Trends-in-Medicine

December 2004

By Lynne Peterson

SUMMARY

Bone loss/fractures and timing with tamoxifen are concerns with all aromatase inhibitors. ♦ **BiogenIdec's** Rituxan looks promising in CLL. ♦ The outlook appears positive for **American Pharmaceutical Partners'** Abraxane, though survival data are still needed. ♦ **Celgene's** Thalomid – and perhaps Revlimid – appears to have activity in recurrent ovarian cancer. ♦ **Cell Therapeutics** appears close to an SPA agreement with the FDA for Xyotax, which would be a positive sign. ♦ **Genentech's** Herceptin may be safe to use with lower dose anthracyclines, perhaps sequentially instead of concurrently. ♦ New data on **Johnson & Johnson/PharmaMar's** Yondelis suggested that it may be more effective when dosed less frequently. ♦ **Lilly's** Alimta is gaining popularity in combination therapy for lung cancer, and it may move to more front-line use. ♦ **Millennium's** Velcade looks promising in mantle cell lymphoma. ♦ New data indicate the fatigue with **Pfizer**'s SU-11248 is not cumulative and doesn't adversely affect quality of life. ♦ **Roche's** Xeloda may get a boost from the Medicare drug plan in January 2006 – but mostly from oncologists who are unable to organize an efficient, profitable infusion center. ♦ **SuperGen's** Dacogen was filed with the FDA and is likely to challenge **Pharmion**'s Vidaza.

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

CHEMOTHERAPY FOUNDATION SYMPOSIUM

New York, NY
November 10-13, 2004

The Chemotherapy Foundation Symposium, sponsored by Mt. Sinai Hospital, consists of a non-stop series of short presentations on drugs being investigated for various cancers, generally grouped by cancer type. There are no discussants, no critiques, almost no question/answer periods, and no press conferences. Most of the presentations are reviews of the latest data on the topic, but there are some first-time presentations.

ANGIOGENESIS INHIBITORS

Among the agents in development in this category are:

- Novartis's PTK-787. A speaker commented, "The drug many of us are keeping our eye on is PTK-787." The Phase III CONFIRM-1 and CONFIRM-2 trials of this oral agent in first line metastatic colorectal cancer (CRC) or CRC patients who failed CPT-111/5-FU are now fully accrued.
- Bayer/Onyx's BAY-43-9006
- Novartis's AEE-788
- Pfizer's CP-546,632
- Bayer's BAY-57-9352
- Esai's E7080
- Roche's CPD-4

A speaker predicted that targeting only VEGF may not work because inhibitor resistance is likely to occur, which doesn't happen with small molecules because they target a number of pro-angiogenic growth factors.

Among the questions that need to be answered about these agents are:

- How to monitor drug activity.
- How to establish the optimal dose. Circulating progenitor cells may be a reliable marker.
- Why are the effects of chemotherapy sometimes enhanced with these agents?
- Will efficacy be seen only/mainly in first line treatment?
- What about long-term adjuvant treatment?
- What are the optimal combinations?
- How do non-specific small molecules compare to specific antibodies/trap drugs?
- Do angiogenesis inhibitors work with all or some cancers, and if some, which ones?
- What is the toxicity? A speaker said this may be the most important question.

AROMATASE INHIBITORS (AIS)

Doctors are not sure how to use aromatase inhibitors yet – before or after tamoxifen. A speaker commented, "Tamoxifen has been a good friend to us for many years…I tend to recommend anastrozole for patients who just finished primary therapy, unless the patient has a lot of musculoskeletal complaints, and then I may use tamoxifen. The majority of women who've been on tamoxifen for two or three years, I switch to exemestane, but I follow their bone density. Women who have been on tamoxifen for five years, I offer letrozole." Another speaker said, "It may be wise to use aromatase inhibitors up front; you lose some patients when you wait."

Aromatase Inhibitors

Manufacturer	Brand	Generic
AstraZeneca	Arimidex	Anastrozole
Novartis	Femara	Letrozole
Pfizer	Aromasin	Exemestane

How do the various AIs compare? Experts aren't sure. Among the comments made about this were:

- "Exemestane has a role, but we are not sure where – whether it should be third line or fourth line. It may be more upfront if patients relapse than currently thought."
- "I can't say which is better…I don't think we know definitively which is better."

To help figure out how best to give AIs, a variety of AI trials are underway with different approaches, including:

- **Direct comparison:**
  - ATAC – anastrozole. There will be an update on this at San Antonio Breast 2004.
  - BIG FEMTA – letrozole. Data to be reported "soon."
  - TEAM – exemestane. The design is being changed to five years of exemestane vs. five years of tamoxifen – followed by exemestane.
- **Switching:**
  - BIG 97-02 – exemestane after two years of tamoxifen. There will be an update of this trial at San Antonio Breast 2004.
  - ITA.
  - ARNO/ABCSG. Data will be reported at San Antonio Breast 2004.
- **Extended adjuvant:**
  - MA-17. This trial is tamoxifen for five years followed by randomization to either an AI or placebo.
- **Sequencing –** patients start on an AI and then switch to tamoxifen or vice versa:
  - BIG FEMTA.

Other drugs are being investigated in trials with AIs, including Novartis's Zometa (zoledronic acid) and Pfizer's Celebrex (celecoxib).

Is there weight gain with AIs or tamoxifen? An expert said, "There was no increase in a large trial. Women complain they gain weight…and some of my colleagues think they redistribute weight…but I don't get a sense there is a real weight gain problem with AIs."

BONE LOSS AND FRACTURES IN CANCER PATIENTS

One of the concerns with AIs for breast cancer patients, androgen deprivation therapy (ADT) for prostate cancer, and chemotherapy is general bone loss and fractures. Speakers described the various AIs as relatively comparable on this issue. One said, "There is no difference in one AI from another in terms of increased fracture risk."

A speaker explained, "AIs increase bone resorption which translates into decreased BMD…This is a major problem…ASCO guidelines suggest that women >65 on an AI and men >70-75 on ADT should have baseline BMD and yearly follow-up…A 3% increase in BMD predicts a 46% reduction in long-bone fractures over 1-3 years.

Among the studies to watch in this area are:

- ZO-FAST/Z-FAST study of letrozole+immediate Zometa vs. letrozole+Zometa as needed.
- A study of Amgen's AMG-162 given subcutaneously every 3-6 months.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Both BiogenIdec's Rituxan (rituximab) and Berlex's Campath (alemtuzumab) were described as "quite promising" in CLL – but in combination with chemotherapy, not as single agents. Single agent Rituxan has only a 10%-13% response (all PR) in previously treated CLL, and the median durability is only 12-15 weeks. A speaker said, "If you increase the dose as a single agent, you might get more responses but not as wonderful as we would like to see."

The speaker suggested these Rituxan combinations.

- Fludarabine+cyclosphosphamide+Rituxan (FCR), which was described as producing "an amazingly positive result."
- Fludarabine+Rituxan (FR), with Rituxan given monthly for up to six months. Both concurrent and sequential administration have acceptable toxicity, but concurrent administration appears to have better CR (47% vs. 28% for sequential).

Campath may also have a role as adjuvant therapy after FCR or FR.

COLORECTAL CANCER (CRC)

"The bottom line," a speaker said, "is that IFOX (Iressa+FOX) is highly active in advanced CRC, though it is associated with more nausea and vomiting than FOLFOX4…Does Iressa (AstraZeneca, gefitinib) really add to clinical benefit? We really need a Phase III, and that probably will never be done – for many reasons, including practice and economic reasons."

Is EGFR inhibition by oral drugs equivalent to monoclonal antibodies? A speaker said, "This is a huge question in oncology. We have a growing number of agents, literally hundreds of such drugs are being developed by biotech and big pharmaceutical companies, and many of them hit the same targets. That (monoclonals vs. orals) is the kind of Phase III trial we should start thinking about…And combining inhibition of EGFR and VEGFR will soon be possible with some small molecules."

Anti-VEGFs in Development to Treat CRC

Manufacturer	Drug
Approved	
AstraZeneca	Iressa (gefitinib)
Genentech/OSI	Tarceva (erlotinib)
Genentech	Avastin
Phase III	
Bayer	BAY-43-9006
Novartis	PTK-787
Pfizer	SU-11248
Phase I/II	
Amgen	AMG-706
AstraZeneca	ZD-6474 ZE-2171
Cephalon	CEP-755
N/A	BW-786034
Regeneron	VEGF-TRAP

CUTANEOUS T-CELL LYMPHOMA (CTCL)

The agents in development to treat CTCL that appear the most exciting are:

- **BIOCRYST'S BCX-1777** (a PNP inhibitor). Data from the Phase I dose escalation study were not presented at ASCO 2004, but an abstract has been accepted at American Society of Hematology (ASH) 2004. Dr. Madeleine Duvic of MD Anderson, probably the leading authority on cutaneous T-cell lymphoma (CTCL), described this as "a small study, and the response rate was very tentative…It was mostly a PK study." She said the design of that Phase I study was: Patients got 9 infusions at the hospital, and then went home. "Response – impact on the skin – was measured not when it was happening in the hospital but when they came back to the doctor – which was too late…The design was unfortunate…there was a clinical benefit, but the timing (of the measurement was off…We did find that patients got enough drug to lower DGUO levels to a dose that was able to kill T-cells…It is promising to go forward…I had one patient with very good response – almost CR – after three courses…There is a dramatic white count response in leukemias."

"There is no rebound" when the drug is stopped, Dr. Duvic insisted. The disease (skin manifestations) return when the drug is stopped, but they are not worse than before taking the drug, so there is no rebound. However, Dr. Duvic is more excited about the Phase I trial of an oral formulation, commenting, "The daily IV is very difficult to do."

- **COLEY'S PHARMACEUTICALS' CPG**, which is now in Phase II.

- **GENMAB** which "is trying to start a trial" of HuMax-CD-4 in CTCL.

- **IL-12.** In an NCI-sponsored trial of IL-12, patients get IL-12 for 12 weeks and then IL-2 is added if they don't respond. Dr. Duvic described this as "interesting."

- **MERCK/ATON'S suberoylanilide hydroxamic acid (SAHA),** which is in Phase II trials, including a Phase II in patients refractory to Ligand's Targretin (bexarotene).

DNMT INHIBITORS AND HDAC INHIBITORS

DNMT and HDAC Inhibitors

DNMT inhibitors (hypomethylating agents)	HDAC inhibitors (histone deactylase inhibitors)
Pharmion's Vidaza (5-azacitidine)	Merck/Aton's Suberoylanilide hydroxamic acid (SAHA)
SuperGen's Dacogen (decitabine)	Abbott's Depakote (valproic acid)
MGI Pharma's MG-98	Gloucester Pharmaceuticals' Depsipeptide (FK-228)
Zebularine	Triple Crown America's Phenylbutyrate
	Schering AG's MS-275
	Novartis's LAQ824
	Novartis's LBH589

EGFR Inhibitors

A speaker offered this interesting comment, "What is a disappointing thing about these drugs – Iressa and Tarceva – is that when you add them to chemotherapy, they appear to have no effect. The addition of EGFR inhibitors does not add to survival in the general population, though there may be a subgroup that benefits…What we don't know in practice now is how to best sequence the EGFR inhibitors with chemotherapy….Theoretically, if you give one of these, you may sensitize patients to chemotherapy."

➢ **Mutations.** An expert said that oncologists in Japan are finding EGFR mutations in 25%-30% of Japanese patients, which compares to about 5%-10% of U.S. patients with the mutation." The problem with the mutations is that not everyone with a mutation will respond, some patients without mutation do respond. So, it is not a perfect indicator to use to direct therapy with EGFR inhibitors. However, mutations may be used to identify patients who will respond best to an EGFR inhibitor – and maybe early treatment with an EGFR inhibitor will be beneficial in these mutation-positive patients.

Mutations may not predict response to anti-EGFR monoclonal antibodies such as Imclone's Erbitux (cetuximab). An expert said, "It is hard to get tissue from lung cancer patients…We need tissue; biopsies are no longer optional…We are now waiting for prospective studies to see the predictive value of mutations…You don't have to have mutations to get a response, but it does look like if you have the mutation, it is more likely you will have a response."

➢ **Rash.** There is still a debate about whether rash correlates with response to EGFR inhibitors (Iressa and Tarceva), but those who claim there is a relationship appear to be winning. A speaker said, "Initially it was thought rash was not a predictor of response, but more and more data are coming out that it may be a predictor…There also appears to be a correlation between rash and survival." Another expert said, "We need better data (on the relationship of rash to response), but it may be hard to get if we treat the acne upfront (which many doctors are doing)."

➢ **Interstitial pulmonary fibrosis.** A speaker said no interstitial pulmonary fibrosis has been seen in the ongoing trials, which he described as "reassuring."

EPOTHILONES IN NSCLC

Microtubule stabilizers include:

- Bristol-Myers Squibb's
  - BMS-247550 (ixabepilone). Key toxicities to watch are peripheral neuropathy and myelosuppression, which have been difficult.
  - BMS-310705
  - BMS-184476
  - BMS-188791
- Novartis's EPO-906 (an analog of epo B). In vivo data show activity, and it crosses the blood brain barrier in animals. It is not mutagenic, has no cardiotoxicity, and it is better tolerated in humans than in animals. Recent trials have used an every-three-weeks schedule with improved safety and efficacy – with proactive diarrhea management. A Phase I/II dose escalation study is ongoing, and preliminary results were presented at the European Society for Medical Oncology 2004. When the MTD is reached in that trial, a Phase II efficacy trial will begin.
- Sanofi-Aventis's TXD-258

ERYTHROPOIETIC AGENTS

A speaker predicted that new targeted therapies, such as Novartis's Gleevec (imatinib), will change the manner in which we think about cancer therapies, "The integration of new therapies with EPO is important…Gleevec is considered relatively non-toxic, but 50% of patients experience fatigue with 400 mg and 58% have fatigue with 800 mg."

This expert also described the various erythropoietins are fairly comparable. He said, "Essentially, it is pretty hard to tell the difference between the (EPO) agents. Overall, the differences are remarkably subtle. So, at least the field has two very good agents with remarkably similar safety and efficacy profiles."

Another speaker reviewed some data on 175 cases of PRCA reported under the FDA's adverse event reporting system (AERS) with EPOs. This data will be presented in more detail at ASH 2004.

PRCA Patient Outcomes

Treatment	Number of patients	Recovery
Renal transplant	22	95%
Cyclophosphamide ± corticosteroids	13	69%
Other Immunosuppressant therapy	3	67%
Cyclosporine ± corticosteroids	21	57%
Corticosteroids	34	44%
Rituxan	3	33%
IVIG	10	20%
No immunosuppressive therapy	69	1%

GASTROINTESTINAL STROMAL TUMORS (GIST)

A speaker said oncologists are seeing increased resistance to Gleevec in GIST, and he pointed to three drugs to watch in this space:

➢ **Novartis's RAD-001**, an mTOR inhibitor (a rapamycin analog), in combination with Gleevec. He said, "Interesting lesion decreases have been seen with this combination."

➢ **Pfizer's SU-11248**. He said PET scans are an early indicator the drug is working and responses can be seen up to two months earlier than with CT scans. A Phase III trial of 357 patients is underway and is expected to finish enrollment in 1Q05.

➢ **Bristol-Myers Squibb's BMS-3548325**.

NOVEL KINASE INHIBITORS

There are two types of kinase inhibitors:

- **Mitotic kinesins.** These are motor proteins that translate chemical energy into mechanical force and induce movement.

- **Mitotic kinases,** including:
  - Aurora. Both Vertex (VX-680) and Merck have compounds entering the clinic, with VX-680 possibly going into human trials by the end of 2004.
  - Polo.
  - Other.

Kinase inhibitors in development include:

- Cytokinetics' SB-715992. A variety of Phase II studies are underway. There is no alopecia, neurotoxicity, or mucositis, and no premedication is required.
- ZM-447439 is a modified version of an Aurora A inhibitor that inhibits both Aurora A and B.
- Hesperiden, an herb.

SPECIFIC COMPANIES AND PRODUCTS

ABGENIX/AMGEN'S Pantimimumab (ABX-EGFR)

Four trials in CRC are still ongoing, but a speaker reviewed the results of two completed trials of pantimimumab in CRC, concluding:

- In one trial, it was well-tolerated, with only one infusion reaction, but in the other trial there was unacceptable diarrhea.
- No HaHa antibodies have been detected so far.
- OR ranged from 10%-47%, SD from 32%-38%.
- The duration of response was 15 months, and the duration of SD was 56 months.
- There was no relationship between response and exposure to two or three prior drugs or with EGFR status.
- There was a suggestion of a correlation with rash.

AMERICAN PHARMACEUTICAL PARTNERS' Abraxane (ABI-007)

This cremaphor-free formulation of paclitaxel has been submitted to the FDA for the treatment of metastatic breast cancer. The company sponsored an evening symposium at the Chemotherapy Foundation meeting, with Dr. Richard Pazdur, Director of the FDA's Oncology Drug Products, as the featured speaker.

An Abraxane researcher reviewed some of the trial data so far on this agent. Among the points she made were:

- There is no survival data yet from this trial.
- A dose of 260 mg/m^2 was chosen for the Phase III trial, but the investigator said this as easily could have been 240 mg/m^2 or 250 mg/m^2, "We chose 260 mg/m^2 because of a hint of first line response."
- The neuropathy may be due to the paclitaxel and not the cremaphor.
- ASCO 2005 will have data on weekly Abraxane (dosed at 125 mg/m^2) in taxane refractory metastatic breast cancer. So far, an investigator said it has been well-tolerated at full dose, with no need for dose reduction and on 4% Grade 3 neuropathy (which was lower than the expected 10%).
- Asked if there is preclinical evidence for Abraxane accumulation in tumor cells, she said, "That is a good question, but it is difficult to answer…It is very difficult to get tumor biopsies from patients, but there is preclinical data."
- In November 2004, the large, Phase II, NCCTG N-043 Study was expected to start, examining weekly dosing of Abraxane at 100 mg/m^2 in combination with either gemcitabine, capcitabine, or carboplatin.

There will be an abstract at the San Antonio Breast Cancer meeting on Abraxane dosed weekly at 125 mg/m^2. A speaker said, "Weekly administration compares favorably to weekly Taxol (paclitaxel) on neutropenia (1% vs. 5%) and Grade 3 neuropathy (4% vs. 9%)…Phase III data on Q3 dosing vs. our weekly dose suggests these two ways may be effective and well-tolerated."

Abraxane Results

Measurement	Paclitaxel 175 mg/m^2	Abraxane 260 mg/m^2	p-value
CR+PR	18.7%	33.2%	<.001
TTP	16.1 weeks	21.9 weeks	.092
Safety			
Hypersensitivity	Grade 2 = 0 Grade 3 = 1 Grade 4 = 0	Grade 2 = <1 Grade 3 = 0 Grade 4 = 0	---
Flushing	Grade 2 = 5 Grade 3 = 0 Grade 4 = 0	Grade 2 = <1 Grade 3 = 0 Grade 4 = 0	---
Sensory neuropathy	Grade 2 = 10 Grade 3 = 2 Grade 4 = 0	Grade 2 = 20 Grade 3 = 10 Grade 4 = 0	---
Median time for sensory neuropathy to improve or resolve	78 days	22 days	---
Fatigue	Grade 2 = 16 Grade 3 = 3 Grade 4 = <1	Grade 2 = 13 Grade 3 = 8 Grade 4 = <1	---

AMGEN'S Neulasta (pegfilgrastim)

A speaker at an Amgen-sponsored session gave Neulasta a push. She commented, "NHL patients are at greater risk for febrile neutropenia during the first cycle of chemotherapy, so the wait-and-watch approach is not as valid as treating initially."

There will be new data presented at the San Antonio Breast Cancer meeting this year on use of Neulasta for febrile neutropenia in taxotere-treated breast cancer.

ASTRAZENECA'S Iressa (gefitinib)

Iressa does not look very promising in ovarian or cervical cancer.

- A speaker reported disappointing accrual for a cervical cancer trial – and a very poor outcome for those patients who did enter the trial. They were able to stay on drug only a short time because of progressive disease.
- Ovarian cancer patients also progressed rapidly despite the Iressa.
- Drug-related adverse events were pretty severe and treatment-limiting.
- Adverse events were severe and limited therapy.

BAYER/ONYX'S Sorafenib (BAY-43-9006)

A speaker reported on:

- **Renal cell carcinoma (RCC).** In a 484-patient trial of 400 mg BID sorafenib, the primary endpoint was positive, but the side effects included: ~40% grade 1-2 rash and hand-foot syndrome, ~30% other dermatitis, and ~25% alopecia. The conclusion was that sorafenib has activity as a single agent in RCC.
- **Melanoma.** A 39-patient study in stage IV melanoma reported 7 SD and 1 PR. Interestingly, four patients randomized to placebo at Q2W progressed but stabilized again after re-starting sorafenib. A researcher concluded sorafenib has "relatively limited activity as a single agent in melanoma, but it may have more activity in combination with chemotherapy."
- **NSCLC.** This study found 37% of patients had a duration of response for nine months or longer with sorafenib.

BIOGENIDEC'S Zevalin (ibritumomab tiuxetan)

➢ **DLBCL** (diffuse large B-cell lymphoma) accounts for 31% of NHL cases, and Zevalin followed by Rituxan looks promising in relapsed or refractory DLBCL patients not eligible for stem cell transplant. A speaker reported on eight-month data on the first six patients in a 38-patient trial of this therapy in very heavily pre-treated patients (who were elderly with a significant number of prior therapies, some of whom had progressed on prior Rituxan therapy). The initial response was described as "disappointing," but the toxicity was considered "acceptable," and there were no treatment-related complications. However, there was one very serious extravasation that the investigator reported to the FDA and to the company because it is not a listed side effect. This approach is likely to be dead unless an ongoing European trial in relapsed patients is positive.

➢ **Follicular NHL** appears to be a better indication for Zevalin. An investigator reported more results from a multicenter, community-based, Phase II study reported at ASCO 2004 of R-CHOP followed immediately by Zevalin in first-line treatment of 42 follicular NHL patients. He concluded, "This approach is of increasing interest. Early results from four similar trials showed CRs of 67%-80% with Bexxar (Corixa, tositumomab) and 67% with Zevalin in this trial…But all of these studies are too early to draw conclusions."

Phase II Trial of R-CHOP+Zevalin in DLBCL

Measurement	Chemotherapy	Zevalin
Mean follow-up	24 months	
CR	28%	67%
PR	72%	31%
Stable	0	0
Progression	0	2%
PFS	N/A	77% at two years
Grade 3/4 Toxicity		
Neutropenia	---	74%
Thrombocytopenia	---	47%

CELGENE

➢ **Thalomid (thalidomide).** In a small trial, thalidomide showed some "modest" efficacy in recurrent ovarian cancer. A speaker said, "The main benefit is this is extremely easy to administer and has much less toxicity than other (comparable) regimens." There is an ongoing randomized trial of thalidomide vs. tamoxifen.

Another small (40-patient) trial suggests thalidomide also may have activity – a cytostatic effect – in pancreatic cancer. A speaker said, "It did not adversely effect the patients, and it may have improved their quality of life…Mean TTP was 17 weeks (vs. 9 weeks), so it appears there is an improvement in TTP…Gemcitabine+thalidomide appears to have some promise in advanced pancreatic cancer." However, researchers believe Revlimid may be an even better choice than thalidomide, and more studies are planned with the combination of gemcitabine and Revlimid.

➢ **Revlimid (lenalidomide, CC-5013).** A speaker reviewed a 43-patient Phase I/II safety and efficacy study in MDS that

was initiated in March 2002, looking at three dosing regimens: 25 mg QD po, 10 mg QD po, and 10 mg x 21 days.

Revlimid In MDS

Measurement	Revlimid
Prior EPO failures	78%
Prior Thalomid failures	28%
Dose reduction due to myelosuppression	62% at 25 mg po QD 62% at 10 mg po QD 45% at 10 mg x 21 days
Primary endpoint: Erythroid response	67%
Major erythroid response	58%
Thrombocytopenia	6 patients (but one had major platelet response)
Neutropenia	10 patients (but two had major platelet response)
Maximum Hgb achieved	13.4 g/dL
Kariotype 5q-	91% responded
Durability of Response as of 11-1-2004	
51 patients	84+ weeks
Normal kariotype	62+ weeks
Others	56 weeks
5q- patients still responding at 2 years	78%

Researchers also are enthusiastic about the outlook for an ongoing trial of Revlimid in recurrent ovarian/peritoneal cancer. A speaker said, "In the lab, it seems to show significantly more potency than thalidomide, and the safety profile is better, with much less neurotoxicity, no teratogenic effects, and less sedation…Preliminary results indicate that this is much less toxic (than thalidomide), and there appears to be some efficacy."

CELL THERAPEUTICS

➢ **Xyotax (CT-2103).** The STELLAR trials are investigating this new formulation of paclitaxel (with a biodegradable polygutamate polymer) in NSCLC.

- STELLAR-2 – Data for this Phase III trial of Xyotax vs. docetaxel in second line NSCLC will be available in 1H05.
- STELLAR-3 – Data will be available in the first quarter of 2005. This is a Phase III, 447-patient survival trial of carboplatin+Xyotax vs. carboplatin+paclitaxel at front-line treatment in NSCLC patients with poor performance status (PS2). At almost one year it had not yet met the median survival reporting point, with just 254 events of the required 311. More doses have been tolerated than in published data (42% of patients in STELLAR-3 have had 5-6 cycles of therapy).
- STELLAR-4 – No information was available on when the data will be available on this Phase III trial of Xyotax vs. either gemcitabine or vinorelbine for front-line treatment of PS2 NSCLC patients.

Xyotax also is being studied in ovarian cancer. The company has had a "successful" SPA meeting with the FDA and has been granted accelerated approval. A Phase III trial is expected to be initiated before the end of this year as first line maintenance in ovarian cancer.

➢ **Trisenox (arsenic trioxide, ATO).** A speaker at this meeting reiterated the message from ASH 2003: start using either MAC (melphalon + IV arsenic trioxide + IV vitamin C) or Velcade (Genentech, bortezomib) in multiple myeloma patients with renal failure.

GENENTECH

➢ **Avastin (bevacizumab).** In a metastatic CRC (mCRC) trial, the Avastin monotherapy arm was stopped for lack of efficacy, but other randomized Phase III trials found the combination of Avastin+FOLFOX or Avastin+XELOX (Xeloda+Eloxatin) are "highly active regimens" in first line treatment of mCRC. Hand-foot syndrome requires dose modification in most patients (80%). Clinical efficacy data is expected at ASCO 2005 on FOLFOX+Avastin in first and second line treatment of CRC, and randomized Phase III trials are ongoing comparing Avastin+FOLFOX vs. Avastin+XELOX in first and second line settings.

➢ **Herceptin (trastuzumab).** Dr. Edith Perez, of the Mayo Clinic, reviewed the cardiac safety of anthracyclines with Herceptin, suggesting that lowering the dose of doxorubicin or using another anthracycline may improve the cardiac safety of combination therapy. She said, "Trials suggest Her2 patients benefit from anthracycline-based therapy but don't prove it convincingly. The methodology for Her2 testing is not perfect, and we can't be positive of the cardiac risk without better testing….We now limit the amount of doxorubicin to ≤200 mg/m^2, and we use Herceptin sequentially, not concurrently." She also recommended baseline and periodic LVEF monitoring in combination therapy patients.

There are a variety of Herceptin/anthracycline trials testing concurrent and sequential administration that should help answer this question. There will be data at ASCO 2005 on Herceptin used sequentially, not concurrently, with anthracyclines.

She noted that doxorubicin increases the risk of CHF more than peg-doxorubicin or epirubicin.

- Epirubicin. "I can't conclude this will have CHF rate <3% which is what we would probably tolerate, but this regimen is very promising."
- Pegylated doxorubicin. Pilot data presented at ASCO 2003 showed no CHF when combined with Herceptin, and there will be an update at San Antonio Breast 2004. "The challenge with this regimen is hand-foot syndrome."
- Liposomal doxorubicin.

➢ **Omnitarg (pertuxumab, 2C4).** Omnitarg is an antibody designed to inhibit tumor growth and survival by inhibiting HER dimerization; thus, it is a HER dimerization inhibitor (HDI). Preliminary results were presented from a Phase II trial of Omnitarg (420 mg every 3 weeks) as monotherapy in 63 ovarian cancer patients who failed platinum-based therapy. A speaker said, "You may be seeing a similar phenomenon to lung cancer. The mutation rate is small…and there does appear to be a benefit to mutation patients...but there is a small group who benefit who do not have the mutation."

Omnitarg Phase II Results in Ovarian Cancer

Measurement	Results
Grade 1-2 diarrhea	25.9%, mostly manageable with Imodium
Grade 3 diarrhea	9.8%
Drop in LVEF>10%	16.4%
CHF or LVEF<50	0
Infusion reactions	"Some"
Primary endpoint #1: (first 57 patients) Overall response rate	1 PR 5 SD 1 mixed response
Primary endpoint #2: HER2 response (in 50% of patients evaluated)	Detect ed in 1/3 of pre-treatment biopsies. Regression of tumor may be associated with Her2 positivity.

➢ **Tarceva (erlotinib) plus Avastin (bevacizumab).** This combination therapy appears promising in lung cancer. A speaker noted, "Treatment with two targeted therapies with two different pathways is certainly better than one…The FDA was very worried about bleeding in lung cancer patients getting Tarceva, but in a small 40-patient trial there was no bleeding…Tarceva+Avastin is well-tolerated, with the most common adverse events rash and diarrhea but never more than mild to moderate."

GENTA/SANOFI-AVENTIS'S Genasense

In lung cancer, Genasense may have a role as a sensitizer for Iressa. A speaker reported on cell line and xenograft studies of the combination of Genasense and Iressa which showed better effect with the combination than either alone, suggesting synergy.

Genasense also is being tested with other drugs, including Doxil, carboplatin, etoposide, and biologics.

- Accrual is complete in a Phase I study of Genasense with either carboplatin or etoposide, and the results (12-month survival) should mature sometime in 2005.
- A 298-patient, Phase II study will be unblinded "soon" of Genasense and Doxil in Stage IIb/IV second line NSCLC. Toxicity and efficacy data are expected at ASCO 2005.
- Trials with EGFR inhibitors are being discussed.

IMCLONE/BRISTOL-MYERS SQUIBB'S Erbitux (cetuximab, C-225)

The big question is whether Erbitux can move into the Stage 3 locally advanced NSCLC setting. There are about 40,000 Stage 3 patients a year in the U.S. A Phase II study of Erbitux in combination for this indication is ongoing, with 30 patients accrued so far, and accrual was described as "picking up." The first look at the data will be at the RTOG meeting in January.

JOHNSON & JOHNSON/PHARMAMAR'S Yondelis (trabectedin, formerly ecteinascidin and ET-743)

This sea snail toxin derivative was found not approvable by European regulators in 2003, but a late breaker report at the Chemotherapy Foundation meeting suggested that every three week dosing may be more effective than the more frequent dosing that had been tested in the past. A doctor reported on 78 patients in a Phase II trial in advanced or metastatic leiomyosarcoma and liposarcoma refractory to conventional therapy. He concluded, "I believe trabectedin has important second line activity in these patients, and every three week dosing is preferred…There was transient hepatic toxicity but no significant or long-term clinical consequences…Unofficial data since this (preliminary look) support this difference." The study is now being expanded.

Yondelis Results

Manufacturer	Arm 1	Arm 2
Dosing	.58 mg/m^2 over 3 hours	1.5 mg/m^2 over 24 hours
Schedules	Weekly 3 weeks out of 4	Every 3 weeks
Evaluable patients	45	33
Progressive disease	32	17
Stable disease	12	14
Partial response	1	4
Overall benefit rate	28%	51%
Neutropenia	7%	50%
Febrile neutropenia	0	0
Thrombocytopenia	5%	5%
Anemia	4%	2%
ALT elevations	2%	45%
AST elevations	0	31%
Fatigue	32%	43%

Obviously, the issues are hepatic toxicity and ALT elevations. However, these appear to peak in 4-5 days and then resolve in about 10 days, and they are dose-dependent. No liver failure or chronic liver disease was seen, and there was no significant bilirubin elevation.

LILLY'S Alimta (pemetrexed)

➢ **Small cell lung cancer.** A speaker said the ease of administration and convenience of Alimta doublets make this an attractive therapy in small cell lung cancer, but the clinical outcomes from the Phase II trials are needed – and that is not available yet. Another speaker said preliminary results in ES-SLC are "promising."

➢ **NSCLC.** Alimta is approved for second-line therapy of NSCLC, but researchers want to look at it as first line in combination with either carboplatin or oxaliplatin. A Canadian speaker said both regimens appear to provide a favorable risk:benefit profile relative to other combination regimens for the treatment of NSCLC, "I'm looking with preference to carboplatin more than oxaliplatin…It is nothing against oxaliplatin, but it is a matter of money." Another expert said, "My personal opinion is this will likely replace docetaxel in the second line setting…If something works well in second line, it probably will work first line, so platinum+Alimta trials are underway in advanced NSCLC, including a large Phase III trial in Europe of ~1,700 patients comparing cisplatin+Alimta to cisplatin+gemcitabine."

➢ **Mesothelioma.** Folic acid and vitamin B12 must be taken with Alimta in this indication. Supplementation with vitamins improves the ability to deliver this therapy; with vitamin care, a regimen of Alimta+cisplatin is deliverable, and the combination significantly improves survival, TTP, pain, and shortness of breath over cisplatin alone.

MILLENNIUM'S Velcade (bortezomib)

This agent looks promising in mantle cell lymphoma. In a study of Velcade in indolent lymphomas, the highest response rate was in mantle cell lymphoma, where 54% of the 30 patients had an ORR (2 CR, 9 PR), with a median duration of response of 6 months. The DLT is thrombocytopenia, but a speaker said it "doesn't last very long." There also is some sensory neuropathy, but that was reported to be less in lymphoma patients than in multiple myeloma. However, there have been some cases of small vessel necrotizing vasculitis, and that is new and will be discussed in more detail at ASH 2004.

Other major questions about the use of Velcade in lymphoma in general and mantle cell lymphoma in particular are:

- Dosing. These results were achieved with a slightly higher dose than usual – 1.5 mg/m^2 rather than 1.3 mg/m^2.
- Can a "rituximabesque" approach be used?
- How much re-treatment is possible?
- Should patients be treated with a maintenance regimen or an as-needed basis?

There will be numerous presentations on Velcade at ASH 2004.

NOVARTIS'S Everolimus (RAD-001)

This is being studied as a single agent and in combination with PTK-787. A speaker said, "Combination therapy is more likely to succeed than monotherapy with this agent…The ability to select sensitive populations (molecular pathology) may be critical for success…Maybe we can give a fairly low dose and inhibit the target and then move into combination therapy where it may be more active."

PFIZER'S SU-11248

A speaker said what was striking in the Phase II study in CRC was a 33% PR and 3-month SD of 37%. He said, "Historically, at our center, in this setting, the median TTP is 2.8 months, but with SU-11248 the mean time to progression was 8.3 months, which is relatively long."

Fatigue has been reported as a side effect with SU-11248, and new data presented at the Chemotherapy Foundation meeting on quality of life included a fatigue questionnaire. A speaker said, "A high number of patients turned in the assessment, and quality of life was relatively balanced and stayed equal to the normal population. Fatigue was not cumulative over the course of the study."

Comparison of SU-11248 to Other 2nd Line Therapies

Drug	ORR	TTP
SU-11248	33%	8.3 months
IL-2	5%	N/A
Interferon	2%	N/A
Avastin (high dose)	10%	4.8 months
Avastin+Tarceva	21%	11.0 months
Multiple agents in Phase III trials	3%	2.9 months

A 690-patient, randomized, open-label, Phase III trial in first-line therapy is comparing SU-11248 to INF-α started enrolling patients in August 2004 in Europe, Australia, Japan, and four sites in New York. The primary endpoints are survival and TTP.

ROCHE'S Xeloda (capecitabine)

Infused 5FU remains the backbone of CRC therapy, but speakers insisted that oral Xeloda can replace 5FU/LV as both monotherapy and in combination with either Pfizer's Camptosar (irinotecan) or Sanofi-Aventis's Eloxatin (oxaliplatin). A speaker said, "Capecitabine is at least as effective as 5FU/LV. It reduces risk of death and relapse by 13%-16%, has better toxicity, and offers cost savings… Capecitabine is likely to – and should – replace 5FU/LV as both a single agent, and probably in combination…I think we can conclude XELOX (Xeloda+oxaliplatin) is at least as effective as FOLFOX."

Asked what will happen to Xeloda usage in 2006 when the Medicare drug benefit goes into effect, doctors predicted that the situation in oncology may be a little like what happened in rheumatology when infused drugs were introduced – doctors who can set up efficient operations will do infusions, and those who can't or don't find a way to make money with infusions will opt for oral medications. Among the comments were:

- *Washington DC:* "The best way to make money in the new world is to have an efficient infusion operation – to be the fast food of oncology. The more efficient we are at delivery, the better. The best billing code is a one-hour infusion. We will never lose money on 5FU. The one chance the oral medications have is doctors who don't deal with infusions. But the co-pays will sink oncology. Doctors will have to collect it."
- *New York:* "It is hard to know. Oncologists don't want to make money on drugs, but the reimbursement setting has forced that. Large groups with infusion centers may do better with infusions, and others may prefer orals. The (Medicare) donut hole will make it very difficult, too."

SUPERGEN'S Dacogen (decitabine)

Dacogen, to be co-marketed by MGI Pharmaceuticals, was submitted to the FDA on November 1, 2004 for the treatment of MDS. There is no test for myelodysplastic syndrome (MDS); it is diagnosed based on abnormal bone marrow morphology. Survival is only 0.4-5.7 months, but there is a curative treatment – transplant. In Phase II, Dacogen showed clear evidence this drug worked, a speaker said. He reported on some preliminary findings from the Phase III trial (that has not yet been presented), concluding, "It now seems that decitabine will have a role in these two disorders – MDS and AML." There will be more data presented at ASH 2004.

Phase III Trial of Dacogen in MDS

Measurement	Dacogen	Supportive Care	p-value
ORR	25%	2%	.001
Median time to event (by ITT)	338 days	263 days	---
Grade 3/4 neutropenia	87%	N/A	---
Nausea	39%	17%	---
Vomiting	24%	9%	---
Deaths on study	14%	22%	Nss

An expert from MD Anderson Cancer Center said that Dacogen has shown encouraging activity in AML, RAEBT, and CML. However, he warned doctors to be patient because it can take time for patients to get a response, "Patients can go into CR as late as 6-8 weeks into therapy without additional treatments." He also thinks Dacogen may work better in combination with valproic acid or idarubicin.

The Vidaza (Pharmion, 5-azacitidine) approval in MDS was based on very few patients, and he thinks low dose Dacogen will have a similar response rate. He thought Dacogen would have had a better than 33% OR and perhaps a statistically significant impact on TTP if the dose had been pushed for multiple cycles or given indefinitely. He also argued that you can't compare the Phase III trials of these two drugs because the trials were too different and that Dacogen patients were sicker, "My feeling has always been that decitabine is a unique, active agent in MDS and CML, so at MD Anderson we optimize the schedule of decitabine further…and we are trying to develop easier schedules (including subcutaneous administration)."

A study of different Dacogen dosing regimens is underway in very high risk patients, and in the first 53 evaluable patients, there has been no renal or liver toxicity, myelosuppression has been "tolerable," the OR was >70%, and the CR 40%-43%. This expert said, "In my opinion, this is the highest degree of activity of a single agent at a not-intensive chemotherapy dose …And we are looking at patients who got intensive chemotherapy vs. decitabine…So far, it appears decitabine is matching or improving survival compared to intensive chemotherapy, and that is very reassuring."

Comparison of Dacogen and Vidaza

Measurement	Dacogen	Vidaza
IPSS	70	41
Prior therapy	30%	16%
Mean # of courses	3	9
Response criteria	New	Old
Mean duration of MDS	6 months	2 months
Study design	Prospective	Retrospective

Dacogen also is being studied in:

- CML patients who fail Gleevec, and the data so far look "very favorable."
- MDS patients who fail Vidaza.
- As combination therapy with an HDAC, such as Johnson & Johnson's Zarnestra (R-115777) or Celgene's Revlimid.
- In solid tumors.
- Sickle cell disease.

DIAGNOSTIC TESTING

Diagnostic assays also got some attention at the Chemotherapy Foundation meeting.

GENOMIC HEALTH'S Oncotype DX is a clinically validated diagnostic assay that quantifies the likelihood of breast cancer recurrence in women with newly diagnosed, Stage I or II, node negative, estrogen receptor positive breast cancer who will be treated with tamoxifen. The 21-gene assay is

performed using formalin-fixed, paraffin-embedded tissue. An expert said this is real-time PCR, CLIA-approved, available now, and "ahead" of Arcturus' Paradise test (which determines which women are tamoxifen responders). Kaiser reportedly did a controlled study of its own database with this system and liked the results. He commented, "What's exciting is that this test also predicts for chemotherapy benefit…I think you can use this test more to predict chemotherapy use than tamoxifen…With quantitative OR levels and real-time PCR, it is highly predictive of tamoxifen responders. It is very definitive of tamoxifen benefit. If a woman had a lower likelihood of benefit, I wouldn't skip tamoxifen, but I would add something else."

Could this test help doctors decide whether to prescribe tamoxifen or an AI? An expert said, "We haven't looked at AIs. If we can find tissue banks, we would like to do that."

There will be more information about this test at the San Antonio Breast meeting 2004.

ACLARA BIOSCIENCES'S eTAG Assay is designed to help select patients for receptor-targeted therapy (Iressa and Tarceva). The system measures protein dimer targets in small samples of real human tissue, not formalin-fixed samples. The assays are performed on electrophoresis instruments already in place in most clinical research laboratories.

IMMUNICON'S CellTracks. A University of Michigan researcher reported that circulating tumor cells are strong prognostic factors for breast cancer progression, "When elevated at first follow-up, they very likely indicate futile therapy. Do they apply to all patients? No, the data appear less robust for patients on endocrine therapy when we did a subset analysis, but we are not sure, so we are doing a new trial to test that." In addition, a prospective trial is planned to start in patients getting first-line chemotherapy for breast cancer with tumor cells drawn at first follow-up. Those without elevated cells will stay on the same therapy; those who don't have elevated cells will stay on therapy or try a new therapy."

THE REGULATORY PERSPECTIVE

Dr. Richard Pazdur, Director of Oncology Drug Products for the FDA, reviewed some of the issues in the drug approval process and trial design problems with which the Agency is struggling. Following are some interesting excerpts from his talk:

- "The mantra in real estate is location, location, location, and in oncology the mantra is clinical benefit, clinical benefit, clinical benefit."
- "The constant battle I have in (within) the FDA is convincing people that regulation in oncology is different than other drugs in FDA due to:

1. **The life-threatening nature of the disease**…There is always tremendous tension in the oncology community for getting drugs out quickly vs. the necessary data package for a drug. *We cannot penalize patients because drug companies do a bad job in developing their drugs*, but we have to be confident the drug meets certain requisites."

2. **Drugs with multiple action modes or combination therapy.** This is different from other areas like arthritis or antibiotics.

3. **The risk:benefit ratio.** We have a different perspective on serious adverse events. Our acceptability of Grade 3-4 toxicity obviously would not be accepted in other therapeutic areas. Our drugs are safe because we say they are safe and accept their safety profile. If I looked at these drugs in areas other than oncology, I doubt the reviewers would accept the toxicities we accept. We have a history of accepting these toxicities. We also have a 'living' product label in that it is somewhat always changing, and we have a lot of off-label use. And unlike other therapeutic areas, we have a lot of indications that are not labeled for. It is very difficult for our product labels to keep up with the ever-changing investigation …From the get-go, (our drugs) are used in different combinations, different doses, and different conditions."

4. **The investigational nature of the discipline**…There are cooperative groups, cancer centers, the NCI, etc.

5. **The wide variety of products used by oncologists** – chemotherapy, biotherapy, supportive care, diagnostic devices, surgery.

6. **Oncology is a very risky business to develop a drug in.** We have >100 indications or diseases one could develop a drug in…We have a far greater spectrum of diseases (than other disciplines), and, to be honest, our preclinical models don't predict where those drugs should be developed for the most part.

7. **Lack of predicting models.**

8. **The move away from dose ranging studies.** We generally treat at MTD.

9. **With Velcade** we were very much influenced that the responses were maintained over a period of a year. That is much more meaningful than a response that lasts 4-5-6 weeks."

Among the oncology trial concerns Dr. Pazdur cited were:

- **Minimizing bias.**
- **Magnitude of change of the endpoint.**
- **Clinical significance of the findings.**
- **Underpowered trials.** He said, "It is very difficult for investigators and pharmas to estimate the true effect of their drug. It is somewhat of a guessing game, and many times patient allocations and patient numbers are chosen by how quickly the trial needs to be done or the costs."
- **Isolating the effect of the drug.**
- **Endpoints for drug approval.** He said, "I am particularly concerned about this…Survival is an unambiguous endpoint that is not subject to investigator interpretation or bias…(But) it requires a large sample size and long follow-up, and the crossover of patients can 'wash out' a survival effect…So we have tried to take a look at other endpoints – TTP, PFS, DFS – because of the problems with survival…These require smaller sample size and shorter follow-up…We don't care what criteria you want to use…but stick with it…We like response rates, but they are very complicated." He said he was surprised that at a lung cancer endpoint conference, "the 'lung-cancer mavens' were more for a survival endpoint than general oncologists, who favored more TTP or PFS."
- **Patient reported outcomes.** These are problematic, but the Agency is interested in looking at this.
- **Missing data.**
- **International studies.** He said, "We need international studies on all continents. We look very closely at international data. We are increasingly seeing trials being done in the former Soviet Union, China, and Eastern Europe, but we have to have confidence these trials produce good, quality data and are representative of clinical care here in the U.S."

Dr. Pazdur also had some predictions:

- "I foresee we will have a greater number of candidate drugs, and the oncology community will have to decide which agents will be taken forward."
- "We are looking at progression-free survival endpoints, and I could see it being adopted, but that depends on the magnitude of change on that endpoint. In survival, we have accepted any incremental change *as long as it is meaningful*, but here, where we are talking about a time-to-event endpoint, we need to look at the magnitude of change."

The audience had a number of questions for Dr. Pazdur:

Question: *If TTP were doubled, would that be sufficient?*
Answer: "That is something we would entertain."

Q: *What is the FDA's relationship with other regulatory agencies?*
A: "It is improving. We have a new agreement that allows us to discuss with European regulators – who are our most equal counterpart in the world – on a more open basis. We plan to have teleconferences with the EMEA looking at certain applications on a regular basis."

Q: *How do you view drugs seeking approval where no other drugs are approved but many drugs are used off-label?*
A: "The way the accelerated approval regulations are written, it is 'improvement over available therapy.' It doesn't say approved therapy. And that is important in oncology where there is a lot of off-label drug use. And there should be 'compelling evidence' for that drug in the literature."

Q: *What is the FDA's view of Special Protocol Assessments (SPAs)?*
A: "Usually, these are Phase III registration trials…The FDA reviewer agrees on a 'lock in,' so if the trial is successful, that will lead to drug registration. It gets away from criticism of the FDA changing its mind, that it is arbitrary and capricious…But), there is a provision that if the standard of care changes or there is a major issue, then one has to look at the agreement."

Q: *Where is the agency going with markers like C125 and PSA?*
A: "These are very controversial. We had one panel already on PSA, and we are looking at data internally on that…We are looking at clinical trials, particular taxotere clinical trials. We are not opposed to the concept of looking at that endpoint, but we need some degree of confidence that it is a reliable and reproducible endpoint that warrants approval."

DATA TO WATCH

American Society of Hematology (ASH) 2004:

- **Biocryst's BCX-1777** – Data from the Phase I dose escalation study.
- **Erythropoietins –** More detail on the cases of PRCA reported under the FDA's adverse event reporting system (AERS) with EPOs.
- **Millennium's Velcade** (bortezomib) **–** There have been some cases of small vessel necrotizing vasculitis, and that is new and will be discussed in detail. There will be numerous other presentations on Velcade at ASH 2004.
- **SuperGen's Dacogen** (decitabine) – More data on use in MDS.

San Antonio Breast Cancer Symposium 2004:

- **AstraZeneca's Arimidex** (anastrozole) – ATAC trial update.

- **Pfizer's Aromasin** (exemestane) – BIG 97-02 trial update on exemestane after two years of tamoxifen.
- **ARNO/ABCSG trial** – An AI trial.
- **American Pharmaceutical Partners' Abraxane** – Dosed weekly at 125 mg/m2 – abstract
- **Amgen's Neulasta** (pegfilgrastim) – New data on febrile neutropenia in taxotere-treated breast cancer.
- **Genentech's Herceptin** (trastuzumab) – Update on pilot data presented at ASCO 2003 on cardiac side effects of the combination with pegylated doxorubicin.
- **Genomic Health's Oncotype DX** – More information on this diagnostic assay.

ASCO 2005:

- **American Pharmaceutical Partners' Abraxane** – Data on weekly dosing at 125 mg/m^2.
- **Genentech's Avastin** (bevacizumab) – Phase III clinical efficacy data on Avasitin+FOLFOX in first and second line treatment of CRC.
- **Genentech's Herceptin** (trastuzumab) – Data on using Herceptin sequentially with anthracyclines.
- **Genta's Genasense** – Toxicity and efficacy results from a 298-patient, Phase II study of Genasense and Doxil in Stage IIb/IV second line NSCLC. And possibly results from a Phase I study of Genasense with either carboplatin or etoposide which is due to mature some time in 2005.

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