Trends-in-Medicine

December 2005

by Lynne Peterson and Edward Susman

SUMMARY

Sources were very excited about **Glaxo-SmithKline's Tykerb** (lapatinib) not only for Herceptin failures but also eventually in lieu of or combined with Herceptin. ♦ The E-2100 trial showed **Genentech's Avastin** significantly improves progression-free survival in metastatic breast cancer, but doctors were not "wowed" with the data. ♦ Use of **Genentech's Herceptin** is ***not*** increasing in the adjuvant setting – because doctors are already using it there, not because of cardiac toxicity concerns. The BCIRG-006 trial did not convince most U.S. doctors to stop prescribing Herceptin to Adriamycin patients, and a Finnish trial has not yet convinced doctors to shorten the duration of Herceptin treatment from 52 to 9 weeks. ♦ Use of **American Pharmaceutical Partners' Abraxane** is increasing slowly, due to cost and side effects, particularly neurotoxicity. ♦ Use of gene array tests will not increase significantly until there is additional validation. ♦ Tomosynthesis may cause a paradigm shift in mammography within two to five years.

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

SAN ANTONIO BREAST CANCER SYMPOSIUM (SABCS)

San Antonio, TX
December 7-11, 2005

Most of the information presented at this year's SABCS meeting confirmed what oncologists are already doing rather than leading to major changes in clinical practice. Breast cancer is the third leading cause of death for American women, and the leading cause of death in women age 40-55. In the U.S., more than 200,000 new cases of invasive breast cancer and more than 50,000 new cases of in situ breast cancer are diagnosed each year, and more than 40,000 women die from breast cancer annually.

AMERICAN PHARMACEUTICAL PARTNERS' Abraxane (nanoparticle paclitaxel)

Use of Abraxane is increasing, but very slowly. On average, doctors estimated they are using Abraxane for fewer than 5% of their metastatic breast cancer (MBC) patients, with paclitaxel (Bristol-Myers Squibb's Taxol or generic paclitaxel) used for 67% and Sanofi-Aventis's Taxotere (docetaxel) for ~33%. Oncologists who have experience with Abraxane from clinical trials are using it for up to 50% or more of their MBC patients, but other sources reported that problems with the Abraxane cost and side effects, particularly neurotoxicity, are limiting their use. Among the comments on Abraxane were:

- *Texas #1:* "(Abraxane) didn't get a very favorable approval – second line. We use it in trials…and our experience has been good. Use will increase. The company is a Mom & Pop, not very sophisticated."
- *Missouri:* "We generally are not using it because of the cost. So far, I'm not sure there is a real advantage to justify the added cost."
- *Massachusetts:* "Abraxane is not on our formulary, so I only use it in select patients."
- *New England:* "One of my colleagues has tried it, but there is increased neurotoxicity."
- *Vermont:* "Our group has used it, but there is a fair amount of toxicity, and the cytopenias are pretty severe."
- *Texas #2:* "All the data we have right now are safety data. The only place I would consider Abraxane at this time is for patients with a severe allergic reaction to the cremaphor…There are anecdotal reports you can give Abraxane safely to those patients. That is the only time I would do that."
- *Washington:* "The only reason not to use Abraxane is cost. That is truly the only negative."

Doctors said their preference for Taxol over Taxotere is due mostly to the cheaper cost of Taxol, but Taxotere side effects also are a factor for some doctors. A New

England oncologist said, "The nail side effects with Taxotere are a real problem, a really big issue."

A poster by Northwestern University researchers looked at the cost effectiveness of Abraxane and docetaxel and determined that Abraxane is more cost effective in MBC and more efficacious (in terms of ORR).

Cost-effectiveness of Abraxane

Measurement	Abraxane in CA-012 trial	Docetaxel in TAX-311 trial
Total cost	$28,852	$39,552
ORR	33%	32%
Cost per responder	$87,429	$123,601
Median TTP	5.3 months	5.7 months
Cost per PFS month	$5,444	$6,939

AstraZeneca's Iressa (gefitinib)

Dr. Richard Finn of UCLA reported on a molecular study which suggested that Iressa may be effective in a subgroup of breast cancer patients, those who are ER-positive/PR-negative. Dr. Finn also suggested that the platform he used to make this finding may be useful as a way to develop other targeted agents. He added, "It doesn't take long or cost a lot."

A 66-patient Australian study found monotherapy with Iressa (500 mg/day) produced no response in MBC. In fact, the study had planned to enroll 90 patients but was stopped early because of lack of response. Based on this study, a researcher said her group would not, therefore, do a study in ER-positive/PR-negative patients, but she said that other groups may do that study.

Other studies suggested there is a hint of activity with Iressa, but the problem is identifying the patients who respond. An expert is concerned that AstraZeneca will abandon Iressa before the subgroup in which it works is identified.

Bristol-Myers Squibb's ixabepilone (epothilone-B)

Ixabepilone is a an epothilone analog, and it appears to be the farthest along in this new class of anti-neoplastic agents. It is in Phase III trials in MBC and Phase I/II for other cancers. Other epothilones include:

- Novartis's patupilone.
- Roche/KOS Pharmaceuticals' KOS-862.
- Schering-Plough's ZK-EPO – development halted.
- Bristol-Myers Squibb's BMS-310705 – development on hold.

Studies presented at SABCS showed ixabepilone may be a useful neoadjuvant therapy for patients with primary breast cancer, with a manageable safety profile consistent with taxanes. The 40 mg/m^2 dose weekly is being tested in a Phase III trial, which a source said is accruing rapidly. A source said, "In breast cancer, we are running out of chemotherapy agents for patients with advanced disease. We are using anthracycline and Taxol early. I think this would be used when patients fail ACTH, and ixabepilone could move forward."

At a Bristol-Myers Squibb-sponsored dinner, Dr. Sandra Swain of the Uniformed Services University of the Health Sciences in Bethesda MD argued that epothilones are less likely to become victims of multi-drug resistance than paclitaxel. She said ixabepilone is very active in breast cancer, does not require steroid pre-medication, has minimal hypertensive and gastrointestinal side effects, but causes peripheral neuropathy in ~3%-5% of patients. She reported that combination studies using ixabepilone and cytotoxic drugs are in progress.

Bristol-Myers Squibb also is working on a gene analysis to predict responders to ixabepilone. Dr. José Baselga of Vall d'Hebron University Hospital in Barcelona, Spain, presented the results of a Phase II trial which found that ER is a predictive marker for treatment response to ixabepilone, demonstrating:

- A two-fold increase in positive predictive value, with 92% negative predictive value.
- Multi-gene models may be superior to ER gene expression.
- ER, measured by immunohistochemistry, is not an adequate predictor of response to ixabepilone.

Genentech's Avastin (bevacizumab)

Genentech plans to submit Avastin (a humanized monoclonal anti-VEGF antibody) to the FDA for approval in breast cancer in 1H2006, based on the progression-free survival primary endpoint in the E-2100 trial. Updated results from that Phase III trial in locally recurrent or metastatic breast cancer (without brain mets) were presented at SABCS, and reactions were mixed.

Some doctors were convinced that Avastin has benefits in first-line MBC, but the reaction of others was more muted. Many oncologists did not appear convinced that Avastin added much of a punch to treatment with other cytotoxic drugs. Dr. Julie Gralow of the University of Washington, one of the study co-authors, said, "There is a 5.5 month improvement in PFS, and that is significant, with minimal toxicity. I'm already getting this approved (for reimbursement) based on this data. The magnitude of the benefit is very, very good…I think the angiogenesis inhibitors work better first line. Virtually all the adjuvant and neoadjuvant trials are now looking at incorporating Avastin."

E-2100 was a randomized, 680-patient trial powered to show a 33% improvement in PFS (8 months instead of 6 months), and Avastin showed much more than that. However, there was no

statistically significant difference in overall survival or quality of life. So, the questions for the FDA are (1) whether any "clinical benefit" has been shown, and (2) if not, is the improvement in PFS sufficient for approval?

24-Month Results of E-2100 Trial

Measurement	Paclitaxel n=339	Avastin+paclitaxel n=341	p-value
Primary endpoint: PFS	6.11 months	11.4 months	<.0001 (HR 0.51)
ORR	13.8%	29.9%	<.0001
Overall survival	25.2 months	28.4 months	0.12 (HR 0.84)
Hypertension (Grade 3/4)	0	<16%	<.0001

Doctors not involved in the E-2100 trial were divided as to the impact of the trial, especially in view of the cost of Avastin therapy and reimbursement issues. Among the comments were:

- "I haven't used Avastin yet, but I think the data are convincing, and I will use it for more people immediately – patients with very aggressive first-line MBC. Reimbursement is not an issue…The label could be hard (to get), but doctors will use it anyway."
- *California:* "I haven't used Avastin yet. I might consider it for a few select patients, but I haven't found any that were appropriate yet."
- *Texas:* "I'm concerned with the cost and with reimbursement. I can't get it reimbursed for breast cancer, only lung or colon cancer. If I used it, it would be in first-line MBC; it doesn't work well in last-line…I don't think there will be a Compendia listing for some time, so there won't be reimbursement, though some upper class women will pay for it…The people I've talked to who have used it all say they see a signal, responses, so it is active…But the FDA will require more than PFS for approval."
- *Kansas:* "We're not using Avastin, and we have no plans to start because of the cost and lack of reimbursement. I'm not impressed with the results. There were no 'wow' data. First line is only where it works, and I know Taxotere has a survival benefit in first line."
- *Massachusetts:* "We used Avastin in studies, so we are comfortable with it. We are using it similar to how it was studied – first line in MBC with Taxol. The data were convincing. I saw some incredible responses in the trial, and that tends to sway you."
- *Vermont:* "We discussed it and came up with a policy to use it as in the trials – first-line MBC, but not all first-line MBC patients. Avastin is expensive, and it has a lot of side effects. There is some efficacy, but it is only reasonable for a small subset of patients, though we haven't figured out which patients yet. We need to be careful before implementing it broadly."
- *New England:* "We use Avastin, and it is reimbursed, but we are very careful about which patients get it."
- *Michigan:* "Herceptin annually costs about $106,000 with echo, and $98,000 without echo. Avastin makes Herceptin look cheap."

Currently there are no surrogate markers to measure the effectiveness of anti-angiogenic therapy or to identify patients who might benefit from targeted therapy. However, circulating endothelial cells (CECs) are a potential marker of response to anti-angiogenic therapy. In preclinical data, CECs have correlated with tumor volume and prognosis, and they correlated with response to metronomic chemotherapy, leading a speaker to suggest they may prove to be a non-invasive serum marker for Avastin. In a study in MBC, the change in CECs from Week 0 to Week 3 surprised researchers, predicting PFS (p=0.01). Combining CEC and circulating tumor cell (CTC) analysis is also being considered. *(See Veridex on page 9)*.

GENENTECH'S Herceptin (trastuzumab)

Overall, doctors at this meeting said use of Herceptin is ***not*** increasing since they already are using it in the adjuvant setting, though some experts said there may be some hold-outs in the community setting who are not maximizing Herceptin use yet.

Cardiac toxicity with Herceptin is a concern, but doctors said that is not really limiting use. Doctors are using Herceptin for high risk lymph node negative (LNN) patients as well as node positive patients, but they are avoiding use of Herceptin in patients with low ejection fraction or cardiac problems, but they estimated that this is fewer than 5% of their patients.

NCCTG did an exploratory analysis of the randomized Phase III N-9831 trial, looking at clinical characteristics that might predict cardiac toxicity with adjuvant administration of Herceptin. Among the findings that researchers reported were:

- Adjuvant Herceptin after anthracycline-based chemotherapy results in a three-year cumulative incidence rate of ~2.5%-3.5% of significant clinical cardiac events.
- Cardiac function patients who developed CHF generally improved following medical treatment.
- There is a trend toward increased risk of cardiac toxicity with increased age.
- There does not appear to be a correlation between XRT and the risk of cardiac toxicity.
- ~15% of patients who took Herceptin and paclitaxel concomitantly and who had a satisfactory post-anthracycline cardiac evaluation had to discontinue Herceptin due to symptomatic or asymptomatic cardiac adverse events.

The BCIRG-006 trial was probably ***the*** major study presented at SABCS. It found that Herceptin, when added to two different treatment regimens, dramatically reduced the chances that a woman would have a recurrence of her breast cancer. BCIRG-006 looked at 1,074 women with early-stage, HER2+ breast cancer. It was a 23-month, randomized trial comparing three different regimens:

- ACT – Pfizer's Adriamycin (doxorubicin), carboplatin, and Taxotere.
- ACTH – ACT+Herceptin.
- TCH –Taxotere, carboplatin, and Herceptin.

23-Month Results of BCIRG-006 Trial

Measurement	ACT	ACTH	TCH
No recurrence	73%	84%	80%
CHF side effect	3 patients	17 patients	4 patients
Deaths	147 patients	77 patients	98 patients (Nss vs. ACTH)

Once again cardiac toxicity was reported with the combination of Herceptin and an anthracycline. The principal investigator of BCIRG-006, Dr. Dennis Slamon of UCLA's Jonsson Comprehensive Cancer Center, said, "This phenomenon is real…And it is long-lasting." However, Dr. Slamon said he will continue to give Herceptin to patients on Adriamycin, "Despite the indication of this problem, I would still be inclined to treat my breast cancer patients with both regimens and Herceptin."

Observers thought that Dr. Slamon's emphasis on the cardiac side effects with ACTH regimen might have been a "Vioxx reaction," suggesting that the controversy over the cardiac side effects of Merck's arthritis drug, Vioxx (rofecoxib), is leading other doctors to emphasize even small risks with other drugs to avoid any future suggestion that there was a concealment of data. Dr. William Gradishar of Northwestern said he believes the CHF can be managed if it occurs, and he is concerned that a non-anthracycline regimen may prove to be inferior when the data matures.

Most U.S. doctors did not expect the BCIRG-006 trial to change their clinical practice, and they plan to continue to prescribe ACTH rather than TCH. However, the trial gives them more comfort in withholding Adriamycin safely in patients who develop a problem on ACTH or in whom it is contraindicated for some reason. Comments included:

- *California #1:* "It supports the ASCO studies showing Herceptin in the adjuvant setting has significant activity, that a non-anthracycline regimen has activity with Herceptin. Essentially, TCH is equivalent to ACTH, so far."
- *Texas:* "Progression-free survival is usually associated with improved symptoms, so with a longer period of time, patients should do better on Avastin. And psychological distress is important. Quality of life scores are very inaccurate. The FDA review should be interesting, but I think it will be approved…Because of this, cardiac patients or low LVEF (but still normal) will avoid anthracycline, but that is ≤5% of patients over age 50."
- *Canada:* "BCIRG-006 won't change my practice. The standard is still ACTH, with Herceptin for one year."
- *California #2:* "It won't change anything for the majority of patients, but for patients with a cardiac risk who are HER2+, it is nice to know there is a regimen with Herceptin that is as good as ACTH. But I'll still give ACTH to most patients."
- *Missouri:* "The trial won't change the way I practice, but maybe I'll be a little more comfortable skipping the anthracycline in patients with cardiac problems, but that's fewer than 5% of patients."
- *Massachusetts:* "For patients with pre-existing heart conditions, TCH is now a nice option, but that only applies to <5% of patients. No big changes in practice will be made until there is longer follow-up. This is the anthracycline era."

BCIRG-006 also suggested that one-third of HER2+ patients who overexpress Topo2 are the only patients in whom anthracyclines are beneficial, and in those patients the benefits of anthracyclines outweigh the cardiac toxicity risk. Experts pointed out that this is only one test, but the concept has the influential support of Dr. Slamon. A source said, "This is only one study, and it was an exploratory analysis. I want another study before I accept the findings as real."

Sources said they do not plan to do Topo2 testing, explaining that there isn't a reasonably-priced, ***recognized*** Topo2 test available yet. However, the idea of a Topo2 test caught the attention of many doctors at the meeting, and experts said this should spur development.

Abbott Laboratories/Visys already has two DNA FISH products for detection of the TOP2A gene. This is an ASR assay that shows either deletion or amplification. It is available at some major medical centers, but it is not offered through major labs yet. Quest reportedly is looking into offering this test. A source predicted, "Topo2 will be a big test in six months."

Another study suggested Herceptin may not need to be given for the full 52 weeks for patients to benefit. Researchers in Finland reported that just nine weeks of Herceptin prevented recurrences and didn't increase the risk of heart failure. In that 3-year study, chemotherapy+Herceptin was compared to chemotherapy alone for nine weeks, and DFS was 89% in the Herceptin arm vs. 78% without Herceptin.

U.S. oncologists found this study "intriguing," but they said they intend to continue to prescribe Herceptin for 52 weeks in the adjuvant setting. However, they indicated that the trial

will make them – and their patients – more comfortable when Herceptin must be stopped earlier than that, and if the results are duplicated in other studies, they might consider a shorter course of Herceptin in the future. A Missouri doctor said, "The Finnish study makes me more comfortable stopping Herceptin if a cardiac problem develops. It is a comforting study, but I'll continue to give Herceptin for 52 weeks unless the patient develops a problem." A New England oncologist said, "The trial was not convincing." Another oncologist said, "I won't stop Herceptin sooner (than 52 weeks), but the trial was very interesting, and it needs to be looked into. And if a patient in the adjuvant setting develops problems, I would now feel more comfortable stopping Herceptin earlier than 52 weeks." A West Coast doctor said, "It is a fascinating study, but the numbers are small. I'd like to design a trial with less Herceptin, but you probably can't do that in the U.S. The French are doing a trial of Herceptin for 6 months vs. 12 months. But if the HERA trial shows a benefit for two years of Herceptin over one year, we'll never do less than 52 weeks of Herceptin. Any trials in the U.S. are on hold until we have the HERA results."

HERA is a 3,387-patient trial of Herceptin following adjuvant chemotherapy in women with HER2-positive invasive early breast cancer, comparing Herceptin (8 mg/kg → 6 mg/kg) on a 3 weekly schedule vs. observation only. The primary endpoint is DFS, and the first interim efficacy analysis will occur at 475 events. At one year, DFS was 7.5% with Herceptin vs. 13.0% with observation.

GlaxoSmithKline's Tykerb (lapatinib, GW-572016)

Sources were very excited about this tyrosine kinase inhibitor, which appears to work when Herceptin fails (metastases to the brain). It may eventually replace Herceptin or be given in combination with Herceptin. If Tykerb gets FDA approval – and sources are optimistic it will – it is likely to be used, initially, in Herceptin failures, but trials are underway or beginning that could quickly move it upfront. A New England oncologist said, "Herceptin relapses in the CNS (brain mets), and lapatinib is perfect there. I hadn't thought of it as a Herceptin replacement, but I suppose it could be. If it is cheaper than Herceptin, we'll use it." A West Coast doctor said, "Lapatinib is clearly on everyone's radar screen. It will be incorporated into all new adjuvant trials…It could replace Herceptin eventually or be given in combination with Herceptin…The question is whether it works in HER2-negative patients."

An open-label, Phase I study presented at SABCS found the optimal tolerated regimen in combination with Herceptin is 1000 mg/day. The most frequent adverse events were diarrhea, rash, fatigue, nausea, anorexia, and vomiting. Preliminary biomarker results from a Phase II randomized study of Tykerb as first-line treatment in advanced or metastatic breast cancer also was presented, and researchers reported response rates similar irrespective of ErbB1, ER, or PgR status, and no association with the level of PTEN expression.

Among the ongoing or planned Tykerb trials are:

- A multicenter, international Phase II trial has begun enrolling patients into two cohorts based on performance status:
  - Women with brain mets and ErbB breast cancer and ECOG performance status of 0-1 and 0-2 who have received Herceptin.
  - Women with ECOG performance status ≥2.
- A European trial is substituting lapatinib for Herceptin: chemotherapy+Herceptin vs. chemotherapy+lapatinib.
- The proposal for an Intergroup trial in the U.S. is for all patients to get ACTH for three months and then randomized into one of three arms:
  - Herceptin alone for 9 months.
  - Herceptin+lapatinib for 9 months.
  - Lapatinib for 9 months.

Taiho Pharmaceutical's TAS-108

In preclinical studies this steroidal anti-estrogen compound showed antitumor activity against tamoxifen-resistant breast cancer cell lines. A poster on a 16-patient Phase I open-label, non-randomized, dose-finding study presented at SABCS reported all patients experienced adverse events, with the most common drug-related adverse events hot flushes, alanine aminotransferese increases, and arthalgia. Endometrial hypertrophy was reported in one patient (at 80 mg). The ORR was 13.3%.

Wyeth's temsirolimus

Preliminary results from a 24-week, randomized, 92-patient Phase II trial in Spain – presented in a poster at SABCS – found that temsirolimus, an mTOR inhibitor, extends PFS in postmenopausal women with locally advanced or MBC in combination with Novartis's aromatase inhibitor Femara (letrozole) more than Femara alone. The FDA has granted Fast Track status for temsirolimus for first-line treatment of poor-prognosis patients with advanced renal cancer and for renal cancer patients after failure of initial therapy.

24-Week Phase II Temsirolimus Results in Breast Cancer

Measurement	Temsirolimus 10 mg + Femara 2.5 mg n=33	Temsirolimus 30 mg + Femara 2.5 mg n=30	Femara 2.5 mg n=29
Median PFS	12.9 months	18.0 months	9.5 months
Stable disease (SD)	27%	37%	21%
Dose reductions	2 patients	5 patients	0
Grade 3/4 toxicities occurring in >2 patients	Hyperglycemia, anemia, hypokalemia	Hyperglycemia, asthenia, hypertension, back pain	0

A randomized, double-blind Phase III trial of temsirolimus in combination with Femara in breast cancer patients is actively enrolling. Additional Phase III studies with temsirolimus also are ongoing in renal cell cancer and mantle cell lymphoma, and several Phase II trials are underway in other cancers, including a trial in metastatic or locally recurrent endometrial cancer.

ANTHRACYCLINES

A study presented on the last day of SABCS compared TC (docetaxel/cyclophosphamide) to AC (doxorubicin/cyclophosphamide) in 1,016-women with early stage breast cancer. The trial was powered to show a 10% difference between TC and AC. It showed only about a 6% difference, the trial still met the primary endpoint, and researchers concluded that TC should replace AC for adjuvant therapy. Dr. Joyce O'Shaughnessy of Baylor-Sammons Cancer Center commented, "All of us need to look at the data and see what we think. I look at it and say TC is better and less toxic. I think I will switch from AC to TC."

66-Month Results of TC vs. AC Trial

Measurement	TC n=506	AC n=510	p-value
Primary endpoint: DFS	~85%	~78%	0.015 (HR 0.67)
Secondary endpoint: Overall survival	~86%	~83%	0.131 (HR 0.76)
Local or distant relapses or second cancer	12%	16%	---
All cause death	11%	14%	---
Death without relapse	1%	2%	---
Death on treatment	<1%	0	---
Any neutropenia	63%	58%	---
Grade 3/4 neutropenia	59%	55%	---
Neutropenic fever Grade 3/4	6%	3%	---
Nausea	53%	81%	---
Grade 3/4 nausea	2%	7%	---
Side effect summary	More low grade myalgia, arthralgia, edema	More nausea and vomiting	---

AROMATASE INHIBITORS (AI)

The ASCO guidelines say all patients should get an aromatase inhibitor, but the guidelines don't specify which one or whether the AI should be given instead of tamoxifen, after a short course of tamoxifen, or after five years of tamoxifen. A speaker described two biomarker papers presented at SABCS as "somewhat shocking." One study, which looked at the ATAC trial, found an extra advantage of an AI (AstraZeneca's Arimidex, anastrozole) only provided an extra advantage in patients who were ER-positive and PgR-negative. In contrast, a study looking at the BIG-FEMTA trial, didn't find any real difference based on PgR status. The speaker said, "So, there is a complete conflict in ATAC and BIG-FEMTA, and that causes uncertainty in how to select patients (for an AI)...The thinking also was that an AI would be especially favorable in ER+/HER2+ patients, but they (researchers) found no significant difference based on HER2 positivity…That leaves us at sea in clinical practice in the selection of patients (for an AI)…At this point there is no way in clinical practice to select patients for an AI specifically."

How long after stopping tamoxifen can a patient benefit from starting an AI? A Canadian study previously found that Femara had to be started within three months of stopping tamoxifen, but another study suggested that even a gap of a year wasn't too long. A speaker said, "In my practice that means, particularly for high risk patients who got five years of tamoxifen and have been off tamoxifen for a year or more, I'm thinking of informing some of them to reconsider if they want to take an AI – letrozole (Femara) because it was the only one tested in this indication."

How long should an AI be given? An expert said, "My bias is that an AI should probably be continued indefinitely. That is based on two things: (1) After stopping an AI, hormone levels will recover, and (2) It may be more difficult to develop resistance to estrogen deprivation than it is to develop resistance to tamoxifen."

BISPHOSPHENATES

NOVARTIS'S Zometa (zoledronic acid)

A 31-patient, prospective, open-label Phase II study presented in a poster at SABCS suggested that switching bisphosphenates in breast cancer patients with progressive bone mets may be beneficial. In the study, patients who had progressed while on either clodronate or pamidronate were given three monthly infusions of second-line Zometa 4 mg. By Week 8, patients had experienced a statistically significant improvement in pain control. Researchers concluded, "While it is standard clinical practice to change hormonal or chemotherapy in patients with progressive bone metastases, clinicians tend to continue the patient on the same bisphosphenate. This is the first prospective study to show that patients with progressive bone mets who are on either clodronate or pamidronate can have relevant palliative benefits…with a switch to Zometa." The results still need to be confirmed in a randomized trial.

8-Week Phase II Results of Zometa

Measurement	Zometa	p-value
Improvement in pain control	41.9%	<.001
Urinary NTX level	Down	.028
Quality of life	Unchanged	---

ROCHE'S Boniva (ibandronate)

Roche researchers presented several posters on Boniva. The key thrust was that 50 mg QD of oral Boniva (which is 20 times the osteoporosis dose) is equivalent to, or better than,

Zometa in treating bone metastases and bone pain in breast cancer patients. The 50 mg Boniva dose is not approved in the U.S., but worldwide studies are ongoing to lead to registration. One of these studies found that a high IV loading dose of Boniva, followed by 50 mg/day orally, had a good effect on bone pain. An IV dose was administered on Days 1, 2, and 3, and then oral Boniva was started three weeks later on Day 24.

Two other posters compared oral Boniva and IV Zometa on safety and the markers of bone turnover and found Boniva non-inferior to Zometa.

Safety of Oral Boniva vs. Zometa

Measurement	Boniva 50 mg n=128	Zometa 4 mg n=126
Any adverse event	65%	76%
GI side effects	23%	18%
Bone pain as an adverse event	12%	21%
Serious adverse events	5.8%	8.0%
Withdrawals due to adverse events	2.9%	5.1%
Markers of bone turnover *(change from baseline)*		
S-CTX	-76%	-73%
U-CTX	-78%	-86%
BAP	-37%	-26%
P1NP	-47%	-39%
OC	-35%	-26%

STATINS

A University of California, San Francisco, researcher presented an interesting retrospective study suggesting that lipophilic statins may decrease the likelihood of developing ER-negative breast cancer, and the results appeared to hold up across all age groups. The study looked at 2,141 patients on a statin more than three years from the Kaiser Permanente database. Kaiser patients only were prescribed three statins, and all were lipophilic.

Lipophilicity of Various Statins

Lipophilic statins	Lipophobic statins
Pfizer's Lipitor (atorvastatin)	AstraZeneca's Crestor (rosuvastatin)
Merck's Zocor (simvastatin)	Bristol-Myers Squibb's Pravachol (pravastatin)
Merck's Mevacor (lovastatin)	
Novartis's Lescol (fluvastatin)	

Findings from Kaiser Database

Measurement	Statin use >1 year before breast cancer diagnosis	Statin use ≤1 year before breast cancer diagnosis	p-value
ER-negative tumors	2%	17%	<.001

Additional tests are planned or underway with statins, including:

- Tamoxifen+statins is being tested in vitro.
- Testing on non-tumorgenic cell lines is planned in the future.
- A pilot biomarker study is looking at Lescol 20 mg and Lescol 80 mg to see if a breast cancer subgroup can be identified that is more sensitive to statins. The data may be ready for SABCS 2006.
- A study (probably by Memorial Sloan Kettering Cancer Center) will look at BRACA-1 and BRACA-2 patients to see if statins reduce the incidence of breast cancer in those patients. A protocol is currently under review.

DIAGNOSTICS

Use of gene array tests in breast cancer is expected to remain fairly constant for at least the next year. Doctors generally agreed they need to see the results of additional tests and trials before usage of any of these tests will increase significantly. Dr. Daniel Hayes of the University of Michigan said, "We should look at the new factors the same way we use lymph nodes, which have a HR of death >2.0. That should be a bar to accept new things. Weak prognostic factors like ER/PgR and HER2 are not used routinely for prognosis." Even a Veridex official admitted that widespread use of CellSearch (and other gene assays) may be several years (~5) away.

A statistician suggested some criteria for biomarker assay development and validation:

- **Development**
  - Training and validation sets should be similar, homogenous, and clinically relevant.
  - Training sets should be large "enough."
  - Raw data should be made publicly available.
- **Validation**
  - Independent validation.
  - Adequate sample size.
  - Completely specified classifier.

Among the comments made about gene array testing were:

- "The information is only useful if we can explain who it should be used for and how it should be interpreted."
- *Massachusetts:* "I don't use any gene array tests. I can't get them reimbursed. But I will start using them if I can get them reimbursed."
- *New England:* "I don't use any of the tests. There are a lot of ways to look at genomic profiles, and I don't think they are refined enough yet. There are other ways to make decisions that are good and are clinically-driven."
- *Vermont:* "These tests are not ready for prime time yet. They only apply to a small subset of patients, and I'm worried people will use them in clinical settings where they don't belong."

The number of companies with tests designed to help predict the response to breast cancer therapy continues to grow. Following is a review of what appear to be the leading technologies as well as some other assays that bear watching:

AGENDIA'S MammaPrint (referred to as the "Amsterdam signature"). This 70-gene assay, which is performed on fresh tissue, is both predictive and prognostic. It is not FDA approved yet, but it is available in the U.S. through Molecular Profiling Institute for ~$3,200.

NUVERA BIOSCIENCE'S ER reporter gene expression index. Researchers from M.D. Anderson Cancer Center reported that this 200-gene assay positively correlates with ER status. They found measurement of ER gene expression (ESRI) and a defined index of ER reporter genes (RI) from Affymetrix U133A microarrays can assess ER-related genomic activity in FNA or tissue samples. Based on an initial study of 96 patients, they said ESRI and RI predicted relapse-free survival after adjuvant tamoxifen therapy independent from tumor stage, grade, and patient age. They suggested that diminution of ER-related gene expression in advanced stage ER+ breast cancer might indicate endocrine insensitivity in relapses disease and might not be evident in the original primary tumor sample. The suggestion was that ESRI and RI could potentially be combined into a continuous scale of endocrine sensitivity for clinical use.

A statistician was dubious about some of the assumptions the researchers made. She said, "This is a bit of a made-up scale …but it correlates nicely with some other things you might expect…and it is highly correlated with RNA expression by the chips…My suggestion is to start with a dataset where you know the patients responded to tamoxifen or an aromatase inhibitor and have that as a selection group to say these are the really estrogen-activated cases, rather than imputing something based on correlations." Dr. W. Fraser Symmans of M.D. Anderson Cancer Center, who is helping develop this assay, responded, "I appreciate the suggestion, but we wanted this to be different from an empirical approach. The concept is to have a genomic pathway that can be identified. If you take that and remodel it based on a small validation study, then you are intellectually polluting what we want to do."

Ki-67. Belgian researchers reviewed Ki-67 as a possible prognostic marker for breast cancer and determined that various tests had so many heterogeneic cutoffs and other criteria that none were likely to be viable as a reliable test. They did not appear confident that there would be a reliable Ki-67 test any time in the near future. Korean researchers also looked at Ki-67, determining it is an independent prognostic factor in lymph node negative (LNN) breast cancers, with the effect more significant in patients >age 50, with tumor size ≤2 cm, ER+, and received chemotherapy. They suggested that combining Ki-67 expression and the St. Gallen classification could provide a useful therapeutic guideline for LNN breast cancer patients.

ARCTURUS BIOSCIENCE. Last year, the company's breast cancer assay, Paradise, was being suggested as a way to determine which patients were responding (or not responding) to tamoxifen. After an Italian trial failed to validate the predictive nature of the HOXB13:IL17BR ratio in a cohort of mostly node positive patients, Arcturus gave up on that use and is now suggesting that the assay will be useful to determine breast cancer recurrence. The assay is still in development, but it is expected to be available some time in 2006.

Arcturus CEO Anthony Schuh insisted Paradise identifies an MBC patient earlier than node status, "You can use it to put a patient in a risk bucket. If a patient is node-negative, but the HOXB13:IL17BR ratio is high, then you want to look at the patient as if the woman was node-positive (a higher risk patient)…The marker has no predictive value in node-positive patients." Paradise is expected to be priced "significantly below (Genomic Health's) Onco*type* DX." Schuh estimated that ~100,000 patients a year would be eligible for this test.

Comparison of Leading Breast Cancer Detection and Monitoring Tests

Issue	Arcturus Bioscience's Paradise	Genomic Health's Onco*type* DX	Johnson & Johnson/Veridex/Immunicon's CellSearch
Type of test	Tamoxifen signature technology	Real time PCR assay for adjuvant breast cancer	Measures circulating tumor cells in MBC
What is measured	HOXB13:IL17BR ratio	21-gene RT-PCR assay	76-gene assay
Samples	Formalin-fixed samples ≤5 years old	Paraffin-embedded tissue	7.5-10 mL of whole blood
FDA status	Not approved yet	FDA approved	FDA approved
Availability	Not available	Through the company	Through Quest
Comments	No data on ability to predict response to aromatase inhibitors	Expensive (~$3,500), reimbursement uneven	Good predictor of distant metastases and well validated, but no data that changing therapy based on the results will affect survival
Initial area of use	Confirm value of tamoxifen therapy	Prediction of response to tamoxifen and predicting benefit to chemotherapy in early breast cancer	Monitoring response to chemotherapy and determining prognosis in metastatic breast cancer
Cost	N/A	~$3,460	~$600

Cancers of Unknown Origin (CUPs). During SABCS, Arcturus announced that Quest Diagnostics licensed its gene-based assay to identify the primary site of CUPs. In CUPs, cancer cells are found somewhere in the body, but the place where they originated cannot be identified from physical exam, pathologic analysis, or other diagnostic testing. CUP is estimated to represent 3%-15% of newly diagnosed cancers, and an estimated 70,000-100,000 new CUP patients are diagnosed each year in the U.S., with the prognosis usually poor. An Arcturus official said, "CUP is the 7th most prevalent cancer. Only 25% of patients are ever diagnosed before the patient dies."

The assay, which uses biopsy tissue, is not FDA-approved yet, but it can identify 39 different tumor types. Earlier identification of the primary tumor could increase the odds of successful cancer treatment and overall survival. The test costs $1,500-$1,700, and the results take about two weeks.

GENOMIC HEALTH'S Oncotype DX. A Genomic Health official said there are 2,500 doctors in the U.S. ordering Oncotype DX. He indicated there is a lot of regional and employer variability in reimbursement, but he predicted that payors would more evenly cover the test when it is covered by Medicare, and the company is working on getting Medicare coverage. Among the problem areas for reimbursement appear to be: Pennsylvania, New York, Ohio, and southern California. Some major insurers had been paying for Oncotype DX without questioning it but have recently been giving it new scrutiny.

A study presented at SABCS found the Oncotype DX recurrence score demonstrated a similar association between recurrence score (RS) and the risk for locoregional failure (LRF) as was previously shown for RS and the risk of distant failure. The study analyzed samples from the NSABP-B14 and NSABP-B20 trials. Researchers reported that:

- RS predicted LRF in node-negative, ER+ patients treated with tamoxifen, with chemotherapy+tamoxifen, and, to a lesser extent, patients treated without adjuvant therapy.
- RS score was an independent predictor of LRF along with age and surgery type.

Oncotype DX to Detect Locoregional Failure

Measurement	Placebo n=355	Tamoxifen n=895	Chemotherapy +tamoxifen n=424
Primary endpoint: 10-year locoregional failure rate			
RS <18	10.8%	4.3%	1.6%
RS 18-30	20%	7.2%	2.7%
RS ≥31	18.4%	15.8%	7.8%
Overall	---	HR 2.16 (p=0.005)	---
Age ≥50 vs. <50	---	HR 0.40 (p=0.0002)	---
Mastectomy vs. lumpectomy+XRT	---	HR 0.62 (p=0.047)	---

Several sources said they are waiting for the results of the Intergroup TAILORRX trial before expanding their use of Oncotype DX. That ~4,400 patient trial is still in the planning stage. Current plans call for the trial, which is expected to start in late spring or early summer 2006, to look at node-negative ER-positive and/or PgR-positive breast cancer patients, all of whom will be tested with Oncotype DX:

- Arm 1 – RS <11, a hormone therapy registry.
- Arm 2 – RS 11-30, randomized to either hormone therapy or hormone therapy+chemotherapy.
- Arm 3 – RS >30, chemotherapy+hormone therapy (registry or other trials).

Oncologists also will be closely watching a European trial, DISMAL.

Among the comments about Oncotype DX were:

- *User:* "We use this quite a bit where NSABP has suggested it helps – node-negative, ER-positive patients who say they would take chemotherapy. If a patient wouldn't take chemotherapy for a 1%-2% benefit, then I wouldn't do the test."
- *California:* "We use Oncotype DX for only 1%-2% of our patients, but use is increasing."
- *Michigan:* "Oncotype DX probably is ready for prime time right now…but our use is not likely to increase much over the next year."
- *Missouri:* "We use Oncotype DX for about 5% of patients, but use is not expected to increase."
- *Kansas:* "We don't use Oncotype DX because it wouldn't change what I do and reimbursement is an issue."
- "I'm not using Oncotype DX because it doesn't do anything that is new, but it does look at things in a better way. I can see value to it, but I have no plans to use CellSearch."
- *Vermont:* "I've had difficulty with reimbursement, so I'm not using it."
- *Washington:* "I use Oncotype DX in node-negative, ER-positive patients where I want to given hormone therapy but am on the fence about chemotherapy."

JOHNSON & JOHNSON/VERIDEX/IMMUNICON'S CellSearch. ASCO guidelines say that specialized techniques to detect isolated tumor cells are not a required part of sentinel lymph node evaluation at this time. Experts predicted that eventually CTC measuring will be more routine, but most do not believe use of this test will increase substantially over the next year.

New data were presented at SABCS from a multicenter, 180-patient European validation study of CellSearch. The study found 94% of "good signature" patients were metastasis-free

at 10 years compared with 65% of "poor signature" patients. A researcher commented, "We identified and validated the 76-gene expression application to all lymph node negative breast cancer patients, irrespective of age, menopausal status, tumor size, or tumor grade." A doctor in the audience commented that data are still needed to show that treating the poor signature patients affects their outcome.

SWOG is planning a trial (SWOG-0500) using CellSearch in first-line MBC at first follow-up to predict PFS. Samples will be drawn prior to administration of first-line chemotherapy. If circulating tumor cells (CTCs) by CellSearch assay are not elevated, patients will go in Arm A (control). If CTCs are elevated, patients will go into ARM B and get chemotherapy. Then at first follow-up, patients with no elevation of CTCs will be assigned to Arm B1 and will continue the current first-line chemotherapy until progression, and patients with elevated CTCs will be assigned to Arm B2 and be switched to an alternate, second-line chemotherapy until progression.

At a Veridex-sponsored dinner, a Virginia oncologist presented an analysis of the use of CellSearch in his practice from August 2004 to the present. The 60-patient study found 43% of MBC patients had no CTCs, 30% had <5 CTCs, and 24% had ≥5 CTCs. He said, "CTCs are a highly accurate indicator of therapeutic success or failure. They are more accurate than mucin markers, and the results are independent of type of therapy. They can be effectively used to minimize futile therapy."

Among the comments about Veridex's CellSearch were:

- *California:* "I haven't used the (CellSearch) test yet, but I will start when I get home to monitor treatment. I've done a few Onco*type* DX tests, but use is not increasing because it is heavily weighted for prognostic factors we already know."
- *User:* "We don't use it as a baseline test, and we don't use it at first follow-up. We use it in patients who are difficult to follow, patients with no measurable disease but who have bone pain…There are only a handful of patients where it is helpful. It will remain a very niche test unless the results of the randomized trial that is just getting started is positive."
- *Texas supporter:* "CTCs have a strong prognostic significance…The probability of death at two years is 19% with <5 CTCs but 49% with >5 CTCs…There are two distinct groups of MBC – indolent and aggressive. These can be identified by CTC count at diagnosis: <5 is indolent, and ≥5 is aggressive disease…CTCs are a valid surrogate, and there is no reason to deny this test to patients."
- "Why aren't clinicians using this more often? My feeling is that I haven't seen enough data to correlate the CTCs with known prognostic factors like HER2neu, etc. Why is this test any better?" A CellSearch user responded, "This will stratify patients to better and worse prognosis. This is better than any other marker."
- *Michigan:* "I use (CellSearch) in patients with a particularly poor prognosis where it is likely I will only get one chance to treat them, and I need to be sure to pick the right therapy. Usually if a patient doesn't respond (to a therapy), you have time to go to another therapy, but for patients I expect will be dead within the next two months, I don't want to pick the wrong therapy…(But) I don't see baseline CTC measurements having that kind of power."

ROCHE DIAGNOSTICS. Dr. Howard Robin of Pacific Rim Pathology in San Diego presented a poster on Roche's assay of p53 gene point mutations. He said the assays showed strong relationships to breast cancer predictions and may be available soon to help in treatment decisions and outcome predictions for breast cancer patients.

IMAGING: TOMOSYNTHESIS

Digital tomosynthesis, which uses multiple x-rays to create a 3D picture of the breast, was described by experts at SABCS as a technology that is likely to cause a paradigm shift in mammography within two to five years. Four companies are developing mammography machines with this capability – General Electric, Hologic, Siemens, and Planmed. The first device is expected to be available in about two years. A California radiologist said, "Tomosynthesis will revolutionize mammography. I think it will cause a real paradigm shift in mammography. It is not better than MRI, which shows different things, but I think this will be done first (before MRI)…Tomosynthesis will be the screening tool." A Texas doctor was less optimistic about the outlook for tomosynthesis, "Adoption will be very difficult. We need trials like we have for digital mammography first. There won't be a major shift to tomosynthesis in the next two to three years."

With standard mammography, which uses two x-rays of each breast taken from different angles (top-to-bottom and side-to-side), the breast has to be compressed against a glass plate, and women find that very uncomfortable. With digital tomosynthesis, the breast does not need to be compressed to take the x-rays. The x-ray tube moves in an arc around the breast while 11 images are taken during a seven-second examination, but the total radiation dose is no higher than in standard mammography.

Dr. Elizabeth Rafferty of Massachusetts General Hospital, where tomosynthesis was developed, said, "Initially, I thought this platform might not be suitable to all mammography detectors…but it is now clear a selenium-based detector is equally able to perform tomosynthesis, and that is what allowed other manufacturers (besides GE) to get involved…Most important, tomosynthesis is mammography. It improves on a proven technology. It addresses the potential flaw of mammography and makes it better. It's building on skills already familiar to radiologists, who can interpret it without additional training. It provides a platform in which

you can add other technology...This could be the poor man's MRI…It could have FDA approval in the next two years, and I think it will be common in five years."

Dr. Rafferty cited these advantages to tomosynthesis:

- Increased lesion visibility, increased sensitivity.
- Facilitation of margin analysis – more accurate diagnosis.
- Reduction in call-back rate from screening. False positives are expected to be cut almost in half.
- Lesion localization.

In the future, Dr. Rafferty said tomosynthesis will include:

- Contrast enhancement.
- Computer-aided detection. Two different tomosynthesis datasets could be fused, and the computer could analyze differences.
- Fusion with other modalities, such as ultrasound and PET.

MISCELLANEOUS

ASCEND THERAPEUTICS' TamoGel (afinoxifene, 4-hydroxytamoxifen). This topical gel is being investigated as a method of reducing breast density. A 4-6-month study in healthy premenopausal women missed the primary endpoint, but researchers suggested that follow-up may have been too short, and the dose may not have been optimal. Additional trials are planned.

Effect of Afinoxifene on Breast Density

Breast density	Afinoxifene	Placebo	p-value
Primary endpoint: ≥10% reduction in breast density at 6 months (n=65)			
50%-80%	4%	0	Nss
>80%	22%	0	Nss
Secondary endpoint: ≥10% reduction in breast density at 4 months (n=65)			
50%-80%	20%	0	0.026
>80%	0	0	Nss

CEPHALON'S Treanda (bendamustine). There was nothing on this alkylating agent at SABCS.

ONCBIOMUNE. This private company is working on an autologous breast cancer vaccine, using IL-2 and GM-CSF as the adjuvants. In a 41-patient Phase I/II study presented in a poster at SABCS, 75% of patients had some immune response. A researcher said, "I think the adjuvant is the key to this working." Further development (a Phase III trial) is on hold until other sites can be recruited. The company plans to start a prostate cancer trial in mid-2006 in patients with rising PSA post-radiation.

Intensity-Modulated Radiation Therapy (IMRT). This extremely precise external beam radiotherapy is used primarily for prostate cancer, metastatic brain tumors, primary brain tumors, and head and neck cancers. However, a poster presented at SABCS by Canadian researchers suggested it may have significant utility in breast cancer. The Canadian study, using a Varian machine, found IMRT:

- Did not increase planning or treatment time.
- Offered more homogeneity and increased conformity.
- Reduced radiotherapy to the heart and left lung. Because IMRT is so precise, higher than normal daily dosages can be used, resulting in shorter treatment times. IMRT software links treatment planning with delivery, resulting in a more optimal radiation dose for the patient.

Weight gain in breast cancer. More than one poster reported on weight gain in women diagnosed with breast cancer. One study found younger women with normal body weight were more likely to gain weight after a breast cancer diagnosis than older, heavier women. The study also found women gained some weight the first year, but more weight the second year, and then their weight tended to plateau.

♦