LEARNING OBJECTIVES

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 research leaders 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

OVERALL EFFECTIVENESS OF THE FACULTY MEMBERS

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

Please be as specific as possible about individual faculty.

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

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

☐ Yes ☐ No

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.....

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

.....

.....

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

.....

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POCB306

CME EVALUATION

Patterns of Care in Medical Oncology

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