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Breast Cancer® UPDATE

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

EDITOR

Neil Love, MD

INTERVIEWS

Matthew J Ellis, MB, BChir, PhD
Michael Gnant, MD
Hyman B Muss, MD

SPECIAL FEATURE

Fellows Rounds with Dr Charles Vogel — Five Young Mothers with Metastatic Breast Cancer

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OVERVIEW OF ACTIVITY

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing clinician must be well informed of these advances. Featuring information on the latest research developments along with expert and patient perspectives, this CME program is designed to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Review the biologic subtypes of breast cancer, and determine how disease phenotype impacts patient prognosis and treatment.
- Develop an evidence-based adjuvant treatment algorithm for patients with localized breast cancer, addressing the individualized selection of chemotherapy and the optimal schedule and duration of endocrine therapy.
- Discuss the adjunctive role of oral and intravenous bisphosphonates in the management of hormone receptor-positive early breast cancer, and identify patients who may benefit from this course of therapy.
- Recognize the unique clinical challenges that accompany the care of elderly breast cancer patients, and recommend treatment strategies that optimize clinical benefit and minimize toxicity.
- Explain the benefits and risks of HER2-directed therapy for patients with early and advanced breast cancer, and discuss how combination treatment regimens may overcome the development of resistant disease.
- Review the role of VEGF inhibitors in the first-line management of metastatic breast cancer, and discuss their safety and efficacy when combined with evidence-based chemotherapeutic partners and in patients with existing brain metastases.
- Implement a therapeutic algorithm for the sequential use of combination and/or single-agent chemotherapy that enables multiple lines of treatment for patients with metastatic breast cancer.
- Describe the patient perspective on living with breast cancer, and use this insight to deliver comprehensive and compassionate oncology care.
- Counsel appropriately selected patients with breast cancer about the availability of ongoing clinical trial participation.

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EDITOR'S NOTE

Neil Love, MD

Austrian tag team

When the 2008 American Society of Clinical Oncology (ASCO) program arrived at my doorstep in mid-May, I was struck by the plenary session's distinct and somewhat unsettling European flavor (Figure 1). There, first in the lineup, in ASCO's highest-profile position, was an update of a well-known trial, ABCSG-12, studying adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid (ZDA), in premenopausal women with ER-positive, Stage I and II breast cancer. I noted the familiar name attached to this presentation: Michael Gnant, the Viennese breast cancer surgeon first interviewed for this series at the 2004 San Antonio Breast Cancer Symposium.

The abstract to the latest update of this trial wasn't posted — and wouldn't be until the first day of the meeting — but my assumption was that the study had been given top billing because of the endocrine question. However, when a prominent breast cancer investigator visited our office in Miami a week or so before ASCO, he intimated (off the record) that the paper might have a few surprises, but he refused to respond to my gentle arm-twisting about the details.

With that thought in the back of my mind, I headed out to ASCO and after the usual delayed landing at O'Hare was quickly on the way to our first interview with prostate cancer researcher Nancy Dawson. To my surprise, our conversa-

1 ASCO 2008 Plenary Session Presentations

Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with hormone-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12. (Abstract LBA4) — *Michael Gnant, MD; Vienna, Austria*

Radiotherapy versus carboplatin for stage I seminoma: Updated analysis of the MRC/EORTC randomized trial (ISRCTN27163214). (Abstract 1) — *R T Oliver, MD; London, England*

KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience. (Abstract 2) — *Eric Van Cutsem, MD, PhD; Leuven, Belgium*

FLEX: A randomized, multicenter, phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC). (Abstract 3) — *Robert Pirker, MD; Vienna, Austria*

tion began with Nancy asking if I had seen the Austrian breast cancer paper that had just been posted.

Needless to say, I opened up my computer, went right to the ASCO website and was soon on the phone trying to track down Dr Gnant. When Mike arrived at our temporary recording studio the day after his presentation, he joked that this would be approximately his 200th interview in 24 hours. He also noted that most of those had been simply to acquire a media sound bite or two and that he was prepared to and would enjoy spending a long time together dissecting the details of this historic paper.

Of course, the "late-breaking news" here is that ZDA and not anastrozole lowered the relative risk for relapse — in this case, by a stunning 35 percent. Our discussion was much longer than the time allotted to the presentation the day before, as we reviewed this complex data set. Dr Gnant started by commenting that although none of these young women with node-positive and node-negative tumors had received chemotherapy, only about six percent had experienced cancer relapse at five years. This suggests yet again that optimal endocrine therapy and not chemo is the key to management of ER-positive, HER2-negative disease.

During our chat, Mike and I covered a variety of topics, including Martine Piccart-Gebhart's spectacular "seed and soil" discussion that followed his presentation. I also reminded him of another European Mike — Michael Baum — who had essentially predicted this moment at the 2001 San Antonio meeting, when he presented for the first time initial findings from the ATAC trial demonstrating an advantage for anastrozole compared to tamoxifen in postmenopausal women. The only major downside reported at that time was an increased risk of fracture.

The same morning as Dr Baum's talk, Trevor Powles presented findings from a UK trial suggesting, but not proving, that adjuvant clodronate lowered the rate of breast cancer recurrence. Dr Baum — whose passion for clinical science had an enormous impact on the field in the 1980s and 1990s — challenged the San Antonio throng to consider a future matrimony of a bisphosphonate and an AI that would solve not only the bone problem but also perhaps much more.

As is often the case in oncology, there have been a variety of responses to the 2008 Austrian ASCO ZDA data set and what it means to daily practice. During our interview, Mike G commented that "If my sister had ER-positive breast cancer, I would recommend zoledronic acid." However, Dr Piccart-Gebhart cautioned from the podium to wait for more data, which should be available this year.

Perhaps more important than the current clinical stance of investigators is the possibility that we are witnessing a major paradigm shift in breast cancer treatment, particularly because of the quite unexpected finding that the use of ZDA was not only associated with fewer bone mets but also fewer metastases at other sites and fewer contralateral breast primaries. This led Martine to speculate that bisphosphonates may have antitumor activity, both to prevent metastatic implantation (ruining the soil) and at the same time perhaps having a direct antitumor effect (striking the seed).

With so few events in the Austrian study, most people agree that the issue of optimal hormone choice needs more data and the continuation of existing trials like SOFT and TEXT, but Dr Gnant pointed out that even if other studies don't demonstrate a recurrence advantage with AIs versus TAM for ovarian-suppressed patients, the Austrian data confirm prior findings for postmenopausal women demonstrating fewer thrombotic events and endometrial cancers in patients receiving the AI. Another critical observation presented in Chicago was that ZDA given according to this schedule and at this dose was not associated with any confirmed cases of osteonecrosis of the jaw.

Dr Gnant was followed to the podium by an Austrian colleague, Dr Robert Pirker, who also met with me for an interview at ASCO as part of our lung cancer audio series. Dr P presented the much-discussed FLEX trial in non-small cell lung cancer, which demonstrated a five-week survival advantage with the addition of cetuximab to chemotherapy as first-line therapy of metastatic disease.

Although I was initially underwhelmed by this modest advance, Dr Pirker was able to convince me that at the least this option needs to be discussed with patients — particularly those who would not have met the entry criteria for the ECOG-E4599 study of paclitaxel with bevacizumab, such as patients with squamous cell cancer.

The other two ASCO plenary talks included a UK-led equivalency trial of carbo versus radiation therapy in Stage 1 seminoma and a paper by Belgian investigator Eric Van Cutsem on the value of K-ras status in identifying patients with colorectal cancer who don't benefit from cetuximab — both worthwhile advances that are unfortunately not likely to result in more immediate cancer cures.

Walking out of the session that Sunday afternoon, I was distraught that the most financially fortunate country on the planet was so underrepresented at the podium, and that ASCO 2008 in general failed to come up with any Gleevecian home runs.

Michael Gnant, MD

Robert Pirker, MD

It is curious and discouraging that 35 percent of Austrian women with breast cancer enter clinical trials compared to less than five percent in the US. In our conversations since 2004, Dr Gnant has repeatedly reminded me that the reason his country of only eight million people has contributed so much to cancer research is that, well...they think it's important.

If the ZDA-bisphosphonate adjuvant story plays out, it is a cause for some optimism, and one can argue that more recurrences will be avoided even than with trastuzumab, but we need a lot more steps forward to see the beginning of the end to this merciless disease.

The more likely future of cancer research is that the status quo will continue, and I will crawl back in my CME hole and try not to remember that the resources and talent exist in this country to squash the cancer problem under our soles like a bug. If in the future we somehow do get our act together, ASCO and its plenary and other sessions will be bringing much more hope to desperate patients and weary oncologists. ■

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
August 11, 2008

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INTERVIEW

Michael Gnant, MD

Dr Gnant is Professor of Surgery at the Medical University of Vienna in Vienna, Austria.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Can you discuss the Austrian Breast Cancer Study Group (ABCSG) trial in premenopausal women you presented at ASCO this year?

DR GNANT: The ABCSG-12 trial began with the issue of endocrine therapy. However, we became concerned about what might happen to bone density during aromatase inhibitor therapy. Our goal was to protect the bone, and we thought bisphosphonates might also have antitumor activity, so we decided to address both issues — endocrine therapy and the use of bisphosphonates — in ABCSG-12 (Gnant 2008; [1.1]).

After our bone substudy was first reported in 2004 (Gnant 2004), we assembled an international advisory board to determine how to proceed. The bisphosphonates completely reversed bone loss from aromatase inhibitors, and among premenopausal patients, even tamoxifen could not completely protect the bone in those treated with goserelin.

Distinguished bone specialists such as Jean-Jacques Body and others said that we needed to answer the antitumor question. They were concerned that the sample size, which was 1,250 at the time, was not large enough. We decided to increase it to 1,800, knowing that we would have the power to detect at least a major effect from the bisphosphonate.

DR LOVE: What were the eligibility requirements, and what kinds of patients ended up enrolling?

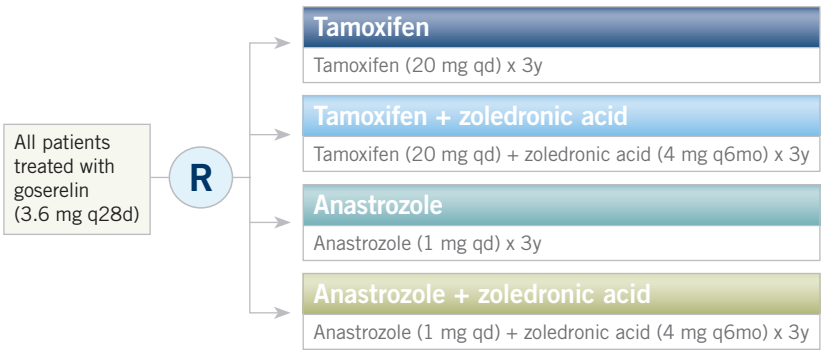
DR GNANT: Formally, the inclusion criteria were early-stage breast cancer and endocrine-responsive disease, meaning ER-positive and/or PR-positive tumors. We do not have a single patient in the trial with negative or unknown receptors. The trial was open to patients with node-negative disease in addition to patients with 10 or fewer positive nodes. In practice, physicians suggested participation in this trial for patients with few affected nodes.

DR LOVE: Can you discuss the results of the study?

1.1

Phase III Study Comparing Adjuvant Tamoxifen to Anastrozole Alone or in Combination with Zoledronic Acid for Premenopausal Patients with Hormone Receptor-Positive Breast Cancer Treated with Goserelin

Protocol ID: ABCSG-12
Accrual: 1,803 (Closed)



Eligibility

- No chemotherapy, except neoadjuvant
- Premenopausal
- ER-positive and/or PR-positive breast cancer
- Stage I and II (≤10 positive nodes)

SOURCE: Gnant M et al. *Proc ASCO* 2008;**Abstract LBA4**.

DR GNANT: At five years of follow-up, we observed only 137 disease-free survival events. Obviously this good prognosis is wonderful for our patients, but it's not good for trialists. I believe it's a mature trial. It has 1,800 patients, with six to seven percent having experienced any event. I don't believe that these results will change in the future.

In her commentary at ASCO, Martine Piccart-Gebhart remarked that ABCSG-12 is underpowered to rule out the benefit of substituting anastrozole for tamoxifen. However, we showed that anastrozole and tamoxifen yielded strikingly similar results (Gnant 2008; [1.2]) in patients receiving an LHRH agonist.

DR LOVE: One of the issues that Dr Piccart-Gebhart brought up was the efficacy of ovarian suppression with an LHRH agonist. Did you evaluate that?

DR GNANT: Only clinically. None of our patients was menstruating during treatment. I agree with Martine that some patients may have more effective estradiol suppression than others, but in terms of the clinical relevance for daily practice, it's well accepted that ovarian suppression works with the monthly administration of goserelin.

DR LOVE: Can you summarize what you saw in terms of the endocrine issue?

DR GNANT: We observed no difference in disease-free survival, recurrence-free survival or overall survival between anastrozole and tamoxifen in the presence of ovarian suppression. The curves are virtually overlapping.

1.2

ABCSG-12: Disease-Free Survival (DFS) Events with Adjuvant Tamoxifen (TAM) versus Anastrozole (ANA) — Both with Monthly Goserelin

	First DFS event per patient, n	
	ANA (n = 903)	TAM (n = 900)
Locoregional recurrence	14	16
Distant recurrence	41	29
Contralateral breast cancer	6	10
Secondary malignancy	10	9
Death without prior recurrence	1	1

Hazard ratio (95% CI) for DFS, versus TAM = 1.006 (0.78-1.53), $p = 0.503$

SOURCE: Gnant M et al. *Proc ASCO* 2008;**Abstract LBA4**.

Track 9

DR LOVE: Can you discuss the dosing schedule and results of zoledronic acid in ABCSG-12?

DR GNANT: We administered four milligrams of zoledronic acid every six months, for a total of seven infusions over three years. Initially, we started the

trial with a higher dose of eight milligrams monthly, but we were forced to change due to safety concerns. In 2000, reports surfaced that renal safety was endangered in some patients with multiple myeloma who were being treated with zoledronic acid, and at that point all the trials around the world reduced the dose to four milligrams.

We went back to what we believed would be mostly a bone-protection dose. Therefore, it's particularly striking that we are not only protecting bone at this dose but that we are also keeping the cancer at bay (Gnant 2008; [1.3]).

Two more observations are also exciting. One is the magnitude of the effect: A 36 percent improvement in disease-free survival, translating to at least a nonsignificant trend toward better overall survival. That's an accomplishment usually observed with interventions such as taxane chemotherapy. We observed that efficacy with an acceptable side-effect profile (1.4).

More importantly, we're not only preventing bone metastases, but we're also seeing benefit in various event subcategories, including locoregional recurrence, contralateral breast cancer and distant metastasis outside of the bone (such as liver or lung disease). That's something most of us did not expect.

1.3

ABCSG-12: Zoledronic Acid (ZDA) Added to Adjuvant Endocrine Therapy Prolongs Disease-Free Survival (DFS) in Premenopausal Patients with Hormone Receptor-Positive Early Breast Cancer

	First DFS event per patient, n	
	ZDA (n = 899)	No ZDA (n = 904)
Locoregional recurrence	10	20
Distant recurrence	29	41
Contralateral breast cancer	6	16
Secondary cancer	9	10
Death without prior recurrence	0	2

Hazard ratio (95% CI) for DFS, versus no ZDA = 0.643 (0.48-0.91), $p = 0.011$

SOURCE: Gnant M et al. *Proc ASCO* 2008;**Abstract LBA4**.

Track 11

DR LOVE: What about osteonecrosis of the jaw (ONJ)?

DR GNANT: When we started the trial in 1999, nobody was aware of ONJ. When the first reports were published, we made an effort to educate physicians and patients, saying, "Be careful with your dental procedures. Report symptoms early."

We identified three suspected cases and examined the original dental films. We did not find evidence of a single case of confirmed ONJ (1.4). This is in

line with what is known about that dose and frequency of administration of zoledronic acid. Basically, all the reports suggest that ONJ with IV bisphosphonates occurs with more intense regimens or higher-dose schedules. I would say that ONJ is not a problem in the adjuvant treatment setting.

DR LOVE: Robert Marx, who was one of the oral surgeons involved in identifying ONJ, makes the recommendation that patients who receive bisphosphonates should see a dentist prior to initiating the bisphosphonate to ensure that they don't have any major problems (Marx 2007). Is that your approach?

DR GNANT: Yes, I support that recommendation. I believe that it's prudent to recommend a dental exam for everyone ahead of receiving bisphosphonates.

1.4

ABCSG-12: Select and Serious Adverse Events

	TAM (n = 435)	TAM + ZDA (n = 434)	ANA (n = 436)	ANA + ZDA (n = 439)
Adverse event				
Arthralgia	11.5%	14.5%	24.7%	33.3%
Bone pain	20.8%	29.4%	28.3%	41.1%
Fever	2.0%	7.6%	2.4%	10.2%
Depression, sleep disturbances	15.5%	16.5%	21.4%	17.8%
Periodontal disease	1.1%	0.7%	0.0%	1.3%
Serious adverse event				
Arthralgia	0.0%	0.2%	0.0%	0.2%
Bone pain	0.0%	0.0%	0.0%	0.2%
Fever	0.2%	0.2%	0.2%	0.4%
Fracture	1.3%	0.9%	0.9%	1.6%
Thrombosis	0.7%	1.1%	0.0%	0.0%
Uterine polyp	8.9%	11.4%	1.6%	1.1%
Periodontal disease	0.0%	0.2%	0.0%	0.2%

SOURCE: Gnant M et al. *Proc ASCO* 2008;**Abstract LBA4**.

Track 12

DR LOVE: Are the results of your study ready for prime time? Martine was somewhat cautious (1.5), suggesting that we need to wait for another study before considering ZDA off protocol.

DR GNANT: I see two sides to that answer. As a scientist, I would like to have confirmation for everything I do. At least for now, the application of these results should be confined to the population in which they were derived. We should be careful in extrapolating them to other patient populations, such as patients with hormone receptor–negative disease.

DR LOVE: "Careful" as in don't do it?

DR GNANT: Probably for now, particularly because we will have confirmatory data soon. The AZURE (BIG 1-04) study, which is examining zoledronic acid in pre- and postmenopausal women with node-positive disease, is expected to report by the end of this year in San Antonio.

DR LOVE: In hormone receptor-negative and hormone receptor-positive disease?

DR GNANT: Yes, in both, with at least 20 percent of patients having hormone receptor-negative disease. Robert E Coleman is the principal investigator.

They have recruited 3,300 patients, and they will conduct the first analysis in September. So that's the scientific interpretation: It's prudent to be conservative.

On the other hand, I will answer as a doctor and as a person. Obviously we don't have approval for any of these practices currently, so patients may come across availability and reimbursement issues.

But frankly, if my sister were diagnosed next week — if she were premenopausal and had endocrine-responsive disease — she would evaluate the data and say, "That's seven infusions of 50 minutes each over the course of three years.

1.5

Dr Piccart-Gebhart's Perspective on the Clinical Implications of ABCSG-12 Data on Zoledronic Acid

"As clinicians, we are clearly left with a long list of open questions. What is the mechanism of the beneficial effect; seed, soil or both? Is the magnitude of benefit larger for an aromatase inhibitor or even restricted to an aromatase inhibitor? Are the efforts at tailoring adjuvant zoledronic acid worthwhile in an era in which women are screened and treated with this agent for osteoporosis? Could a more intensive schedule of zoledronic acid be even more effective — but will it be safe? How long should zoledronic acid be continued? And last, but not least, what are the implications for other tumor types?

Now, before recommending the wide use of zoledronic acid in routine clinical care, I am convinced that we have to wait until the results of at least one of these other important first-generation adjuvant bisphosphonate trials, and in particular, for the interim results of the BIG 1-04 AZURE trial, which are expected in the summer, with 472 disease-free survival events. This is an even larger trial than ABCSG-12, which uses a more intensive schedule of zoledronic acid and targets a higher-risk population that includes women receiving adjuvant chemotherapy, which is certainly more in line with clinical practice, at least in the United States.

So, in conclusion ABCSG 12, I think, is not yet a practice-changing trial, but is an important trial, announcing a paradigm shift targeting both seed and soil. And it is certainly a trial opening a plethora of new strategies likely to further improve outcome of women with early breast cancer."

SOURCE: Piccart-Gebhart M. Discussant, Plenary Session. ASCO 2008.

It's well tolerated. The toxicity is either low or nonexistent, and what to watch out for is well defined. It's already been proved effective in protecting bone against the side effects of endocrine treatment, and it's now been shown to keep the cancer at bay by an additional one third. Let me have that." It would be a struggle for me to say, "Wait for approval. Wait for another 12 months."

DR LOVE: What if it were your older, postmenopausal sister?

DR GNANT: That's a little more difficult. I would try to stay disciplined and say that we will know the answer in six months. We can probably start the bisphosphonate in six months, once we demonstrate the positive effects, so let's wait. ■

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INTERVIEW

Hyman B Muss, MD

Dr Muss is Professor of Medicine in the Hematology Oncology Unit at the University of Vermont and Vermont Cancer Center in Burlington, Vermont.

Tracks 1-17

Case Discussion with Drs Vogel and Muss

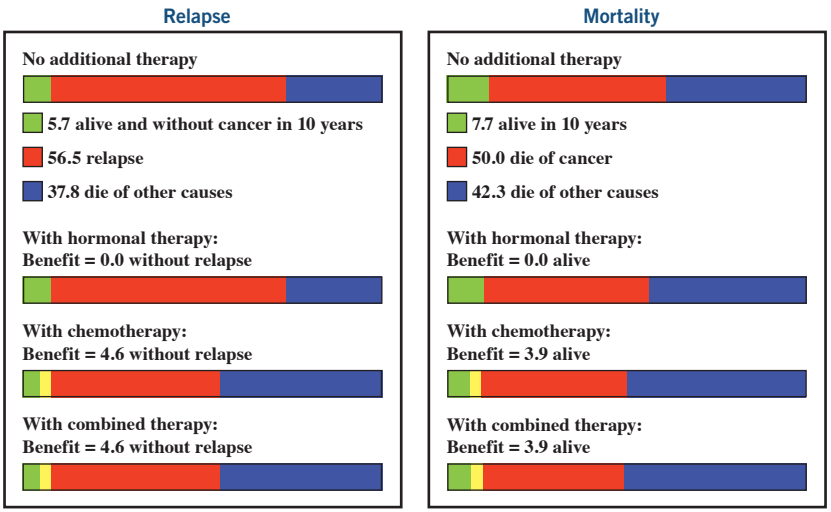
A Case Submitted from the Practice of Dr William Adler

An 86-year-old woman with hypertension, severe kyphosis and moderate renal insufficiency underwent a mastectomy for a 3.5-cm, Grade III, triple-negative breast tumor with eight positive nodes and no evidence of other disease. She has a good performance status and desires adjuvant systemic therapy, even for a modest benefit.

SOURCE: Tracks 1-3.

2.1

Adjuvant! Online: 10-Year Risk of Recurrence and Death and Benefit from Second-Generation Adjuvant Chemotherapy Regimens for an 86-Year-Old Woman with Good Performance Status and a 3.5-cm, Grade III, Triple-Negative Breast Tumor with Eight Positive Nodes



SOURCE: www.adjuvantonline.com/breastnew.jsp (Version 8.0).

DR LOVE: Dr Adler showed this patient the Adjuvant! Online data, which suggest a modest benefit in mortality and recurrence over 10 years with "second-generation" adjuvant chemotherapy (2.1). She understands that this is ER-negative/PR-negative disease and that if it recurs, it may be in the next two to three years.

Dr Adler's question is, "What are your thoughts about the benefits of therapy for this elderly woman, and if you would treat her, which regimen would you utilize?"

DR VOGEL: I haven't treated many 86-year-olds with chemotherapy. This lady has a poor prognosis across the board. On the other hand, her likelihood of dying of other causes according to Adjuvant! Online is extraordinarily high.

It's a tough case because this woman is different from the average 86-year-old in that she is physically well and strongly desires chemotherapy. Most elderly women wouldn't even consider chemotherapy. I would probably suggest observation, but if she persisted in wanting to be aggressive, then I would probably treat her.

I don't believe I would use anything beyond docetaxel/cyclophosphamide (TC) for four cycles with pegfilgrastim, which circumvents the doxorubicin-associated concerns about cardiac dysfunction and leukemia in addition to emerging issues related to the value of doxorubicin for patients whose disease is almost certainly TOPO II-negative.

I haven't treated many patients over eighty with adjuvant TC, but I have treated patients in their seventies. In accord with the guidelines, we add pegfilgrastim for patients older than age 65, even though the rate of febrile neutropenia in Steve Jones's study was much below that which would mandate prophylactic growth factor support.

DR MUSS: An 86-year-old woman in perfect health might have a five-year average survival, and her risk of recurrence with this disease is probably substantial within that five-year range. Approximately 70 to 80 percent of the recurrences will occur in that five-year range.

If she received TC chemotherapy, she may have a one third proportional reduction in risk. I estimate that she might increase her chance of survival by a few percent. If she were interested in that benefit, then I might consider something like adjuvant TC and pegfilgrastim.

However, it's "iffy." It would interfere with her quality of life, and she would experience some toxicity. She would need to be in perfect health, and I would let her know about my ambivalence in treating her.

Select Excerpts from the Interview with Dr Muss

Track 4

DR LOVE: Can you discuss the analysis you did of the effect of TC in older versus younger patients?

DR MUSS: I'm not a US Oncology member, but I met with the principal investigator of the 9735 trial and said, "Steve, you have a huge study here. You have a number of elderly patients on this study. No one has data on this. Let's evaluate it." We ended up studying those 167 patients.

I'm meticulous, so we conducted a multivariate analysis. I wanted to make sure that it was not a quirk, and sure enough, those older patients experienced a survival advantage. The paper was sent recently to the *Journal of Clinical Oncology*.

The older patients exhibited similar proportional benefits to the younger patients. They have poorer overall survival because of competing causes of death, but their proportional benefit in relapse is similar to that of younger patients (2.2). They experienced a little more toxicity — eight percent versus four percent neutropenic fever (2.3). I tend to use growth factors from the beginning with these patients. I'm using more TC in general in my practice.

DR LOVE: What age would cause you to start using growth factors with TC?

DR MUSS: I believe age 65 is a reasonable cutoff, possibly younger for a patient with substantial comorbidities — for example, patients with COPD who may develop pneumonia and become septic.

DR LOVE: How do patients in their seventies tolerate TC in your practice?

DR MUSS: From our data, TC is well tolerated. We see fatigue with all chemotherapy, but I believe more fatigue is associated with docetaxel, whatever the mechanism — whether it's making more IL6 or TNF, or whatever is happening — it's a bit tougher on patients.

The nice facet is that you're not worried about a cardiac toxicity profile. The neutropenia is of concern when you use 75 mg/m^2 of docetaxel: Most patients become neutropenic, but neutropenic fever has been uncommon.

2.2

Exploratory Analysis of Disease-Free Survival for Key Subgroups in the US Oncology Adjuvant Clinical Trial of TC versus AC

No. of patients per subgroup	TC (n)	AC (n)	Hazard ratio	Confidence interval
HER2-negative	55	69	0.56	0.30-1.05
HER2-positive	28	18	0.73	0.32-1.70
ER- or PR-negative	136	158	0.70	0.44-1.10
ER- or PR-positive	368	351	0.79	0.56-1.13
Age ≥ 65	78	82	0.70	0.40-1.24
Age < 65	428	428	0.76	0.55-1.04

Hazard ratio < 1.0 favors TC

SOURCE: Jones S et al. San Antonio Breast Cancer Symposium 2007;**Abstract 12**.

2.3

Select Grade III/IV Toxicities in Patients ≥65 and <65 Years Old in the US Oncology Adjuvant Clinical Trial of TC versus AC

	<65 years old		≥65 years old	
Adverse event	TC (n = 428)	AC (n = 428)	TC (n = 78)	AC (n = 82)
Hematologic				
Anemia	<1%	1%	<1%	5%
Neutropenia	60%	54%	52%	59%
Febrile neutropenia	4%	2%	8%	4%
Thrombocytopenia	<1%	1%	0%	<1%
Nonhematologic				
Asthenia	3%	4%	6%	9%
Fever	4%	3%	6%	4%
Infection	7%	10%	6%	2%

SOURCE: Jones S et al. San Antonio Breast Cancer Symposium 2007;**Abstract 12**.

Track 5

DR LOVE: What do we know about the relationship between chemotherapy-induced leukemia and age?

DR MUSS: If you evaluate the SEER data on women older than age 65, you find that about one percent have a risk of AML. The hazard ratio if you focus on chemotherapy is in the 1.6 to 2.0 range, and with anthracyclines the hazard ratio is approximately 2.1 to 2.2. So I believe concern does arise with age and anthracyclines, which are associated with those chromosomal abnormalities for TOPO II-inhibiting agents and leukemia. Those leukemias tend to occur four to eight years out.

When we evaluated our CALGB data for toxicity and treatment-related deaths among the elderly, we found MDS and AML to be a major problem. The issues were not heart related, probably because we put healthy patients on the trial. The incidence of AML or MDS was 0.7 percent in the most recent update of our CALGB-9741 trial (Muss 2007), which is high. When you enter all of these factors into Adjuvant! Online and a one percent survival benefit appears, administering chemotherapy is something you really have to consider.

Track 8

DR LOVE: Would you discuss the CALGB-49907 randomized Phase III study focusing on the elderly that you reported at ASCO 2008 (Muss 2008)?

DR MUSS: We compared standard chemotherapy — physicians could choose CMF with oral cyclophosphamide or AC as defined by the NSABP — to capecitabine administered orally for two consecutive weeks out of every three weeks. To be eligible, patients of any nodal and HER2 status had to be 65 years of age or older, have a tumor greater than or equal to one centimeter, an estimated survival of five years and normal organ function.

The trial was performed based on data from trials in metastatic breast cancer under the hypothesis that single-agent capecitabine would be noninferior. This was a clever, adaptive and unique design by Don Berry based on Bayesian statistics. We selected a specific point, between 600 patients and a maximum of 1,800 patients, to calculate what the likelihood would be that capecitabine was noninferior to AC.

We also had cutoffs at which we would stop the trial if the capecitabine was inferior or likely to be inferior. In November of 2006, after accruing 600 patients, we performed our first analysis and found it likely that capecitabine was inferior to CMF or AC, and we halted accrual. Analysis of the data revealed a highly significant benefit in both relapse-free and overall survival for patients treated with standard chemotherapy, either classic CMF or AC, compared to patients treated with capecitabine (2.4).

We also performed an unplanned subset analysis and found an interaction between treatment and outcome. Specifically, patients with hormone receptor-negative — ER-negative, PR-negative — disease obtained the greatest value from CMF or AC treatment compared to capecitabine. For patients with hormone receptor-positive disease, the difference was not as obvious.

2.4

CALGB-49907: Efficacy of Standard Chemotherapy (CMF or AC) versus Capecitabine for Patients 65 Years Old or Older with Early Breast Cancer

Endpoint	Events	Hazard ratio (HR)	95% CI for HR	*p*-value
Relapse-free survival*		2.09	1.4-3.2	0.0006
CMF/AC (n = 326) Capecitabine (n = 307)	35 (11%) 60 (20%)			
Hormone receptor-negative/ all others†	93 (15%)	4.39	2.9-6.7	<0.001
	Deaths			
Overall survival*		1.85	1.1-3.1	0.019
CMF/AC (n = 326) Capecitabine (n = 307)	24 (7%) 38 (12%)			

HR > 1.0 favors standard chemotherapy
CI = confidence interval

* Multivariate analysis controlling for tumor size, number of positive lymph nodes and hormone receptor status

† Unplanned multivariate analysis of receptor interaction — Capecitabine in hormone-receptor negative:all others (n = 622)

"In conclusion, in this trial, standard adjuvant treatment with CMF or AC was superior to capecitabine for both relapse-free and overall survival. Toxicity was moderate for all regimens, but patients on AC received the largest number of scheduled treatments. There were two drug-related deaths in the entire trial in patients treated with capecitabine. In an unplanned subset analysis, the major benefit of CMF/AC was in patients with hormone receptor-negative tumors."

SOURCE: Muss HB et al. *Proc ASCO* 2008;**Abstract 507**.

Track 9

DR LOVE: Would you discuss the ICE trial, which is evaluating ibandronate with or without capecitabine?

DR MUSS: This is an ongoing European trial led by the German group, in which patients with hormone receptor-positive and hormone receptor-negative disease receive ibandronate and are then randomly assigned to capecitabine or no additional treatment (2.5). I met Dr Von Minckwitz, chair of the German group, at the ASCO meeting, and he told me that they have accrued approximately 1,350 of the planned 1,500 patients. This trial will tell us a lot about the use of the oral agent and will provide important data in the context of our trial.

Their patient population may be at lower risk than ours, but I believe that early on, many of the patients will fare well and will probably gain little benefit from the chemotherapy. The patients with hormone receptor-positive disease receive endocrine therapy. For the patients with hormone receptor-negative disease, I'd like to believe that capecitabine will have value. It may not be as great a value as more aggressive chemotherapy, however.

Evidence supporting that theory comes from Don Berry's analysis in *JAMA* evaluating patients with ER-negative, PR-negative disease treated on the CALGB trials. He reported that as you use more aggressive chemotherapy and taxanes and progress to dose-dense therapy, you observe more improved proportional reductions in the relapse rate among patients with ER-negative, PR-negative disease (Berry 2006).

So I'd like to believe that capecitabine would be helpful, but it wouldn't be as effective as a more modern, more aggressive regimen.

2.5

Ibandronate with or without Capecitabine in Elderly Patients with Early Breast Cancer (ICE)

Protocol IDs: GBG32, BIG 4-04, NCT00196859
Target Accrual: 1,500 (Open)

Eligibility

- Histologically confirmed unilateral or bilateral primary carcinoma of the breast
- Any nodal status
- Age ≥ 65 years
- ECOG PS ≤ 2
- Estimated life expectancy of at least five years

SOURCES: NCI Physician Data Query, July 2008; www.clinicaltrials.gov.

Tracks 10-11

DR LOVE: What is your treatment algorithm for the management of metastatic disease in the older patient, and does it change when the patient reaches age 70 or 80?

DR MUSS: I don't think so. I use a lot of capecitabine in the first-line setting. Capecitabine is an excellent choice to initiate chemotherapy in metastatic breast cancer, irrespective of age. It's well tolerated, though I start with a lower dose. I don't believe enough data exist to tell me the ideal dose to use. The package insert dose is too high.

Many of my patients say, "Dr Muss, I don't want any chemotherapy and I certainly don't want to get sick." I try to reassure them that an oral agent is available, that it's real chemotherapy, and I start it at a low dose. I can always escalate it later, but if the patient develops a terrible toxicity from the beginning, I've lost a good option.

DR LOVE: What about the issue of capecitabine versus a taxane alone or with bevacizumab in the first-line metastatic setting?

DR MUSS: In Kathy Miller's pivotal ECOG-E2100 trial evaluating paclitaxel

with or without bevacizumab, a meaningful improvement was observed in progression-free survival (Miller 2007). Without an overall survival benefit in a clean trial, this tells me that I can use kinder, gentler therapy with capecitabine up front without compromising the longevity of my patient.

I lean toward paclitaxel/bevacizumab for a patient with more extensive metastases, but I suspect that most of the patients we see today are minimally symptomatic, especially with physicians who still prefer numerous scans and follow-up studies. In that situation, you don't have to be highly aggressive, worrying about a tumor doubling and impairing your opportunity to treat with capecitabine.

DR LOVE: So for a patient with metastatic disease who has never received a taxane, you would administer capecitabine? At some point, if she experiences disease progression, will you then administer a taxane and bevacizumab?

DR MUSS: Yes, and I realize that the data don't exist to support me in the second-line setting, but I have done that.

DR LOVE: What are your thoughts on combining *nab* paclitaxel with bevacizumab?

DR MUSS: I believe that *nab* paclitaxel is an exciting drug. It has a different mechanism of action, but it's never been compared to weekly paclitaxel, only to docetaxel in Bill Gradishar's randomized Phase II trials (Gradishar 2007). I use paclitaxel, but if we see allergic reactions or other issues, I switch to *nab* paclitaxel.

I would love to see a randomized trial evaluating *nab* paclitaxel. The CALGB is launching a study in the metastatic setting in which all patients will receive bevacizumab and will then be randomly assigned to receive *nab* paclitaxel, paclitaxel or ixabepilone. We will learn a lot from that trial.

Track 15

DR LOVE: One of the adjuvant issues that's been debated with older patients or those with comorbidities is using trastuzumab alone, particularly for patients with comorbidities for whom you normally wouldn't consider chemotherapy. What do you think about that strategy?

DR MUSS: It would be great to have a clinical trial of trastuzumab versus not, especially for older patients, although I believe it would be hard to complete conceptually because if patients were healthy, they would receive chemotherapy and trastuzumab.

You'd be left with patients who were sicker and more frail, and then you'd have to randomly assign them. They'd have smaller tumors and lower event rates. Once we sat down and evaluated what kind of sample size we needed, such a trial would be difficult to conduct.

DR LOVE: Have you used trastuzumab without chemotherapy?

DR MUSS: No, I have not. A trial run by Dana-Farber, in which we're participating, is evaluating weekly paclitaxel and trastuzumab in the adjuvant setting. We know that paclitaxel/trastuzumab is an effective combination in the metastatic setting. Weekly paclitaxel has been a reasonably well-tolerated chemotherapy, irrespective of age. I believe it's a good design. It's a modest amount of chemotherapy — 12 cycles of weekly paclitaxel. Should you use that outside of a clinical trial? I would administer something like TC with trastuzumab as in the HERA trial if the patient were healthy enough.

Track 16

DR LOVE: How do you choose between lapatinib and trastuzumab or both in terms of anti-HER2 therapy of HER2-positive metastatic disease?

DR MUSS: If the patient has metastatic breast cancer, does not have CNS metastases and has never received trastuzumab, I use a trastuzumab-containing combination. I've used vinorelbine, which I believe is a user-friendly drug. It's a little myelosuppressing, but otherwise it's well tolerated. Or you can use paclitaxel. I don't know if a vast difference exists there.

If someone presented now with de novo brain metastases who had been on neither of the agents, quite honestly I'd probably pick lapatinib, and I might even consider something like capecitabine — which penetrates the CSF — along with it. ■

SELECT PUBLICATIONS

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Cameron D et al. **A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: Updated efficacy and biomarker analyses.** *Breast Cancer Res Treat* 2008;[Epub ahead of print]. **Abstract**

Crivellari D et al. **Breast cancer in the elderly.** *J Clin Oncol* 2007;25(14):1882-90. **Abstract**

Gradishar W et al. **Randomized comparison of weekly or every-3-week (q3w) *nab*-paclitaxel compared to q3w docetaxel as first-line therapy in patients (pts) with metastatic breast cancer (MBC).** *Proc ASCO* 2007;**Abstract 1032**.

Jones S et al. **Extended follow-up and analysis by age of the US Oncology adjuvant trial 9735: Docetaxel/cyclophosphamide is associated with an overall survival benefit compared to doxorubicin/cyclophosphamide and is well-tolerated in women 65 or older.** San Antonio Breast Cancer Symposium 2007;**Abstract 12**.

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

Miller K et al. **Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer.** *N Engl J Med* 2007;357(26):2666-76. **Abstract**

Muss HB et al. **Standard chemotherapy (CMF or AC) versus capecitabine in early-stage breast cancer (BC) patients aged 65 and older: Results of CALGB/CTSU 49907.** *Proc ASCO* 2008;**Abstract 507**.

Muss HB et al. **Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: The Cancer and Leukemia Group B Experience.** *J Clin Oncol* 2007;25(24):3699-704. **Abstract**

INTERVIEW

Matthew J Ellis, MB, BChir, PhD

Dr Ellis is Associate Professor of Medicine, Head of the Section of Medical Oncology and Director of the Breast Cancer Program at Washington University School of Medicine in St Louis, Missouri.

Tracks 1-17

Select Excerpts from the Interview

Track 1

DR LOVE: Can you comment on the new assay targeting intrinsic breast cancer subtypes, which you were involved in developing?

DR ELLIS: We've developed an assay based on 50 genes that generate the intrinsic subtypes — luminal A, luminal B, HER2-enriched and basal-like (Parker 2008). The fifth class, called normal-like, is not actually a tumor type.

Rather, it means that the sample is too tumor sparse to identify a subtype.

I believe that this assay will produce a gold standard for naming the intrinsic subtypes of breast cancer, which is important as we move forward and begin designing subtype-specific trials.

Tracks 2-3

DR ELLIS: Another area of my research is the issue of predicting benefit from endocrine therapy. The big conundrum with hormone receptor-positive disease is that some of these tumors are biologically hormone dependent while others are hormone independent. We haven't had a good way of sorting these two groups, so we evaluated what could be considered an in vivo estrogen dependence test simply based on the labeling index of the tumor before and after starting an aromatase inhibitor or tamoxifen.

Mitch Dowsett and I created a relapse score or relapse model that accurately identifies groups of patients who have approximately a 100 percent relapse-free survival at five to seven years. Their tumors are characterized by low stage and low labeling index after the start of endocrine therapy and, interestingly, the maintenance of estrogen receptor in the tumor. Losing estrogen receptor was found to be an independent bad prognostic factor.

Historically, we've been examining baseline tumors and then trying to predict benefit from endocrine therapy. However, I believe that we need to shift the paradigm and profile the tumor after two to four weeks of treatment. When we do that, we obtain a much better prognostic index because while the baseline sample will predict outcomes in the absence of therapy, what we want is to predict outcomes in the presence of endocrine therapy.

For example, any predictive multigene model that includes proliferation markers and estrogen-dependent genes should work much better to predict the outcomes of endocrine therapy in samples taken after starting treatment because those transcriptional signatures will be affected by therapy. Patients in whom the transcriptional signature for proliferation is switched off should fare better than those patients in whom it does not switch off.

When we used our assay in the neoadjuvant setting, we found exactly that. In patients whose tumors had a high-risk profile at baseline because they had a proliferation signature, if that signature was turned off, then those patients fared well in the long term. If the proliferation signature was not switched off by endocrine therapy, then those patients fared poorly and, in fact, those tumors were associated with ER loss at the end of the four months of neoadjuvant endocrine therapy (Ellis 2008).

Track 7

DR LOVE: What do you think about the data presented at ASCO by Pam Goodwin on vitamin D levels and cancer recurrence?

DR ELLIS: The Canadian Clinical Trials Group presented data at ASCO on vitamin D levels and their effect on breast cancer outcomes (Goodwin 2008; [3.1]). It's a little complicated, but the message was that patients with extreme vitamin D deficiencies seemed to have worse relapse-free survival rates. This is consistent with other data suggesting that a low vitamin D level may be associated with a higher breast cancer incidence.

I believe that we need to conduct more detailed studies, and a number of studies have already addressed diet, exercise and relapse-free survival. Women may be able to take several steps to improve their outcomes, such as being physically active, taking adequate vitamin D and maintaining a relatively low body mass index.

I measure the vitamin D level in every breast cancer patient I see, and if the result is in the osteomalacia range, I administer 50,000 units weekly for three to six months. It's frightening how much severe vitamin D deficiency one sees in a breast cancer population.

3.1 Association between Vitamin D Deficiency and Breast Cancer Outcomes

	Vitamin D level			
Endpoint	Deficient <50 nmol/L	Insufficient ≥50-72 nmol/L	Sufficient >72 nmol/L	*p*-value
Distant DFS				
Hazard ratio (95% CI)	1.94 (1.16-3.25)	1.37 (0.80-2.33)	1.00	0.02
Five-year	82%	85%	88%	NR
10-year	69%	79%	83%	NR
Overall survival				
Hazard ratio (95% CI)	1.73 (1.05-2.86)	1.01 (0.59-1.73)	1.00	0.02
Five-year	87%	93%	92%	NR
10-year	74%	85%	85%	NR

DFS = disease-free survival; CI = confidence interval; NR = not reported

SOURCE: Goodwin PJ et al. Presentation. ASCO 2008; **Abstract 511**.

Track 8

DR LOVE: What was your reaction to the ASCO data from Joyce O'Shaughnessy's trial evaluating lapatinib with or without trastuzumab (O'Shaughnessy 2008)?

DR ELLIS: In this modest-sized Phase III trial, patients with trastuzumab-resistant metastatic breast cancer were, upon disease progression, randomly assigned to lapatinib alone or the reintroduction of trastuzumab with lapatinib.

The data showed that the combination seemed relatively safe, and the number of patients with progression-free disease at six months increased from 13 percent with lapatinib alone to 28 percent with trastuzumab/lapatinib (O'Shaughnessy 2008; [3.2]).

That seems to suggest that in the resistance setting, continuing trastuzumab and adding lapatinib is a better strategy than stopping trastuzumab and replacing it with lapatinib.

While a case is beginning to be built for the combination of trastuzumab and lapatinib without chemotherapy, I certainly would not recommend that as standard at this point. We don't have enough data, and we need to confirm it.

3.2

Lapatinib (L) with or without Trastuzumab (T) for Heavily Pretreated Patients with Metastatic Breast Cancer Experiencing Disease Progression on Trastuzumab Therapy

Parameter	L (n = 145)	L + T (n = 146)	Odds ratio	*p*-value
Response rate[1] (95% CI)	6.9% (3.4, 12.3)	10.3% (5.9, 16.4)	1.5 (0.6, 3.9)	0.46
Clinical benefit rate[2] (95% CI)	12.4% (7.5, 18.9)	24.7% (17.9, 32.5)	2.2 (1.2, 4.5)	0.01

Parameter	L (n = 145)	L + T (n = 146)	Hazard ratio	*p*-value
Median progression-free survival (95% CI)	8.1 weeks NR	12.0 weeks NR	0.73 (0.57, 0.93)	0.0008
Median overall survival[3] (95% CI)	39.0 weeks NR	51.6 weeks NR	0.75 (0.53, 1.07)	0.106

[1] Confirmed complete responses (CR) + partial responses (PR)
[2] CR + PR + stable disease ≥ 6 months
[3] Intent-to-treat population
CI = confidence interval; NR = not reported
Odds ratio > 1, hazard ratio < 1 favors L + T

SOURCE: O'Shaughnessy J et al. *Proc ASCO* 2008;**Abstract 1015**.

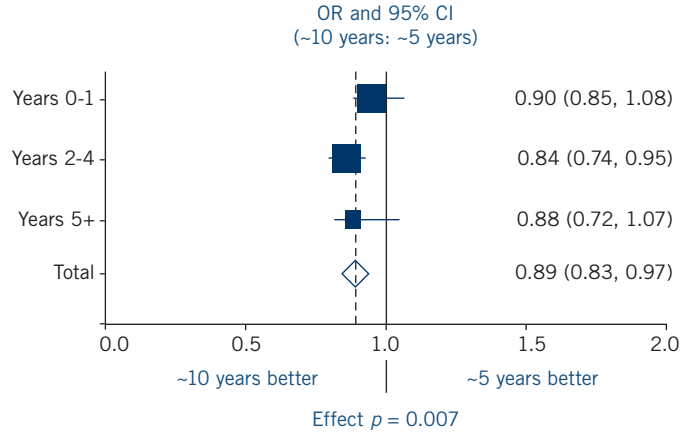
Tracks 12-13

DR LOVE: How do you feel about the data from the aTTom and ATLAS trials, both evaluating 10 versus five years of adjuvant tamoxifen?

DR ELLIS: With full acknowledgment that the effects seen are muted by the inclusion of patients with hormone receptor-negative disease and that compliance problems emerge with such long exposure to endocrine treatment, both trials provide evidence that a longer duration of tamoxifen — essentially beyond five years — is better than a shorter duration (Gray 2008; [3.3]).

3.3

Combined Data from ATLAS and aTTom: Effect of Extended Adjuvant Tamoxifen in ER-Positive or ER-Untested Breast Cancer According to Follow-Up Period



SOURCE: Gray RG et al. Presentation. ASCO 2008;**Abstract 513**.

DR LOVE: How do you approach this decision clinically when you see a patient who has completed five years of tamoxifen or an aromatase inhibitor?

DR ELLIS: I use a shamelessly risk-adapted approach. For patients at high risk, I recommend 10 years of endocrine therapy.

You may ask, where's the evidence for administering an aromatase inhibitor for 10 years? We don't have any data yet. We have evidence for administering 10 years of tamoxifen. Certainly, continued letrozole appears more effective after five years of adjuvant tamoxifen (Goss 2005) than 10 years of tamoxifen, even in the most optimistic scenarios in aTTom and ATLAS.

Although we don't have evidence to support administering 10 years of an aromatase inhibitor, they are more potent than tamoxifen and should, theoretically, provide even more benefit with longer durations.

For patients at lower risk, five years may be enough. Obviously, this becomes a long discussion with my patients after they've completed five years of endocrine therapy.

Track 15

DR LOVE: Can you describe your study of estrogen at high and low doses for metastatic breast cancer?

DR ELLIS: We've recently completed a multicenter study with 66 patients, evaluating 30 versus six milligrams of generic estradiol for patients who

experienced disease progression while receiving an aromatase inhibitor. In this study, if the patient benefits from estrogen therapy, she is switched back to the aromatase inhibitor she was receiving before the progression.

The study is designed to determine whether oscillating between an aromatase inhibitor and estrogen therapy will produce a prolonged clinical benefit, and some tumors do appear to respond in that way. We will be presenting the data at the annual San Antonio Breast Cancer Symposium in December of this year.

Essentially, we're seeing 10 to 15 percent actual responses — some quite dramatic — and approximately a 30 percent clinical benefit rate. Interestingly, the responses can be predicted by a PET flare.

We obtained a baseline PET image, and then 24 hours after treatment we examined the difference in glucose uptake. We found that the patients with a dramatic glucose uptake were the ones who went on to respond, so a biomarker for response does exist.

The 6-mg dose was as effective as and safer than the higher dose. We were careful to exclude patients with uncontrolled hypercalcemia and a history of thrombotic events or myocardial infarction.

In the trial, we saw no venous thrombotic events and found that the therapy was well tolerated. However, the flare reactions that you read about in textbooks are real.

Track 17

DR LOVE: What was your take on the ASCO data from the AVADO trial of docetaxel with or without bevacizumab as first-line therapy for patients with locally recurrent or metastatic breast cancer (Miles 2008)?

DR ELLIS: I am concerned because progression-free survival is a difficult and rather unstable endpoint, and in the ECOG-E2100 trial of paclitaxel and bevacizumab, I see a disconnect between an amazing effect on progression-free survival and almost no effect on overall survival (Miller 2007).

The differences between the two arms in the AVADO trial seem narrow (Miles 2008; [3.4]) — not nearly as impressive as the ECOG-E2100 data (Miller 2007) — which underscores my point. I do believe that bevacizumab/taxane is an active combination, but I'm concerned about how much benefit you obtain versus the cost.

I reserve bevacizumab for patients in visceral crisis because those patients need a combination with a high response rate. A number of combinations can be used, such as paclitaxel with vinorelbine or gemcitabine, but I prefer paclitaxel with bevacizumab because I believe it has less toxicity and the E2100 data suggest that it's somewhat better. ■

3.4

AVADO: A Phase III Study of Docetaxel versus Docetaxel/Bevacizumab at 7.5 mg/kg versus Docetaxel/Bevacizumab at 15 mg/kg as First-Line Therapy for Patients with Locally Recurrent or Metastatic Breast Cancer

Parameter	Docetaxel + placebo (n = 241)	Docetaxel + bevacizumab 7.5 mg/kg (n = 248)	Docetaxel + bevacizumab 15 mg/kg (n = 247)
Overall response rate *p*-value (vs control)	44% —	55% 0.0295	63% 0.0001
Median PFS (ITT) Hazard ratio (95% CI)	8.0 months —	8.7 months 0.79 (0.63-0.98)	8.8 months 0.72 (0.57-0.90)
Median overall survival Hazard ratio (95% CI)	Not reached —	Not reached 0.92 (0.62-1.37)	Not reached 0.68 (0.45-1.01)
One-year survival	73%	78%	83%

PFS = progression-free survival; ITT = intent-to-treat population; CI = confidence interval

SOURCE: Miles D et al. *Proc ASCO* 2008;**Abstract LBA1011**.

SELECT PUBLICATIONS

Ellis MJ et al. **A poor prognosis ER and HER2-negative, nonbasal, breast cancer subtype identified through postneoadjuvant endocrine therapy tumor profiling.** *Proc ASCO* 2008;**Abstract 502**.

Ellis MJ, Ma C. **Letrozole in the neoadjuvant setting: The P024 trial.** *Breast Cancer Res Treat* 2007;105(Suppl 1):33-43. **Abstract**

Gissel T et al. **Intake of vitamin D and risk of breast cancer — A meta-analysis.** *J Steroid Biochem Mol Biol* 2008;[Epub ahead of print]. **Abstract**

Goodwin PJ et al. **Frequency of vitamin D (Vit D) deficiency at breast cancer (BC) diagnosis and association with risk of distant recurrence and death in a prospective cohort study of T1-3, N0-1, M0 BC.** *Proc ASCO* 2008;**Abstract 511**.

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

Gray RG et al. **aTTom (adjuvant Tamoxifen — To offer more?): Randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6,934 women with estrogen receptor-positive (ER+) or ER untested breast cancer — Preliminary results.** *Proc ASCO* 2008;**Abstract 513**.

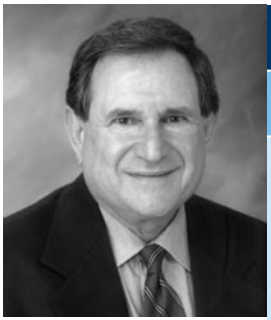
Ingraham BA et al. **Molecular basis of the potential of vitamin D to prevent cancer.** *Curr Med Res Opin* 2008;24(1):139-49. **Abstract**

Miles D et al. **Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO.** *Proc ASCO* 2008;**Abstract LBA1011**.

Miller K et al. **Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer.** *N Engl J Med* 2007;357(26):2666-76. **Abstract**

O'Shaughnessy J et al. **A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy.** *Proc ASCO* 2008;**Abstract 1015**.

Parker J et al. **A supervised risk predictor of breast cancer based on biological subtypes.** *Proc ASCO* 2008;**Abstract 11008**.



INTERVIEW

Charles L Vogel, MD

Dr Vogel is Senior Research Advisor for Breast Cancer at Aptium Oncology, practices at Boca Raton Community Hospital's Lynn Regional Cancer Center West Campus and is the Scientific Advisor for Cancer Research Network Inc in Boca Raton, Florida.

Tracks 1-14

Track 1 **Case discussion:** Continued treatment of a patient who received paclitaxel/trastuzumab for mBC on the trastuzumab pivotal trial in 1995

Track 2 Side effects and tolerability of lapatinib

Track 3 A patient with a response to lapatinib in brain metastases

Track 4 Treatment algorithm for patients experiencing disease progression on trastuzumab

Track 5 **Case discussion:** A woman with HER2-negative, hormone receptor-positive breast cancer with 25/36 positive nodes with metastases diagnosed eight years after initial breast cancer diagnosis

Track 6 Long-term management of hormone receptor-positive early breast cancer

Track 7 Clinical use of capecitabine with or without bevacizumab for mBC

Track 8 Preferential use of *nab* paclitaxel for taxane-containing regimens

Track 9 Utility of tumor markers in patients with mBC

Track 10 **Case discussion:** A patient with significant weight gain during treatment with paclitaxel/bevacizumab for mBC

Track 11 Efficacy and tolerability of ixabepilone

Track 12 High-dose estradiol for patients with hormone receptor-positive, heavily pretreated mBC

Track 13 **Case discussion:** Response to single-agent capecitabine in a woman with liver, bone and brain metastases

Track 14 Clinical use of bevacizumab for patients with brain metastases

(See Audio Program for Interviews with These Patients)

CASE 1: Ms G, a woman treated with multiple lines of trastuzumab-containing therapy for metastatic breast cancer during the past 13 years since enrollment on the trastuzumab pivotal trial in 1995

Tracks 1-2, 15-16

Tracks 1-3

DR VOGEL: This patient was diagnosed with hormone receptor-positive, HER2-positive early breast cancer in the early 1990s, for which she underwent bilateral mastectomies followed by adjuvant chemotherapy.

Approximately one year later, she developed extensive bony metastases and was enrolled on the pivotal trastuzumab trial (Slamon 2001).

After her disease progressed, she was enrolled on the extension trial and received cisplatin/trastuzumab. Subsequently she was treated with vinorelbine/trastuzumab, but her longest response to therapy was seven years while receiving toremifene and trastuzumab after she underwent an oophorectomy. She stayed in remission from 1998 to 2005.

DR LOVE: Obviously this is an unusual case. She has been treated for metastatic breast cancer for the past 13 years entirely on an outpatient basis, and she appears to be completely healthy. What has happened to her recently?

DR VOGEL: We decided to keep her on hormonal therapy for as long as possible, so after her disease progressed on toremifene she was treated with exemestane, then fulvestrant — all in combination with continued trastuzumab.

Most recently, in May 2007, we elected to continue trastuzumab and treat her with capecitabine/lapatinib. Her bone lesions have been stable for the past year, but she has suffered from a troublesome acneiform rash.

DR LOVE: What side effects have you observed with lapatinib?

DR VOGEL: We have seen some liver function test abnormalities, which is apparently a new finding, but they resolve when the drug is discontinued. Except for the current patient, rash is not usually a problem. Diarrhea has been a troubling complication for some of my patients, but we have not observed other significant issues.

Track 4

DR LOVE: This patient is an extreme example of continuing trastuzumab in combination with other therapies for the treatment of HER2-positive metastatic breast cancer. Do you have other patients like her, for whom trastuzumab was continued through multiple lines of therapy (4.1)?

DR VOGEL: I have several such patients. One patient with bone metastases has been treated for 10 years, and she refuses to come off treatment. Another patient has been treated with liver metastases for eight years.

DR LOVE: Do you have any patients who have experienced relapse after treatment with adjuvant trastuzumab? How do you determine whether to restart trastuzumab, use lapatinib or both?

DR VOGEL: I have four such patients. I govern my approach by the time to

relapse after cessation of trastuzumab. If the relapse occurs within one year, then I treat with lapatinib.

4.1

Continued Use of Trastuzumab After Progression on Prior Trastuzumab Therapy in HER2-Positive Metastatic Breast Cancer

"Whether to continue trastuzumab after objective evidence of disease progression or not is an important unanswered clinical question for women with metastatic disease. This question is also relevant for those who relapse after adjuvant trastuzumab-containing therapy. Unfortunately, there is little evidence to guide decision-making....

At least two randomized trials with no trastuzumab in the control arms were attempted but failed to accrue patients. In the absence of results from a randomized clinical trial, a central registry program that collects information longitudinally from a large number of patients with HER-2 positive breast cancer during the course of their disease was initiated (**RegistHER**, **www.registher.com**) to learn about the long term side effects and benefits of prolonged trastuzumab therapy."

SOURCE: Pusztai L, Esteva FJ. *Cancer Invest* 2006;24(2):187-91. **Abstract**

(Editor's note: For details of the study population, see Yardley DA et al. **registHER: Patient characteristics, treatment patterns, and preliminary outcomes in patients with HER2-positive (HER2+), hormone receptor-positive (HR+) metastatic breast cancer (MBC).** *Proc ASCO* 2007;**Abstract 21007**.)

CASE 2: Ms M, a woman with HER2-negative, hormone receptor-positive breast cancer, with 25/36 positive lymph nodes, that recurred with metastases eight years after diagnosis

Tracks 5-9, 20-23

Tracks 5, 7-9

DR VOGEL: This woman was 40 years old when she was diagnosed with breast cancer in 1996. She underwent a modified mastectomy and had 25 out of 36 positive nodes. She received adjuvant AC followed by docetaxel, comprehensive nodal and chest wall irradiation therapy and oophorectomy with tamoxifen, which she discontinued after three months solely due to hot flashes.

In 2004 she developed a painful recurrence in her bone and underwent hemipelvic radiation therapy. She was enrolled on a clinical trial with letrozole and also received the Theratope® vaccine.

Unfortunately, her disease progressed quickly, and she was enrolled on EFECT, on which she received exemestane. After seven months her disease progressed again and was treated with fulvestrant, but she developed liver metastases after two months.

DR LOVE: At the point when you felt this woman would not respond to hormonal therapy, you approached her about enrollment on the RIBBON 1 trial (4.2)?

DR VOGEL: Yes. She was still experiencing pain while on fulvestrant, and during a workup we were surprised to find liver metastases, so we felt it was probably better to treat her with chemotherapy.

I chose capecitabine for nearly all of my patients enrolled on RIBBON 1. It meshes with my basic philosophy of care to use the least-toxic chemotherapy possible. She received capecitabine with either bevacizumab or placebo. She's had the longest response of my patients on RIBBON 1 receiving capecitabine, and she continues on the regimen now approaching two years.

Patients enrolled on RIBBON 1, after their disease progressed on initial therapy such as capecitabine with or without bevacizumab, had the option after that of receiving open-label bevacizumab with chemotherapy. I chose *nab* paclitaxel as my drug of choice for the postprogression phase of the study. Most of these patients have responded to *nab* paclitaxel with open-label bevacizumab and have fared nicely on that regimen.

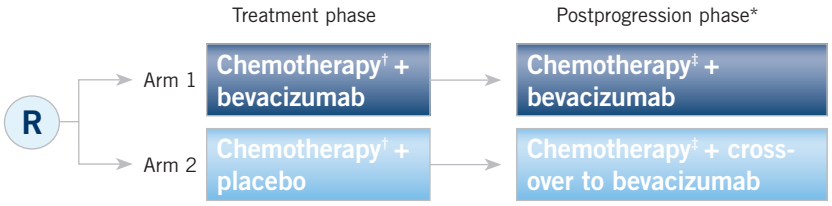
I'm more impressed with that regimen than I am with capecitabine/bevacizumab. I'm aware of the XCaliBr data, in which patients with ER-positive disease seemed to fare better on capecitabine and bevacizumab than those with ER-negative disease (Sledge 2007).

DR LOVE: What is your opinion about *nab* paclitaxel with bevacizumab compared to paclitaxel with bevacizumab?

DR VOGEL: Wherever possible, I use *nab* paclitaxel rather than paclitaxel. I believe it's possible that *nab* paclitaxel may represent a superior way of admin-

4.2

RIBBON 1: A Phase III Trial Evaluating the Safety and Efficacy of Bevacizumab in Combination with Chemotherapy in the First-Line Chemotherapy Setting for Metastatic Breast Cancer



Bevacizumab = 15 mg/kg q3wk (or 10 mg/kg q2wk during postprogression phase)

* Optional, per investigator's discretion
† Anthracycline-based combination chemotherapy, q3wk taxane (docetaxel or *nab* paclitaxel) or capecitabine, as determined by the investigator before randomization
‡ Chemotherapy per investigator's discretion

SOURCES: NCI Physician Data Query, July 2008.
Genentech BioOncology, Protocol Schema, October 2006.
www.cancer.gov.

istering paclitaxel, and you avoid the longer infusions associated with paclitaxel. Because of all the premedications required for paclitaxel, I believe *nab* paclitaxel is probably better tolerated.

DR LOVE: What do you think about the Phase II randomized trial results presented by Dr Gradishar, suggesting that *nab* paclitaxel was more effective than docetaxel (Gradishar 2007; [4.3])?

DR VOGEL: That trial is being repeated here in the United States. It would certainly be interesting if it showed the same results. It is a Phase III randomized trial, as I understand it, and a trial that is truly needed. The science is compelling, and the preliminary data are interesting. I wouldn't be surprised if *nab* paclitaxel proves superior to paclitaxel, and I wouldn't be surprised if it were superior to docetaxel, either.

4.3

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

	Nab paclitaxel 300 mg/m² q3wk (n = 76)	*Nab* paclitaxel 100 mg/m² weekly 3 out of 4 weeks (n = 76)	*Nab* paclitaxel 150 mg/m² weekly 3 out of 4 weeks (n = 74)	Docetaxel 100 mg/m² q3wk (n = 74)
Objective response rate by investigator assessment	43%	62%*	70%†	38%
Grade III/IV neutropenia	44%	25%	43%	94%
Grade III/IV peripheral neuropathy	17%	9%	16%	11%
Grade III/IV fatigue	4%	0%	3%	19%

* *p*-value = 0.002 versus docetaxel arm; † *p*-value = 0.003 versus docetaxel arm

SOURCE: Gradishar WJ et al. *Proc ASCO* 2007;**Abstract 1032**.

CASE 3: Ms T, a woman with hormone receptor-positive, HER2-negative bone, liver and nodal metastases who was treated with paclitaxel and bevacizumab but experienced a 35-lb weight gain

Tracks 10, 24-28

Track 10

DR VOGEL: This patient had advanced disease, with bone, liver and nodal metastases. She was treated with paclitaxel/bevacizumab and went into a nice remission.

She developed fatigue, neuropathy and weight gain. She gained 35 pounds after starting therapy.

I believed the weight gain was probably a side effect of the steroid administered with paclitaxel. We decided she needed a break, so we put her back on hormonal therapy but were unable to maintain the remission, although she lost the weight she had gained previously.

When we decided to reinitiate chemotherapy and bevacizumab, I administered *nab* paclitaxel, which she has tolerated much better (4.4) and without weight gain.

4.4

Nab Paclitaxel and Bevacizumab as First-Line Chemotherapy for Metastatic Breast Cancer

Background: In a clinical trial of 722 patients (pts) with locally recurrent metastatic breast cancer (MBC) solvent-based paclitaxel 90 mg/m^2 was administered intravenously (IV) over 1 hr weekly for 3 weeks followed by a week of rest (q3/4w) alone or in combination with bevacizumab 10 mg/kg every 2 weeks (q2w) (Miller et al, ASCO 2005). As compared with single agent, the combination had a greater median progression-free survival (PFS; 11.4 vs 6.11, $p < 0.0001$) and overall response rate (ORR; 30% vs 14%, $p < 0.0001$).

Methods: In this multicenter, open-label study in the US Oncology Research Network, HER2-negative pts with MBC, receiving first line chemotherapy were given weekly *nab*-paclitaxel 125 mg/m^2 IV infused over 30 minutes on days 1, 8, and 15, and bevacizumab 10 mg/kg on days 1 and 15 of a 28-day cycle.

Results: The confirmed ORR was 30% (8/27 pts with a partial response). Stable disease >16 wks was 22% (6/27). The median PFS was 9.2 months (95% confidence interval: 5.3 - >16.1). Grade 3, 4 hematologic adverse events were neutropenia (30%, 16%) and anemia (8%, 3%). The most common nonhematologic grade 3, 4 adverse event was sensory neuropathy (10%, 2%).

SOURCE: Danso MA et al. *Proc ASCO* 2008;**Abstract 1075**.

CASE 4: Ms J, a woman with hormone receptor-positive, HER2-negative breast cancer with bone, liver and brain metastases

Tracks 13-14, 29-31

Tracks 12-14

DR VOGEL: This patient is a quiet, soft-spoken nurse who was diagnosed with de novo Stage IV disease in 2003, and she received sequential hormonal therapy for several years with letrozole/goserelin, fulvestrant/goserelin and exemestane/goserelin.

She developed liver and bone metastases and was treated on a clinical trial evaluating docetaxel with capecitabine. Her disease showed a good response, but she experienced toxicity from the combination.

Then she received tamoxifen with goserelin for a year and a half. When her disease progressed in May 2007, she received high-dose estrogen with

goserelin, but unfortunately she did not respond.

So we were completing a workup to start her on the RIBBON 2 trial, which is chemotherapy of a number of different types with or without bevacizumab in the second-line chemotherapy setting. If I intend to treat a patient with bevacizumab, it's my policy to ensure that brain metastases are not present. Lo and behold, she had relatively small, asymptomatic brain lesions, so she was ineligible for that trial.

Her tumor did not progress on docetaxel/capecitabine, so we decided to treat with capecitabine. The question was, what do we do with the asymptomatic brain metastases?

I toyed with the idea of treating her with the gamma knife but decided that because these lesions were not bothering her, we would simply observe her on capecitabine alone and would not treat her with radiation therapy of any sort.

The precedent for this approach came from an old study by Dutzu Rosner in the 1980s, in which he used CMF/VP for patients with brain metastases who had not undergone radiation therapy (Rosner 1983, 1986; [4.5]). He demonstrated a definite response rate, so it appears that the blood-brain barrier may not necessarily be intact in patients with brain metastases.

So we treated her with capecitabine and monitored her brain closely. Her first MRI of the brain revealed disappearance of one of the nodules and stability of another.

She continues to be asymptomatic, her liver lesions are improving and her tumor markers are declining on single-agent capecitabine for bone, liver and brain metastases. She has no side effects and is responding beautifully. ■

4.5

"Chemotherapy Induces Regression of Brain Metastases in Breast Carcinoma"*

"One hundred consecutive patients with symptomatic brain metastases documented by radionuclide and/or computerized tomography scan were treated with systemic chemotherapy. Fifty of 100 patients demonstrated an objective response of brain metastases which was similar for extracranial metastases. There were 10 complete responders (CR), 40 partial responders (PR), 9 stable, and 41 nonresponders. Median duration of remission was 10+ months for CR and 7 months for PR (range, 2-72 months).

The median survival for CR and PR was 39.5 months and 10.5 months, respectively, in contrast with nonresponder patients who had a median survival of 1.5 months. Thirty-one percent of all treated patients survived more than 12 months. These findings suggest that the chemotherapeutic agents used penetrate the blood-brain barrier inducing regression of brain metastases. This approach offers a significant benefit by simultaneously controlling extracranial disease, improving the response and prolonging survival."

SOURCE: * Rosner D et al. *Cancer* 1986;58(4):832-9. **Abstract**

SELECT PUBLICATIONS

Akerley WL et al. **Acceptable safety of bevacizumab therapy in patients with brain metastases due to non-small cell lung cancer.** *Proc ASCO* 2008;**Abstract 8043**.

Archer V et al. **Risk of symptomatic central nervous system (CNS) progression and secondary hemorrhage in patients with non-squamous non-small cell lung cancer (NSCLC) receiving bevacizumab (BV)-based first-line therapy.** *Proc ASCO* 2008;**Abstract 8114**.

Gradishar WJ et al. **Randomized comparison of weekly or every-3-week (q3w) *nab*-paclitaxel compared to q3w docetaxel as first-line therapy in patients (pts) with metastatic breast cancer (MBC).** *Proc ASCO* 2007;**Abstract 1032**.

Labidi S et al. **Bevacizumab and paclitaxel for breast cancer patients with CNS metastases.** *Proc ASCO* 2008;**Abstract 12009**.

Mayer TM et al. **A single institution's experience with bevacizumab and cytotoxic chemotherapy in progressive malignant glioma.** *Proc ASCO* 2008;**Abstract 13010**.

Miller K et al. **Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer.** *N Engl J Med* 2007;357(26):2666-76. **Abstract**

Narayana A et al. **Bevacizumab therapy in recurrent high grade glioma: Impact on local control and survival.** *Proc ASCO* 2008;**Abstract 13000**.

Olver IN. **Trastuzumab as the lead monoclonal antibody in advanced breast cancer: Choosing which patient and when.** *Future Oncol* 2008;4(1):125-31. **Abstract**

Rich JN et al. **Phase II study of bevacizumab and etoposide in patients with recurrent malignant glioma.** *Proc ASCO* 2008;**Abstract 2022**.

Rosner D et al. **Chemotherapy induces regression of brain metastases in breast carcinoma.** *Cancer* 1986;58(4):832-9. **Abstract**

Rosner D et al. **Management of brain metastases from breast cancer by combination chemotherapy.** *J Neurooncol* 1983;1(2):131-7. **Abstract**

Saif MW et al. **Capecitabine: An overview of the side effects and their management.** *Anticancer Drugs* 2008;19(5):447-64. **Abstract**

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

Sledge G et al. **Safety and efficacy of capecitabine (C) plus bevacizumab (B) as first-line therapy in metastatic breast cancer.** *Proc ASCO* 2007;**Abstract 1013**.

Traina TA et al. **Phase I study of a novel capecitabine schedule based on the Norton-Simon mathematical model in patients with metastatic breast cancer.** *J Clin Oncol* 2008;26(11):1797-802. **Abstract**

Vogel CL, Franco SX. **Clinical experience with trastuzumab (Herceptin).** *Breast J* 2003;9(6):452-62. **Abstract**

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26. **Abstract**

Vredenburgh JJ et al. **Bevacizumab plus irinotecan in recurrent glioblastoma multiforme.** *J Clin Oncol* 2007;25(30):4722-9. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Patients in the ABCSG-12 trial received adjuvant chemotherapy.**
   a. True
   b. False
2. **In ABCSG-12, goserelin was administered on which schedule?**
   a. Once per week
   b. Once per month
   c. Once every three months
   d. Once every six months
3. **According to findings from ABCSG-12, bisphosphonate therapy appears to provide which of the following benefits for premenopausal patients?**
   a. Reduction in contralateral breast cancer
   b. Reduction in locoregional recurrence
   c. Reduction in distant nonbone metastases
   d. All of the above
4. **Jones and colleagues' US Oncology Adjuvant Trial 9735, evaluating docetaxel/cyclophosphamide (TC) versus doxorubicin/cyclophosphamide (AC), reported similar proportional benefits among elderly patients treated with TC compared to younger patients.**
   a. True
   b. False
5. **Data from the randomized Phase III CALGB-49907 trial for elderly patients treated with standard chemotherapy of CMF or AC versus _____ revealed a highly significant benefit in both relapse-free and overall survival for patients treated with standard chemotherapy.**
   a. Epirubicin
   b. Capecitabine
   c. Bevacizumab
6. **The ongoing ICE trial is evaluating _____ with or without capecitabine for elderly patients with early breast cancer.**
   a. Bevacizumab
   b. Epirubicin
   c. Ibandronate
7. **Data presented by Goodwin and colleagues revealed that women with vitamin D deficiency at diagnosis of breast cancer had a worse prognosis than those without vitamin D deficiency.**
   a. True
   b. False
8. **In a randomized study reported by O'Shaughnessy and colleagues, the combination of lapatinib and trastuzumab resulted in improved progression-free survival compared to lapatinib alone for heavily pretreated patients with HER2-positive metastatic breast cancer progressing on trastuzumab.**
   a. True
   b. False
9. **Preliminary findings from the ATLAS and aTTom trials, comparing five versus 10 years of adjuvant tamoxifen, provide evidence that a _____ duration of therapy is more beneficial to patients.**
   a. Longer
   b. Shorter
10. **In the AVADO trial, docetaxel was compared to _____ as first-line therapy for patients with locally recurrent or metastatic breast cancer.**
    a. Docetaxel with bevacizumab at 7.5 mg/kg
    b. Docetaxel with bevacizumab at 15 mg/kg
    c. Both a and b
11. **The RIBBON 1 trial allowed the investigator's choice of chemotherapy to be combined with _____.**
    a. Ixabepilone
    b. Bevacizumab
    c. Trastuzumab
    d. Lapatinib
12. **In a randomized Phase II trial, weekly *nab* paclitaxel resulted in a significantly higher objective response rate compared to docetaxel at 100 mg/m^2 administered every three weeks as first-line therapy for metastatic breast cancer.**
    a. True
    b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 4, 2008

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Antitumor effects of zoledronic acid in premenopausal patients with hormone receptor-positive breast cancer 4 3 2 1
- Adjuvant docetaxel/cyclophosphamide in the elderly 4 3 2 1
- Trastuzumab, lapatinib or the combination in HER2-positive mBC 4 3 2 1
- Data with capecitabine, docetaxel or *nab* paclitaxel in combination with bevacizumab for mBC 4 3 2 1
- Long-term natural history of hormone receptor-positive breast cancer and extended adjuvant hormonal therapy 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Antitumor effects of zoledronic acid in premenopausal patients with hormone receptor-positive breast cancer 4 3 2 1
- Adjuvant docetaxel/cyclophosphamide in the elderly 4 3 2 1
- Trastuzumab, lapatinib or the combination in HER2-positive mBC 4 3 2 1
- Data with capecitabine, docetaxel or *nab* paclitaxel in combination with bevacizumab for mBC 4 3 2 1
- Long-term natural history of hormone receptor-positive breast cancer and extended adjuvant hormonal therapy 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: . . . . . .

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: . . . . . .

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: . . . . . .

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will be able to:

- Review the biologic subtypes of breast cancer, and determine how disease phenotype impacts patient prognosis and treatment . . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based adjuvant treatment algorithm for patients with localized breast cancer, addressing the individualized selection of chemotherapy and the optimal schedule and duration of endocrine therapy . . . . . 4 3 2 1 N/M N/A
- Discuss the adjunctive role of oral and intravenous bisphosphonates in the management of hormone receptor-positive early breast cancer, and identify patients who may benefit from this course of therapy . . . . . 4 3 2 1 N/M N/A
- Recognize the unique clinical challenges that accompany the care of elderly breast cancer patients, and recommend treatment strategies that optimize clinical benefit and minimize toxicity . . . . . 4 3 2 1 N/M N/A
- Explain the benefits and risks of HER2-directed therapy for patients with early and advanced breast cancer, and discuss how combination treatment regimens may overcome the development of resistant disease . . . . . 4 3 2 1 N/M N/A
- Review the role of VEGF inhibitors in the first-line management of metastatic breast cancer, and discuss their safety and efficacy when combined with evidence-based chemotherapeutic partners and in patients with existing brain metastases . . . . . 4 3 2 1 N/M N/A
- Implement a therapeutic algorithm for the sequential use of combination and/or single-agent chemotherapy that enables multiple lines of treatment for patients with metastatic breast cancer . . . . . 4 3 2 1 N/M N/A
- Describe the patient perspective on living with breast cancer, and use this insight to deliver comprehensive and compassionate oncology care . . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with breast cancer about the availability of ongoing clinical trial participation . . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

. . . . . .

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

.....

May we include you in future assessments to evaluate the effectiveness of this activity?

☐ Yes ☐ No

PART TWO — Please tell us about the faculty for this educational activity

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

Editor	Knowledge of subject matter	Effectiveness as an educator
Neil Love, MD	4 3 2 1	4 3 2 1
Faculty	**Knowledge of subject matter**	**Effectiveness as an educator**
Matthew J Ellis, MB, BChir, PhD	4 3 2 1	4 3 2 1
Michael Gnant, MD	4 3 2 1	4 3 2 1
Hyman B Muss, MD	4 3 2 1	4 3 2 1
Charles L Vogel, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:

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

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

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

City, State, Zip: .....

Telephone: ..... Fax: .....

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Research To Practice designates this educational activity for a maximum of 4 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

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

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BCU408

Breast Cancer® UPDATE

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

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