Trends-in-Medicine

January 2005

By Lynne Peterson

SUMMARY

Use of aromatase inhibitors is increasing, but doctors do not anticipate any significant market share shifts among the three approved AIs. The preference appears to be: AstraZeneca's Arimidex for newly diagnosed breast cancer patients; Pfizer's Aromasin for patients switching from tamoxifen to an AI after 2-3 years; and Novartis's Femara for patients who have taken tamoxifen for five years. ♦ Doctors are excited about American Pharmaceutical Partners' nanoparticle paclitaxel (abraxane). They believe the FDA will approve it, and usage is likely to ramp quickly, especially for metastatic breast cancer, provided the cost doesn't make insurers balk on coverage. ♦ Assays to determine response to tamoxifen and chemotherapy are starting to catch on, and Genomic Health's Onco*type* DX has the lead. Doctors are poised to start using this test now that validation studies have been done. Doctors are interested in Immunicon's less expensive circulating tumor cell test (CellSearch), to be marketed by Johnson & Johnson/Veridex as well as Quest Diagnostics, but it is catching on slower.

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SAN ANTONIO BREAST CANCER SYMPOSIUM

December 8-11, 2004
San Antonio, TX

Attendance at this year's meeting was up 15% to about 6,700 physicians. This report focuses on just five topics at that meeting: Aromatase inhibitors, American Pharmaceutical Partners' new nanoparticle paclitaxel (abraxane), chemotherapy for metastatic breast cancer, detection and monitoring tests, and laboratory problems with flow cytometry reimbursement.

AROMATASE INHIBITORS (AIS)

Tamoxifen has been the gold standard in adjuvant endocrine therapy, but aromatase inhibitors are replacing tamoxifen as front-line therapy for breast cancer. On November 15, 2004, the American Society of Clinical Oncology (ASCO) Technology Assessment Panel released its current guidance on the use of AIs in adjuvant breast cancer:

> *"Adjuvant therapy for postmenopausal women with hormone receptor positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumor recurrence."*

ASCO is currently recommending two options:

- Five years of AI treatment.
- Sequential therapy consisting of tamoxifen (for either 2-3 years or for 5 years), followed by an AI for 2-3 or for 5 years.

Tamoxifen

Advantages	Disadvantages
Improves survival	De novo and acquired resistance
Reduced contralateral breast cancer risk	Endometrial cancer
Bone and lipid benefits	Thromboembolism
	Hot flushes
	Genitourinary side effects

The advantages of AIs include:

- A negative or neutral effect on the endometrium – and possible protection against endometrial cancer.
- No adverse impact on lipids.
- Venous thromboembolism is not increased over placebo.

Among the unresolved questions about AIs are:

- Efficacy.
- Duration of therapy.
- Monotherapy vs. sequential or combination therapy. Does tamoxifen prime cells and make them more vulnerable to AIs? Does short-term tamoxifen "sensitize" patients to aromatase inhibitors? If so, treating with two or three years of tamoxifen before using an aromatase inhibitor may be preferable.
- When to switch agents. A speaker said, "The switching treatment idea is here to stay, and we don't know when to switch. We need better markers."
- Mechanism of resistance.
- Is there synergy between Cox-2 inhibitors and AIs?
- Longer-term end-organ toxicity, especially bone.
- Effect on cognition. A speaker said, "My own impression is that it is hard to measure. In some women, it is noticeable, but in my experience, it is temporary. I suspect it is real, but I don't think it is permanent. I don't think it will lead to a big problem, but I'm not sure." Another expert said, "There is not enough data to suggest estrogen-dependence is related to cognition. Individual women may have greater symptoms than others."
- Identification of prognostic and predictive factors.

Outlook for AI Use

Sources all agreed that AI use is likely to increase over the next year. Most newly-diagnosed breast cancer patients are expected to start on an AI, patients who have been on tamoxifen for two to three years will be switched to an AI, and patients who already took tamoxifen for 2+ years will be encouraged to start an AI. An expert said, "It is not the end of tamoxifen, but it is the end of the tamoxifen era."

Comparison of Aromatase Inhibitors

	Arimidex	**Aromasin**	**Femara**
Generic name	Anastrozole	Exemestane	Letrozole
Company	AstraZeneca	Pfizer	Novartis
Approval date	1995 second-line 2002 adjuvant	1999 second-line	1997 second-line 2004 adjuvant
Approximate current share of AI market	64%	6%	30%
Time-to-progression (TTP)			
AI	8.2 – 10.6 months	8.9 months	9.5 months
Tamoxifen	5.3 – 8.3 months	5.2 months	6 months
	Arimidex ATAC Trial	**Aromasin IES-031 Trial**	**Femara MA-7 Trial**
Increase in DFS vs. tamoxifen	2.4 % at 4 years 2.8% at 5 years 3.3% at 6 years	4.7 at 3 years	2.2% at 2.4 years
Number needed to treat	50	64	109
Endocrine-refractory patients included	Yes	No	No

Other comments included:

- *Maryland:* "Overall, use of AIs will go up, but the percentage share of each will stay about the same…I'm tantalized with the exemestane data in animals, but I'm not sure it is bearing out in humans. If anything goes up, it will be exemestane."
- *Massachusetts:* "AI use will go up because patients will demand it. Arimidex probably will increase because there is more data on it."
- *Austria:* "AI use will go up – mostly anastrozole and exemestane. Letrozole use will be flat."
- *Germany:* "AI use will increase. Arimidex use will go down, and Femara and Aromasin use will go up…AIs are better than tamoxifen, but five years ago we were told Cox-2s are better than aspirin."
- *Illinois:* "In one year, I don't see much change in market share among Femara, Arimidex, and Aromasin."

AIs cost more than tamoxifen, which is available as a generic, but a speaker said the higher cost of an AI is outweighed by other savings. One speaker said, "AIs are less costly to patients because they are less toxic and patients have fewer relapses…And they are less costly to society because recurrences cost money for treatment, particularly the gynecologic toxicity because surgeons are worried about endometrial cancer. A large number of women have unnecessary investigations which can lead to unnecessary operations – all of which are a cost. So costs to patients and to society are reduced with AIs."

Choosing an AI

Doctors indicated they have pretty much segmented the choice of AI into three categories, with a different use for each AI. However, patients often come in asking for a particular AI, and most sources said they would let those patients have their drug of choice. A Maryland doctor said, "Patients are pretty sophisticated, and they come in and ask for one."

Newly diagnosed patients: Arimidex (anastrozole) or tamoxifen

Most but not all U.S. doctors now believe new patients should be started on an AI, but European doctors generally said they still want to use tamoxifen for a couple of years before an AI. Comments included:

- "A sizeable number of patients who start tamoxifen develop (recurrent) cancer. Up until now, once the cancer recurs, that will be fatal. We don't have effective treatments to cure the disease once it recurs. So, my best judgment is to start on the drug most likely to keep a woman free of breast cancer for the long-run."
- "I don't think all women should be started on AIs."

- "I agree…We know from animal models that there is lab basis for assuming the sequence of tamoxifen to an aromatase inhibitors is better than the reverse. On the other hand, there is the ATAC trial…So, if a women is of median age (64) and not osteopenic, I am more likely to start Arimidex than a woman who is in her 50s, barely postmenopausal, and perhaps now looking at some ER-PR permutations." The audience at this session agreed; almost no one thought all postmenopausal women should receive an AI up front. Rather, the audience thought this question remains to be proven.
- "We recommend people start with Arimidex rather than taking tamoxifen for two or three years and then switching."
- "I'm convinced. Now, I will start with an AI…But I don't think there is a lot of difference between Arimidex and Femara…If a patient complains of side effects with Arimidex, I'll switch to Femara."
- "Anastrozole is not good for bone."
- "I'm not convinced we should start all patients on an AI, especially patients who get chemotherapy. There is not enough experience with long-term AI toxicity."

Patients on tamoxifen for 2-3 years: Aromasin (exemestane)

Doctors are convinced that switching from tamoxifen to an AI is beneficial, but they are not sure whether starting with an AI and then switching to tamoxifen will be beneficial. The question is whether there is something about preliminary treatment with tamoxifen that sensitizes women, so the AI treatment is more effective. The BIG-1-98 Aromasin trial should answer this. The results are expected in January 2005. Comments included:

- "Finishing five years of tamoxifen may not be best. Switching now is a better choice."
- "Every woman should have the discussion (with their physician) about starting an AI or switching to one. The decision is up to them, but they all should get the choice."
- "There are thousands of women taking tamoxifen today. These women should now go talk to their physician about why they should remain on tamoxifen because by switching after two to three years, you can cut down on recurrence."
- "I'll use either anastrozole or exemestane at this point."

Patients who have taken tamoxifen for five years: **Femara (letrozole)**

Comments included:

- "The evidence is persuasive that patients should be switched (off tamoxifen) after two or three years…The most data are for exemestane, and because it is a steroidal molecule, it may have less (negative) sexual effect and less (negative) bone effect."
- "We have a lot of tamoxifen patients, so we'll be using more letrozole…One question is what to do with patients who took tamoxifen long-term, but have been off it for a while. I may give them letrozole."

ASTRAZENECA'S Arimidex (anastrozole)

The Arimidex benefits greater in ER+PR- women than ER+PR+ women.

ARNO-95/ABCSG-8 Trials. A pooled analysis was presented of the three year results of the 3,324-patient **ARNO-95 trial** and the 962-patient **ABCSG-8 trial,** both of which looked at which therapy was better after two years of tamoxifen – more tamoxifen or Arimidex. Three-year event-free survival was 92.7% with tamoxifen and 95.8% with Arimidex, a 3.1% absolute difference in favor of Arimidex.

ARNO, run by the German Adjuvant Breast Group, and ABCSG-8, run by the Austrian Breast and Colorectal Cancer Study Group, were both adjuvant trials in metastatic breast cancer. The two trials were designed to be analyzed on a pooled basis. Disease-free survival was longer than that seen in ATAC (2.4 months at 2 years, 2.8 months at 5 years) but less than that seen in the IES-031 trial (in which DFS was 4.7 months with Aromasin).

Pooled Analysis of ARNO-95 and ABCSG-8 Trials

Measurement	2 years of tamoxifen followed by 3 years Arimidex n=1,618	5 years tamoxifen n=1,616
Events	67	110
3-year event-free survival	95.8%	92.7%
5-year event-free survival	40%	.0009
Distant recurrence	46%	75%
Contralateral breast cancer	12%	16%
3-year overall survival	97.1%	96.4%
Fractures in ABCSG-8 trial	2.4%	1.2%

Aromatase Inhibitors

Measurement	Arimidex	Aromasin	Femara
Trial	ARNO/ABCSG-8 pooled analysis	IES-031	MA-17
DFS or EFS advantage (drug vs. placebo) following tamoxifen	EFS 3.1% (92.7 vs. 95.8%)	4.7% (91.5% vs. 86.8%)	6% vs. placebo (93% vs. 86%)

ATAC Trial. A 6-year update (medium follow-up 68 months) of the 9,366-patient ATAC trial of Arimidex vs. tamoxifen in women with early breast cancer was presented. The curves continue to separate, favoring Arimidex.

There were no new adverse events, but there were more cerebrosvascular events with Arimidex, and a small excess of tumor deaths with Arimidex, though no particular tumor type stood out.

Overall survival was almost identical between Arimidex and tamoxifen. Asked why patients should take Arimidex when there is no overall survival benefit, a speaker said, "The important thing is the cost-benefit analysis…If you look at the hysterectomy rates, you can see it is immediately less costly in terms of that. If we treated all patients in the U.K. with an AI, it would only be 4% of the budget spent on breast cancer – about 8 million pounds – which is half of what is spent on taxanes, where there is not much survival advantage. The cost benefit analysis comes out in favor of anastrozole because of the side effects." Another speaker said, "Most patients in this group will die of cardiovascular disease and not breast cancer. We think we may see an overall survival advantage (with Arimidex) in the next two years."

ATAC Results: Safety

Adverse event	Arimidex	Tamoxifen
Pre-specified		
Hot flashes	35.7%	40.9%
Vaginal bleeding	5.4%	10.2%
Vaginal discharge	3.5%	13.2%
Endometrial cancer	0.2%	0.8%
Ischemic cerebrovascular events	2.0%	2.8%
DVT/PE	2.8%	4.5%
Joint symptoms	35.6%	29.4% (p<.001)
Not pre-specified		
Hysterectomy	1.3%	5.1%
Bone fractures	11.0%	7.7%
Fracture rate per 1,000 women years *	22.6%	15.6%
Overall		
Drug-related	60.9%	68.4%
Serious adverse events	4.7%	9.0%
Adverse events leading to withdrawal	11.1%	14.3%

*** The fracture rate in the Women's Health Initiative trial of estrogen+progesterone was 19.1%.**

ATAC Results: Efficacy of Arimidex vs. Tamoxifen

Time period	Disease-free survival with Arimidex	Contralateral breast cancer	Time to distant recurrence	Time to breast cancer death	Overall survival
4 years	2.4 months (86.9% vs. 84.5%)	---	---	---	---
5 years	2.5 months	---	---	---	---
6 years	3.3 months	26% vs. 53% (p=.001)	16% vs. 38% (p=.06)	13% (Nss)	3% (Nss)

NOVARTIS'S Femara (letrozole)

Doctors are very interested in the ongoing BIG-1-98 trial. This is a four-arm study investigating continuous and sequential therapy with:

- Arm 1: Continuous therapy with Femara for five years.
- Arm 2: Continuous therapy with tamoxifen for five years.
- Arm 3: Two years of tamoxifen followed by three years of Femara.
- Arm 4: Two years of Femara followed by three years of tamoxifen.

The results of the two five-year continuous therapy arms (Arms 1 and 2) are due to be reported at the St. Gallen Primary Therapy of Early Breast Cancer conference January 26-29, 2005. If BIG-1-98 shows Femara confers disease-free survival improvement greater than that seen for Arimidex in the ATAC trial (2.4%), and in line with sequential Aromasin therapy in the IES trial (4.7%), the conclusion is likely to be Femara is a more potent drug. The expectation is that BIG-1-98 will report disease-free survival improvement of ~3%-4%.

PFIZER'S Aromasin (exemestane)

An update of the randomized, double-blind, Phase III IES-031 trial in postmenopausal women with ER+ breast cancer reported that disease-free survival at 37 months was reduced by 27% when Aromasin was given after 2-3 years of tamoxifen adjuvant therapy compared to those who remained on tamoxifen for five years. Researchers concluded that Aromasin is better in all respects than tamoxifen except in ER(-) patients because it reduces the risk of:

- Breast cancer recurrence.
- Contralateral breast cancer.
- Death.
- Gynecologic side effects.

Questions were raised about the cardiac safety of Aromasin. Researchers working on AstraZeneca's Arimidex cited this as one reason to choose Arimidex over Aromasin. Aromasin researchers downplayed the significance of the cardiac side effects, but one speaker commented, "We need to be more careful on cardiac data collection."

However, doctors questioned about this issue did not appear very worried about a cardiac risk with Aromasin. Among their

comments were:

- *Maryland:* "I have no concerns. If anything, it is a class effect. Exemestane shouldn't be singled out."
- *Germany #1:* "There is no discussion among doctors about exemestane cardiac safety."
- *Germany #2:* "Exemestane cardiac toxicity merits watching, but it is not a concern yet."
- *Austria:* "There is no concern about the cardiac toxicity of exemestane."

Updated 37-Month IES-031 Trial Results

Adverse event	Aromasin n=2,352	Tamoxifen n=2,372	p-value
Disease-free survival	4.7% risk reduction	---	---
Local recurrence	43 patients	56 patients	---
Distant recurrence	150 patients	208 patients	---
Contralateral breast cancer	12 patients	26 patients	---
Patients with events	262	353	---
Breast cancer deaths	95	124	---
Total deaths	152	187	---
Overall survival	15% risk reduction	---	.08
Osteoporosis	8.3%	6.9%	.08
Arthralgias	19.8%	13.3%	<.001
Muscle effects	3.0%	5.1%	.001
Myalgia	2.4%	1.5%	.004
Thromboembolic disease	1.9%	3.3%	<.001
MI	0.9%	0.4%	.02 *
On-treatment MIs	0.7%	0.3%	Nss (.13)
Uterine hyperplasia	0.9%	1.95	N/A

* **A speaker said this is not statistically significant but did not explain why.**

Bone Loss

Aromatase inhibitors are associated with bone loss, and some experts are recommending that women on an AI also take a bisphosphenate. There is some early and inconclusive data that the problem may be less with Aromasin. A speaker said, "The implication is not that exemestane (Aromasin) prevents BMD loss, but that it may have an androgenic effect on bone…Trials today don't adjudicate whether exemestane increases bone strength…All AIs increase bone resorption. Exemestane may result in fewer fractures…And tamoxifen prior to an AI may offset bone loss."

NOVARTIS'S Zometa (zoledronic acid)

One of the key concerns with aromatase inhibitors is bone loss and the potential for bone fractures, but a three-year BMD substudy of the ongoing ABCSG-12 trial found that adding Novartis's Zometa (zoledronic acid) at 4 mg once every six months in premenopausal women on endocrine therapy prevents any and all bone loss. However, there have been no fractures yet in this trial, so the trial could not determine whether Zometa has a preventive effect on fractures. An expert said, "Loss of bone can be totally prevented by giving a bisphosphenate, including Zometa."

The researchers asked and answered two questions with this trial:

1. ***Is there chemotherapy-induced bone loss (at the spine and trocanter) in patients treated with combination endocrine treatment – AstraZeneca's Zoladex (goserelin) + either tamoxifen or AstraZeneca's Arimidex (anastrozole)?*** **YES**
2. ***Can this be countered by Zometa?*** **YES**

Zometa Substudy of ABCSG-8 Trial (n=401)

Measurement	Zometa use	No Zometa use	p-value
BMD loss (g/cm^2) at lumbar spine and trocanter	0	-14.4%	---
T-score average at lumbar spine and trocanter	0	-1.4 SD	<.001
Fractures	0	0	Nss
Osteoporosis	Up 1%	0 on tamoxifen Up 6% on Arimidex	---

Preliminary results from the Phase III, ~500-patient, five-year Z-FAST trial also suggest Zometa can prevent bone loss in women taking an aromatase inhibitor. Z-FAST, which was initiated in 2002, compares Femara+Zometa (4 mg IV every six months) to Femara+Zometa only when the BMD score drops below -2 SD (or there is clinical or asymptomatic fractures).

A NEW PACLITAXEL? AMERICAN PHARMACEUTICAL PARTNERS' Abraxane

American Pharmaceutical Partners submitted abraxane to the FDA in March 2003 at a 260 mg/m^2 dose every three weeks, but weekly administration at a lower dose may be feasible. Abraxane was filed under a 505(b)(2), which has different requirements than the more common 505(b)(1) NDA. A senior company official said this route was approved by the FDA in advance at the end-of-Phase II meeting. The PDUFA date is January 8, 2005, which means the FDA should make its decision by Friday, January 7, 2005.

There are three routes for new drug applications (NDAs) by the FDA. All are technically NDAs, but the term NDA most commonly refers to the first of these:

- **505(b)(1).** This is an application that contains full reports of investigations of safety and effectiveness. It is usually referred to simply as an NDA.

- **505(b)(2).** This is an application which contains full reports of safety and effectiveness, but at least some of the information required for approval comes from studies not conducted by or for the sponsor and for which the sponsor has not obtained a right of reference from the company or person by or for whom the studies were conducted, customarily the holder of the NDA. This is usually referred to as a 505(b)(2).
- **505(j).** This is used for generic drugs and is referred to as an abbreviated new drug application (ANDA). These applications contain information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance, characteristics and intended use, among other things, to a previously approved new drug.

[NOTE: For more information on 505(b)(2) filings, see ***Trends-in-Medicine*** article "The FDA, Bioequivalency, and 505(b)(2) Applications" in August 2004.]

The chief medical officer of Abraxis Oncology (which will market abraxane) said that the AUC and half-life of abraxane is the same as for paclitaxel, but the C_{max} for abraxane is "much higher because more dose is given over time." Under 505(b)(2) rules, different release formulations actually should have a C_{max} that is outside the range – or they are *unlikely* to get approved. An official explained, "Take the case of a sponsor who comes in with a modified release delivery system for a reference drug with an immediate release delivery system – a drug that is now in tablet form which releases much more slowly with the new formulation – so instead of taking it four times a day, patients can take it one or two times a day. The new product has more drug and releases very slowly…It is very common for a new sponsor to compare an extended release (ER) product to an immediate release (IR) reference product. The characteristics of the extended release product are different because it releases slower…We don't expect it to match completely on absorption…You might have a reference product that is given 100 mg BID, but the new ER formulation is only QD, so the sponsor puts in 200 mg (of active drug). If we look at the actual measurement in a bioequivalence trial, we would hope to see that the material is absorbed the same. The AUC the same is ideal, but because it is released differently, the C_{max} probably wouldn't match if working properly…Usually, there are spikes with IR and a more gradual release with ER…If the product is working correctly, you wouldn't match the C_{max}, but the AUC should match. That is the expected outcome: for AUC but not C_{max} to match."

New data on abraxane was presented by researchers from Baylor-Sammons Cancer Center in Dallas. This poster reported on weekly 125 mg/m^2 dosing, infused over 30 minutes with no steroids or C-GSF prophylaxis. The dose was effective, but there was an increase in Grade 3 sensory neuropathy, though this reportedly is less than the expected rate (30%) for Bristol-Myers Squibb's Taxol (paclitaxel) 100 mg/m^2 in first-line patients. An investigator, Dr. Joanne Blum, said sensory neuropathy was 4% in the Phase III trial (260 mg/m^2 every three weeks), compared to 17% in this trial. Neutropenia was also higher with 125 mg/m^2 than with 100 mg/m^2.

Other points made about abraxane in this poster:

- 10 of 13 (77%) of patients who developed Grade 3 neuropathy restarted abraxane at a reduced dose (75-100 mg/m^2) and received a mean of 12.2 additional doses.
- No severe hypersensitivity reactions despite no premedication.
- 75% of patients were treated at full dose, with no dose reductions due to toxicities.

Abraxane Results in Taxane-Refractory Metastatic Breast Cancer

Measurement	Abraxane 125 mg/m^2 n=106
Evaluable patients	100%
Efficacy	
Evaluable patients	75
Confirmed CR	1
Confirmed PR	8
Overall response rate	12.0%
Disease control (CR+PR+SD>16 weeks)	39%

Abraxane Results by Prior Taxane Therapy

Measurement	Number of patients	Objective Response	Disease Control
Tumor growth during			
Taxol alone	23	13%	39%
Taxotere alone	27	19%	44%
Both	23	0	22%
Weekly			
Taxol alone	17	6%	24%
Taxotere alone	14	21%	43%
Both	8	0	38%

Fifteen doctors were questioned about the outlook for abraxane use if it is approved, and there was surprisingly broad awareness of this drug. All but one doctor plan to use abraxane, mostly in lieu of Taxol, but it will also take some market share from Sanofi-Aventis's Taxotere (docetaxel). No source predicted abraxane would impact use of Lilly's Alimta (pemetrexed). However, sources warned that cost and reimbursement will determine how much use abraxane gets.

Among the comments were:

- *Dr. Blum:* "Where we will eventually place this is unknown, but I think it will eventually replace Taxol…I'll use it in lieu of Taxol where I planned to use weekly

Taxol, and I would use 100 mg/m^2 because it is better tolerated and the activity is comparable."

- "Abraxane is very exciting. It will be a blockbuster. I'll use it in metastatic breast cancer, and for many other uses."
- "I'll use abraxane because it doesn't require premedication, has a shorter infusion (15 minutes instead of 30 minutes), and the efficacy data looks very encouraging, especially with weekly administration. Sensory neuropathy is a concern, but it is transient. Usage may depend on pricing. The major competition (for abraxane) is Taxotere, but abraxane doesn't require steroids, and it has no hypersensitivity reaction. Use depends on the price, but it will be more than a niche product; it definitely could replace paclitaxel and give Taxotere a real run for the money unless it is prohibitively expensive"
- *New York #1:* "Absolutely, I'll use abraxane – for any patient getting paclitaxel. It will be used immediately (when it becomes available). Paclitaxel needs to be given with corticosteroids, and there is a small risk of death from infusion reactions."
- *New York #2:* "Use in metastatic breast cancer is an option. It is somewhat easier to give. There will be some use of abraxane, but it won't replace Taxol because of cost – but it will find a niche."
- *California #1:* "There is limited data, but people will use it. In metastatic breast cancer it looks similar or possibly slightly more effective than paclitaxel, but with less toxicity and very little hypersensitivity reaction, and no need for premedication. Nursing time and costs will be lower, but it wouldn't take much of a price markup to make those advantages go away…If the cost were the same as for paclitaxel, then abraxane will have a real advantage…My expectation is medical oncologists will freely substitute abraxane for paclitaxel. I will not because the data is only in metastatic breast cancer, and there are some biological reasons to think abraxane might be less effective in the adjuvant setting. The major argument they (abraxane supporters) make is vasculature-related, and whether that occurs with micromets is unclear."
- *California #2:* "I'll use it for metastatic breast cancer. The lack of hypersensitivity reactions alone is enough to get people to use abraxane."
- *Maryland:* "I don't know as much as I would like about abraxane, but anything new with some edge in cancer treatment is huge. I would use it. It has shown efficacy even in Taxol failures. But cost is an issue, so I'd start with metastatic breast cancer. It would take more studies before I'd use it in earlier-stage disease…I would pick it right up, but only for Taxol or Taxotere failures. The trend is to start with a taxane at initial relapse, and I would start with other taxanes unless abraxane is cost effective."
- *Massachusetts:* "I won't use it right away. Cost is an issue, especially with the new Medicare reimbursement in 2005. Premedication drugs are cheap."
- *Illinois:* "The data seem to show that Taxol failures get response, and some responses are fairly prolonged. Toxicity is probably less with abraxane than Taxol, which makes it appealing. No steroids are necessary, which helps with quality of life. So, I'll use it instead of Taxol, and possibly instead of Taxotere. Cost will be a big issue. We may choose the drug with the better reimbursement."
- *Florida:* "Abraxane is approvable. It works, and the side effect profile may be more beneficial. But I'm not a big fan of paclitaxel."

Abraxane Safety

Measurement	All	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicities					
Anemia	93%	47%	40%	4%	1%
Leukopenia	89%	23%	30%	33%	3%
Neutropenia	76%	11%	30%	31%	3%
Thrombocytopenia	17%	11%	1%	4%	0
Taxane-associated non-hematologic toxicities					
Sensory neuropathy	77%	28%	32%	17%	0
Fatigue	39%	9%	20%	9%	0
Arthralgia	13%	4%	8%	0	0
Edema	12%	8%	4%	0	0
Myalgia	12%	3%	9%	0	0
Dermatologic					
Alopecia	25%	0	25%	0	0
GI					
Nausea	33%	17%	13%	3%	0
Diarrhea	25%	13%	9%	3%	0
Anorexia	17%	9%	5%	3%	0
Vomiting	13%	5%	8%	0	0
Taste disturbance	11%	9%	1%	0	0
Mucositis	11%	7%	4%	0	0
Other					
Musculoskeletal	11%	70%	3%	3%	0

Among the questions that have been raised about abraxane are:

➢ **The decision to file as a 505(b)(2).** If nanoparticle paclitaxel is a new formulation of paclitaxel, the 505(b)(2) route is appropriate; if it is a new delivery system, then the 505(b)(1) NDA route is required. If the FDA thought a 505(b)(2) filing was inappropriate, it is likely the Agency would have rejected the 505(b)(2) filing long ago, so this appears to be an acceptable route.

An FDA official offered some clarification on this issue:

- "It is true that we have not had many 'nanotechnology' drugs. It is also true that we do not have, at this time, a specific policy regarding nanotechnology drugs. All of our existing policies and guidances apply to all drugs, including nanotechnology drugs."
- "If the nano-formulation was submitted by the same sponsor as that for the original non-nano-formulations, then this was considered a new formuation of the product. However, if the nano-formulation was submitted by a different sponsor, then the application was reviewed as a 505(b)(2)."
- "505(b)(2) means that no, or minimal, toxicology studies would normally be needed. However, in the case of nanotechnology products, we have been requesting sponsors to conduct PK and tissue distribution studies in animals, in order to confirm that the nano-formulation would not cross tissues such as the blood brain barrier or placenta. If these studies did not reveal unusual tissue distribution, no additonal studies have been requested."
- "There is one caveat. If the original formulation was an old drug, with minimal toxicity data, or with inadequate tox studies, then there may be studies requested to bridge the data gap. However…this can still be done under a 505(b)(2)."
- "If the new formulation were to come as a chemistry supplement, and the chemist does not consult the toxicologist, then the nano-formulation may be approved without the additional PK data."
- "We are in the process of developing procedure that will form the basis of policies to help deal with nano-formulations in a consistent manner."

➢ **The use of non-inferiority as an endpoint.** The FDA doesn't like non-inferiority trials, but it recognizes they are often necessary. Abraxane showed superiority, not just non-inferiority.

➢ **Trial size.** Data on fewer than 500 patients was submitted to the FDA, which usually wants 500-1,000 for a 505(b)(1) NDA. This might have been an issue if abraxane had gone the 505(b)(1) NDA route, but it is probably less of a problem since this is a 505(b)(2) filing.

➢ **Response rate endpoint.** Some critics point to this endpoint as problematic, but the FDA likes response rate as an endpoint in oncology trials.

➢ **Non-homogenous patients.** The chief medical officer of Abraxis Oncology (which will market abraxane) said that was an FDA requirement.

➢ **Adjudication of adverse events.** One critic charged that this was done by the head of the clinical program, and not by investigators or an outside DSMB. The Chief Medical Officer of Abraxis Oncology said the determination was made by the investigator, but there wasn't a DSMB. This does not appear to be a killer issue.

➢ **OUS patients.** More than three-quarters of the patients in the Phase III trial were enrolled in Russia, a situation some consider unusual. The FDA is cautious about trials done primarily outside the U.S. or western Europe, but this is not necessarily a major roadblock.

➢ **Firing of the CRO.** The FDA doesn't necessarily consider that a negative, and it could even be a positive.

➢ **Trial protocol details on drug reconstitution.** Abraxane is reconstituted the same way several other drugs are reconstituted, and oncologists frequently reconstitute drugs. However, it may be that there will need to be more details about the method of reconstitution in the formal label.

On balance, it appears that abraxane is likely to get approved, and doctors are willing and anxious to use it. However, usage will depend on price and reimbursement.

CHEMOTHERAPY FOR METASTATIC BREAST CANCER

The benefits of randomized clinical trials have been translated into population-based survival gains for women with breast cancer. That was the conclusion of Canadian researchers. Researchers there examined 4,721 breast cancer cases between 1989 and 1993 to determine the effect of chemotherapy in women under age 50. A researcher said, "There was a reduction in recurrent of about 33% with chemotherapy…Our findings suggest a significant part of breast cancer mortality declines since 1990 have been due to the implementation of adjuvant systemic therapies."

ASTRAZENECA'S Iressa (gefitinib)

The recent news that Iressa failed to show a survival benefit in a Phase III post-marketing study makes the future of this agent questionable. However, speakers at the San Antonio Breast Cancer meeting pointed to several ways Iressa is being explored in breast cancer, including:

➢ **Tamoxifen + Iressa.** Tumors regress but return quickly.

➢ **Trastuzumab (Genentech's Herceptin) + Iressa.** In cell lines, tumors regress but return quickly. Early human data suggest there is no benefit from this combination. A speaker said, "I know this combination is being used ad hoc in the community, and I think this data warrant rethinking of that practice in the community… TTP in patients with Herceptin + Iressa was shorter than that reported in patients treated with Herceptin alone."

➢ **Pertuzumab (Genentech's Omnitarg) + Tamoxifen.** This is effective, but resistance still develops.

➢ **Tamoxifen + Pertuzumab + Herceptin + Iressa.** In cell lines, tumors regress but resistance does not appear to develop. A speaker said, "By putting all these together, we saw complete tumor inhibition in 18 of 20 mice, and

no resistance appeared to develop. When treatment stopped at day 189, there was no tumor regrowth in the next 30 days…All the inhibitors are needed to completely block the pathway."

DETECTION AND MONITORING

Breast cancer is responsible for about 40,000 deaths in the United States each year, but if it is detected early – before it metastasizes -- cure rates are high. While survival for patients with early breast cancer is significantly improved by the addition of chemotherapy, some women can be cured with surgery and hormone therapy alone – but it has not been possible to identify these women. Thus, many women are unnecessarily exposed to chemotherapy and its side effects. An expert said, "For early stage breast cancer, there are about 70%-80% of patients who are cancer-free and don't actually require therapy after they receive a lumpectomy. At this point in time, we have no way of identifying which patients fall into that category."

The ideal diagnostic assay should be:

- Technically accurate.
- Highly standardized.
- Reliable.
- Reproducible.
- Able to separate positive from negative endpoints with large magnitude.
- Statistically valid.

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.

Doctors at one session at San Antonio Breast Cancer Symposium wanted to know what to make of all these tests – and the others – that are available. A Cleveland Clinic doctor responded, "At the end of day, the method which will win will be methodology that has practicality, is easily applicable, and quantitative…One of the messages I take back from this meeting is quantitation is important…and so thinking in terms of a single marker is probably gone. We have decades of literature trying to find ***the*** one marker, and that has been disappointing…Looking at combinations, you can probably increase the power…and I think it will come down to a technology that is widely applicable, affordable, and will do well in predicting clinical outcome." Another expert said, "The first test out of the box may not necessarily be the best."

ARCTURUS'S Paradise Reagent System

At the American Association for Cancer Research meeting in March 2004, this test appeared to be the leader, but two other companies have leapfrogged over Arcturus – Genomic Health and Immunicon. Arcturus's Paradise system is a tamoxifen signature technology which can use formalin-fixed paraffin samples that are up to five years old. Genetic analyses can identify tamoxifen-responders by matching two genes – HOXB13 and IL17BR.

Comparison of Breast Cancer Detection and Monitoring Tests

Issue	Arcturus's Paradise	Exagen	Genomic Health's Oncotype DX	Immunicon/J&J/Veridex's CellSearch	MRI
Type of test	Tamoxifen signature technology	PGA FISH assay	Real time PCR assay	Measures circulating tumor cells	MRI
What is measured	2 genes: HOXB13 and IL17BR	3-gene assay	21-gene assay (16 cancer-related genes and 5 reference genes)	76-gene assay	Score of gadolinium absorption and wash out
Samples	Can use formalin-fixed samples ≤5 years old	Can be done on paraffin-fixed tissue	Paraffin-embedded tissue	7.5-10 mL of whole blood	None
Advantages	Good predictor of tamoxifen response	Works for node negative and node positive patients	Real-time PCR, CLIA approved, FDA approved	Good predictor of distant metastases, extensively validated, affordable (~$600), FDA approved, available through Quest	Easy, no special equipment needed
Disadvantages	No data on ability to predict response to aromatase inhibitors	Needs validation	Expensive (~$3,500)	No data that changing therapy based on the results will affect survival	Works best in homogenous tumors where blood vessels are evenly distributed throughout the tumor
Initial area of use	Confirm value of tamoxifen therapy	N/A	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	Predicting response to neoadjuvant chemotherapy
Cost	N/A	N/A	~$3,460	~$600	N/A

Arcturus had no booth, no presentations, and no new data at the San Antonio Breast meeting. The problems for Arcturus include:

- Lack of data showing that denying tamoxifen to women is clinically feasible.
- The growth of aromatase inhibitors as first-line therapy and the reduction in time women are given tamoxifen.
- Inability to predict response to aromatase inhibitors. An official said the company has not yet been able to get tissue samples from women in aromatase inhibitor trials. If the test could be used to predict response to aromatase inhibitors, it might have greater appeal to doctors, but a source said the pharmaceutical companies control most of the large AI databases so far, and they have been unwilling to share those samples with Arcturus.

A competitor commented, "If the Arcturus test works, it is competitive, but it is not validated yet, and the concern is that it only uses 2 genes and that may not be enough to get to our level of reliability."

EXAGEN DIAGNOSTICS' PGA FISH

An initial validation study presented by Exagen Diagnostics at the San Antonio Breast Cancer Symposium indicated the company's 3-gene set of markers can distinguish good prognosis from poor prognosis in newly diagnosed breast cancer patients based on DNA changes in the patient's tumor. The study, a retrospective look at archived specimens – hormone receptor positive and hormone receptor negative – from 308 Hispanic and white patients with ductal carcinoma who were diagnosed at the University of New Mexico Health Sciences Center between 1986 and 1999. The average follow-up in this study was 8.9 years (minimum four years). Researchers found that two 3-gene sets of markers form a panel that can be used in testing tumor tissue from breast cancer patients, providing same-day or next-day results.

An Exagen official said the company plans to do validation studies quickly and hopes to be on the market in early 2006. At first the test is likely to be available through reference labs. The official wouldn't release the price, saying only that it would be between $600 and $3,500."

Researchers suggested the PGA FISH (pattern of genomic amplification by fluorescent *in situ* hybridization) test could be used to identify patients who would have a good prognosis without chemotherapy or hormonal therapy after tumor removal. The genes used to produce a "prognostic index" were:

- For node positive patients – PDCD6IP, CYP24, and BIRC5. The negative predictive value was 91% in low risk patients.
- For node negative patients – SMARCE1, NR1DA, and BIRC5. The negative predictive value was 100% (though the sample was small).

Physician comments included:

- *New York:* "We may have the ability to withhold therapy from women who don't need and won't benefit. We may well be able to identify women who won't benefit (from chemotherapy) and may need to use investigational approaches early on…but we don't want to jump to conclusions…Today's results are very provocative but need to be validated….Obviously, these (tests) will be used to assess the long-term outcome for individuals and what we might consider staging. These findings may trump the anatomic staging criteria that we currently use …Ultimately, this or related tests will allow us to individualize therapy for patients."
- *Ohio:* "We'll probably use this or the Genomic Health test to get a better idea of how patients do and who needs to be treated."

How might this test change treatment?

- Good prognosis patients could be reassured with minimal or no adjuvant therapy.
- The poor prognosis patients could be offered experimental treatments (chemotherapy+immunotherapy, anti-angiogenesis, signal transduction inhibitors).

GENOMIC HEALTH'S Onco*type* DX

Onco*type* DX is FDA- and CLIA-approved assay to determine the risk of a distant recurrence in women with Stage I or II node-negative, estrogen receptor-positive breast cancer. The 21-gene, real-time PCR assay is performed using formalin-fixed, paraffin-embedded tissue. However, many doctors wanted the Onco*type* DX gene expression assay to be validated before using it. A National Surgical Adjuvant Breast and Bowel Project (NSABP) study that validated the test was simultaneously released in the ***New England Journal of Medicine*** and at the San Antonio Breast Cancer Symposium.

This was a retrospective look at 668 tumor samples, and it showed that Onco*type* could predict both the recurrence of distant metastases and overall survival in node-negative women with breast cancer who had been treated with tamoxifen. A low recurrence score was associated with minimal chemotherapy benefit, and a high recurrence score was associated with a large benefit to chemotherapy. The predictive value of the recurrence score was independent of age and tumor size ($p<0.001$). The recurrence score was also predictive of overall survival ($p<0.001$) and could be used as a continuous function to predict distant recurrence in individual patients. A Genomic Health official said, "We can predict (a) The likelihood of disease recurring over 10 years, and (b) The seriousness of the breast cancer…But patients, even those with low risk may still want chemotherapy…Ninety percent of women are offered chemotherapy, but ≤50% can benefit, and this test can say which those are. It is WOW data."

Validity of Onco*type* DX

	Low Risk	Intermediate Risk	High Risk
Risk level	51%	22%	27%

Asked if these results can be applied to patients who took an aromatase inhibitor instead of tamoxifen, Dr. Soonmyung Paik said, "Since low and intermediate risk patients have different levels of estrogen receptors, it is likely they will get more benefit from an AI, so the benefit of chemotherapy in them is probably even less. For high risk patients, because they are so low in estrogen levels, they may get some benefit from an AI, but the chemotherapy will probably have more value."

An accompanying editorial in the ***New England Journal of Medicine*** warned that before this test is applied to general patients additional, multicenter studies are needed. The editorial made several interesting points, including:

- "Does the recurrence score predict prognosis in women who are not exposed to systemic therapy?"
- "It would be hypothesized that the utility of the assay is restricted to estimating the prognosis of patients who are receiving tamoxifen and thus that it can predict the response to antiestrogen therapy…Another interpretation …is that the promising results…may be difficult to replicate."
- Do the findings apply to patients taking aromatase inhibitors as well as tamoxifen?

A second, community-based study by Kaiser Permanente researchers looked at patients at 14 northern California Kaiser hospitals. The study found a statistically significant association between the Onco*type* DX assay and 10-year breast cancer mortality ($p<.001$), including patients with small tumors.

Genomic Health plans to look at aromatase inhibitors, but an official said, "Finding retrospective tissue on AI patients is an issue."

Right now, there is no reimbursement for Onco*type* DX, which costs about $3,460 per test. A Genomic Health official said the company hopes to get a CMS coverage decision in 2005, "We've also met with payers. They want peer-reviewed data, and the ***New England Journal of Medicine*** article does that. Payers also want a confirmatory study, and we now have a Kaiser study on that."

Doctors were very interested in this test.

- *Kaiser researcher:* "The results of our study (of Onco*type)* would cause me to increase the chemotherapy for high risk patients but not deny chemotherapy to patients with tumors ≥1 cm. But I'm sure there will be women who turn down chemotherapy after this test. Carriers will pay for it because it saves money…This test encourages you to treat high risk patients more, not treat low risk patients less…Kaiser has not decided how to use this data yet."
- *Maryland:* "I will use it to help support me when I don't want to give chemotherapy, but I won't use it not to treat. It is more likely to support use of more chemotherapy… Right now we vastly over-treat. Maybe in time this test will let us treat less."
- *Texas:* "This is a really good test for a doctor in community practice. It is very standardized, and the results are validated. People don't have to be prognostic experts to use it. Reproducibility is the strength…People will use this test as a reason not to use chemotherapy, based on the ***New England Journal of Medicine*** article. It is Level 2 evidence."
- *New York #1:* "It is still experimental. How much does it add? These are not necessarily chemotherapy candidates …It could be the disease that recurs may not be sensitive to chemotherapy. Recurrence patients may not be the same as metastatic patients."
- *Wisconsin:* "We're not moving to use it yet…but this would give women one more factor to be reassured on not taking chemotherapy…The test doesn't seem meaningful to me, but if a patient is considering opting for no chemotherapy, it might reassure her."
- *California:* "We are using this test. We are good at estimating the chance of recurrence, and we want to compare their test with our ability. It could bolster the argument not to take chemotherapy. We give chemo-therapy for a 10% benefit, which means we treat 99 to save 1."
- *Washington, DC:* "I might use it to convince women they don't need chemotherapy."
- *Florida:* "We are using it in selected patients. The ***New England Journal of Medicine*** article will cause more widespread excitement. I won't use it in a 30-year-old woman with a 2 cm tumor, three kids, and ER+/node negative breast cancer; she'll get chemotherapy no matter what. But a 38-year-old with a 1.1 cm tumor who is ER+/node negative who doesn't want to lose her hair might get an Onco*type* DX test, and if she scored 8 with a 9% risk, chemotherapy would only add 1%, so then you could spare chemotherapy with greater confidence…**In one year, I'll probably use this test in 30% of appropriate patients.**"
- *New York #2:* "The Onco*type* test is ready, and we are starting to use it where it is reimbursed, but patients also will pay for it out-of-pocket. This test has ***validated*** data."
- *Missouri:* "The Genomic Health test is very interesting. Now that two additional groups have studied it. It shows the recurrence score is capable of discriminating prognostically and identifying which patients will respond to chemotherapy. I plan to use it for appropriate patients."

IMMUNICON'S CellSearch, marketed by JOHNSON & JOHNSON/VERIDEX

The CellSearch automated tumor cell diagnostic test is starting to catch on, primarily for monitoring response to chemotherapy and determining prognosis in breast cancer patients. Though Immunicon also believes its test has prognostic value for staging newly diagnosed disease, sources generally prefer the Genomic Health system for that. Sources insisted the role for CellSearch, which uses a 76-gene signature, is in metastatic breast cancer.

CellSearch can find a single circulating cancer cell in 7.5-10 mL of blood. The test is approved for use in breast cancer, but an official said it could be used for all solid tumors. The advantages of CellSearch include:

- Prognostic assay.
- Predicts distant metastases with high confidence.
- Has application to ER+/-, pre- and post-menopausal women.
- Has been extensively validated.

An interim analysis was presented on 35 of the 50 patients in a one-year double-blind metastatic breast cancer trial.

CellSearch Trial

Measurement	Results
Average follow-up	2 - 4 months
First line therapy	9%
Second line therapy	26%
Therapy	64% chemotherapy 27% hormonal 6% combination
ER/PR+	72%
Results in the 82 samples analyzed	
0 cells	48%
1-4 cells	29%
5-10 cells	10%
>10 cells	13%

Patient status	Results	
Progression (n=26)	False negative 11/3	True positive 15/21
No progression	True negative 40/13	False positive 3/23
Rotterdam Study (n=171)		
	Relapsers	Non-relapsers
Positive predictive value	52%	60%
Sensitivity	93%	
Specificity	48%	

Future applications for CellSearch include:

- Phenotyping peripheral blood circulating tumor cells to look for target antigens.
- Detection and characterization of micrometastatic cancer cells in bone marrow.
- Detection of circulating normal stem cells in peripheral blood.
- Detection of circulating cancer stem cells in blood and bone marrow.

Remaining questions about measuring circulating tumor cells (CTCs) include:

- What happens with CTCs at subsequent follow-up after first follow-up?
- How do CTCs compare to circulating tumor markers? Data on this is expected at ASCO 2005.
- How to use CTC measurements to change therapy? The BrAT trial by SWOG may answer this.

Quest Diagnostics is offering this test for about $600, but sources generally were not aware of this. Physicians are interested in this test, but they know less about it than about the Genomic Health test, and they are less excited about this. Among physician comments about this system were:

- *Missouri:* "Cost is an issue. It could help monitor response to therapy, but how are we going to get it paid for? If Medicare and other insurers pay, then we will use it. I won't offer it to patients until it is reimbursed. If it were reimbursed, I would use it."
- *Maryland:* "The company says you can tell if a therapy is working after one cycle, and that is scary. I will motivate you to switch (therapy) earlier. I'm really nervous about that. I have the tubes under my desk, but I haven't ordered it yet. Usually, I wait two or three cycles to see if a therapy works…Some study found that patients would go through chemotherapy for a 1% benefit. My cutoff is 2%-3%."
- *Florida:* "I'm going to be in one of their trials. It's interesting."
- *Midwest:* "I don't know enough about this yet to use it. There is not enough data for me yet, but it sounds interesting, and the cost is workable. They need more data."

MRI to predict breast cancer's response to chemotherapy

Duke University scientists have shown they can use MRI to visualize and "score" a breast cancer tumor's ability to respond to chemotherapy. Researchers claim to be able to predict with 90% accuracy which tumors will respond when treated with neoadjuvant chemotherapy and which tumors will not. In the 20-patient pilot study sponsored by the National Cancer Institute, women with locally advanced breast cancer were injected with a tracer, gadolinium-DTPA, which is preferentially absorbed in the tumor. The rate at which the gadolinium washed in and out of the tumor was carefully measured, as it predicted how the chemotherapy would enter

and leak out of the tumor. The MRI images were processed and several parameters relevant to tumor morphology and physiology were extracted.

Each woman was given a score from 0 to 5 based on specific parameters of her tumor, and they were then labeled as likely to be responders, non-responders, or partial responders. The three primary factors in predicting a tumor's response to chemotherapy were:

- Perfusion.
- Permeability.
- Morphology/cellularity.

Tumors with more efficient blood vessels can carry more of the tracer and thus more of the chemotherapy. Tumors that are closely packed with cancer cells do not effectively retain the tracer, the study showed. Tumors in which the blood vessels formed a ring pattern around the center were also resistant to chemotherapy because of collapsed blood vessels in the center.

The best responders were homogenous tumors in which blood vessels were evenly distributed throughout the tumor. In these tumors, the gadolinium tended to wash into and out of the tumor slowly.

CMS Reimbursement Issues

Flow Cytometry

The Clinical Cytometry Society (CCS) and laboratories around the country are very worried about the impact of the new CMS reimbursement schedule that went into effect on January 1, 2005. The fee schedule for the three new Flow Cytometry professional codes was cut by up to 70%, and the technical fees were cut about 40%. The changes – which affect mostly leukemia and lymphoma patients, not HIV testing – were imposed with only about six weeks notice. CCS has been trying to organize a letter writing campaign and hopes to convince CMS to re-adjust the fees later this year.

Laboratory sources said the concern is that many hospitals will be forced to stop offering this service. One source said, "This particularly affects smaller hospitals and community hospitals." An official of a national lab said, "We expect an increase in volume, and we are adding more staff – but that is no bonus for us. We just hope doctors don't order less flow cytometry. That would be bad for patients."

CMS Flow Cytometry Reimbursement

Year	Codes	Average national technical fee	Average national professional fee	Average national global fee for 10 markers
2004	88180	$48.17 x # of markers	$19.79 x # of markers	$679.50
2005	88184,88185 88187,88188	$50.78 for first marker $25.01 for each additional marker	$68.97 for 2-8 markers $86.02 for 9-15 markers $113.31 for ≥16 markers	$361.89

Oncology Drug Payment Changes

CMS also is changing the way oncologists get paid. The profit on drugs was cut this year and additional cuts are coming in the future, but fees have not been increased a comparable amount. There have been dire predictions about what this means for oncologists and cancer patients, including: (1) Doctors will quit practicing, and (2) Patients will be forced to get their chemotherapy at hospitals instead of a doctor's office. However, sources doubted that the reimbursement changes will spur more use of oral medications.

Doctors were questioned at the San Antonio Breast Cancer Symposium about how this will affect them. An Illinois doctor commented, "Practices that succeed will have a good cost analysis to determine which patients have to be sent to the hospital for treatment. I hope we send zero…Practices have built-in overhead, so you can't save money by sending patients to the hospital for chemotherapy…But we will close secondary or tertiary offices, so patients will have to travel farther."

Miscellaneous

Amgen's Neulasta (pegfilgrastim)

Phase III data was presented showing that the majority of neutropenic complications occurred in the first cycle of chemotherapy treatment for breast cancer patients who did not get Neulasta. The study found that administering Neulasta beginning in the first and subsequent cycles of chemotherapy reduced the rate of infection (febrile neutropenia) by >90%. Hospitalization and the use of IV anti-infectives also were significantly lower when Neulasta was administered on this schedule.

♦