Trends-in-Medicine

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By Lynne Peterson

SUMMARY

It was hard to find any really hot topics or buzz words at the meeting this year, but the talk appeared to concentrate on:

Vaccines: but really effective ones are considered 5-10 years away.

Diagnostics: There was excitement over Arcturus' Paradise test to determine which women are tamoxifen responders and a NCI-developed assay to detect ovarian cancer recurrence, but not for Immunicon's assay to measure circulating tumor cells.

HDACs: There are a ream of them, but none is a slam-dunk blockbuster.

Molecular profiling: Expect to hear more about using this to predict therapeutic outcome.

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AMERICAN ASSOCIATION FOR CANCER RESEARCH

Orlando, Florida
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This was one of the quieter American Association for Cancer Research (AACR) meetings in recent years. The hot topics and buzz words that characterized other years were absent, but there was news about:

PREDICTING THE FUTURE

Dr. Daniel Von Hoff, director of the Arizona Cancer Center, has proven a good predictor of promising new cancer drugs. Many of the drugs he highlighted at the 2002 AACR meeting have progressed or gotten approved. At AACR 2004 he offered his latest predictions. Two of the drugs from 2002 have been approved by the FDA, and two are still on his watch list, plus he highlighted several new agents.

Potential sponsors were required to submit their sponsorship request to CMS in January 2004. More than 106 entities sent CMS a letter asking to become a Medicare-approved discount drug provider. Sources expect that about 60 sponsors will eventually be approved. PBMs, insurers, and pharmas are all likely to be big providers/sponsors of Medicare Discount Cards. An expert said, "One-third are Medicare Advantage plans (NOTE: Medicare Advantage is an optional managed care program for seniors that offers a choice of companies offering enhanced coverage over traditional fee-for-service Medicare)…Several of the manufacturers probably will do one…And the others will be supplemental insurers, chain drug stores, PBMs (who will be out in great numbers, no doubt), and a handful of membership organizations like AARP and regional groups."

Dr. Von Hoff's Top New Drug Picks

Company	Drug	Type of Agent	2004 Status/Comments
2004 Picks also on 2002 Pick List			
American Pharmaceutical Partners	Abraxane (ABI-007)	cremophor-free formulation of nanoparticle paclitaxel encapsulated in human serum albumin	Abraxane has been submitted to the FDA for treatment of metastatic breast cancer.
GlaxoSmithKline	GW-506U78 (nelarabine)	analog of guanasine	He said, "It is very active in T-cell leukemia, lymphoma, and CLL."
2004 Picks Not on 2002 Pick List			
Celgene	Revlimid (CC-5013, formerly Revimid)	thalidomide analog	He said, "This has shown very dramatic results in patients with MDS, especially ones with the chromosomal abnormality 5q minus. It is extraordinarily promising."
Genentech	pertuzumab (2C4)	anti-ErbB2 monoclonal antibody for ovarian and prostate cancer	An expert said, "Pertuzumab is going through the paces…So far, I've not been as encouraged with what I've seen as I was with Herceptin…but it is very early…I think 2C4 should go through the same process as Herceptin – looking at rational combinations with chemotherapies and biologics."
Pfizer	SU-11248	tyrosine kinase inhibitor	He said this has shown "extraordinary activity" in renal cell/kidney cancer and GIST.
Bayer/Onyx	BAY-43-9006	raf kinase inhibitor	He commented, "It has good activity in kidney cancer, where that was not expected."
Abbott	ABT-510	thrombospondin-1 mimetic	He said this thrombospondin inhibitor has shown tumor shrinkage when given subcutaneously with no toxicity and called it "pretty impressive."
2002 Picks Not on 2004 Pick List			
Allos Therapeutics	RSR-13	radiosensitizer	FDA advisory panel scheduled for May 3, 2004.
AstraZeneca	Iressa (gefitinib)	EGFR-receptor inhibitor	FDA Approved 2003.
BioChem Pharma	Troxatyl (troxacitabine, BCH-4556)	dioxolane nucleoside analog	---
Eli Lilly	Alimta (pemetrexed, LY-231514)	antifolate antineoplastic agent	FDA approved in February 2004 as an orphan drug to treat mesothelioma.
GlaxoSmithKline	GW-506U78 (nelarabine)	analog of guanasine, for pediatric lymphomas	---
Genzyme/Ilex	Clofarex (clofarabine)	adenosine analog for pediatric and adult acute leukemia	Pediatric approval expected in late 2004 or early 2005.
Johnson & Johnson/PharmaMar	Yondelis (ET-743, ecteinascidin)	sea snail toxin derivative	EMEA found not approvable in 2003.
ProlX Pharmaceuticals	PX-12 (1-methylpropyl 2-imidazolyl disulfide)	thioredoxin redox inhibitor	In Phase I trials.
Telik	Telcyta (TLK-286)	tumor activated small molecule drug	A pivotal Phase III trial in ovarian cancer is ongoing as are trials in MDS and non-small cell lung, colorectal, and breast cancer.
Pfizer	brostallicin (PNU-166196)	synthetic alpha-bromoacrylic, second-generation DNA minor groove binder	In clinical trials for the treatment of recurrent or refractory multiple myeloma.

DRUGS IN DEVELOPMENT

CDK Inhibitors

No news on these at AACR, but researchers were saying that there is a "resurgence" in CDKs.

Cox-2 Inhibitors

Cox-2 inhibitors prevent the over-expression of Cox-2, which correlates with the loss of the basement membrane in ovarian epithelium cells and thus promotes cancer. Previous research has shown that Cox-2 inhibitors slow the growth of tumors, particularly breast and colon cancer, and the National Cancer Institute (NCI) is initiating a multi-center human clinical trial of Cox-2 inhibitors in cancer.

Roughly 10%-40% of all pancreatic tumor cells are considered Cox-2 negative, while all others express Cox-2. A researcher said, "These (mouse) studies suggest that patients can be treated with selected Cox-2 inhibitors, but only based on the Cox-2 expression profile of their pancreatic tumor." The researchers now plan to test other Cox-2 inhibitors in animals to see if they have the same impact on tumor growth.

UCLA researchers reported that the Cox-2 nimesulide, which is approved in some European countries, but not in the U.S., promotes tumor growth in specific types of human pancreatic cancer cells. A researcher explained, "For the first time, we have shown that a selective Cox-2 inhibitor can simulate tumor growth…However, its effects depend on whether the tumor expresses Cox-2 or not."

Another poster found that Pfizer's Celebrex (celecoxib) enhances the anti-tumor effect of docetaxel (Aventis's Taxotere) in mouse lung tumors.

G-Quadruplexes

G-quadruplexes are specialized DNA sequences (3-D knots) that may be able to down regulate the expression of the cancer gene, c-myc. Aventis (A00312307A and A00316360A) and Geron both have G-quadruplexes in development, and Roche may be starting work on one. Several other small companies also are working in this area, but no other big pharmas have yet gotten into this area. An Aventis official said, "Our status is still exploratory."

The lead G-quadruplex agent appears to be CX-3543 from Cylene (formerly Cyternex), a privately-held biotech firm founded by Dr. Von Hoff. CX-3543, which has been dubbed the first "oncogene inhibitor," was highlighted at AACR 2001 and 2002, and a speaker had expected it to start human clinical trials in the spring of 2003, but a Cylene official said the first patients now are expected to be enrolled by the end of this year. He explained, "We've taken CX-3543 into a series of animal models, and we are at the point now where we are enhancing the manufacturing and preclinical development... We've nailed down the structure and selectivity…In 2003, the compounds were not very soluble, and taking an insoluble compound to the clinic will give poor absorption and poor availability…So, this is a newer molecule…Waiting another nine months for this has been worth it."

CX-3543 currently is designed for IV therapy, but oral dosing may be possible in the future. It is being tested in several cancers. Researchers reported CX-3543 effectively reduced c-myc mRNA expression by 85% in colorectal tumor animal models, and it also inhibited the growth of prostate and pancreatic tumor models in mice. CX-3543 selectively suppresses c-myc activity by specifically binding to the c-myc quadruplex. A Cylene official said, "In colorectal cancer, we see 50%-85% reduction in tumor growth, depending on the animal model…And when we pull tumors out of the animals, we find an 80%-85% reduction in c-myc, and we didn't see that in other normal genes…In the pancreatic model, which is very difficult to treat, we saw a 50%-90% reduction, depending on the dose."

Histone Deacetylase Inhibitors (HDACs)

Most of the major pharmaceutical companies are working on one or more HDACs. Toxicity – particularly cardiac toxicity – is an issue with most if not all of the compounds except perhaps Merck/Aton's SAHA. However, SAHA is non-specific, while the others are more specific. Experts believe some of these will succeed, but they generally agreed that HDACs won't be a magic bullet – and will probably have to be given in combination with other chemotherapy agents. One source commented, "I think all HDACs will have to be given in combination, at low doses, and intermittently." A California researcher said, "This is a very exciting class. They definitely will come into their time…There are likely to be big differences among the various agents because the system is so ubiquitous in the body…The (animal and cell) models are consistent, with a broad range of activity. The question is drug delivery – how to dose (continuously or intermittently)." A speaker said, "One of the interesting things about HDAC is the selectivity…Depending on the cell line, only 2%-5% of expressed genes are altered (increased or decreased in expression)." Another expert said, "Certain tumors respond very well to HDACs – such as CTCL or mesothelioma. The $64,000 question is to identify markers that distinguish responders. These are drugs that really will have a shot at markers that predict response, but we will need a lot of patients to sort this out."

Companies with HDACs in development include:

- **TITAN'S pivanex**. An expert said this has a "completely different structure" from the other HDACs. A researcher said, "Clearly, these are not agents with dramatic responses, but there is no toxicity, and some refractory patients had more stable disease than expected…It is as good as you would expect in a second or third line agent. And it is clear that quality of life is improved. Some patients without a clear PR had stable disease and a quality of life that they probably

wouldn't have gotten otherwise…There was no cardiac toxicity with this…As monotherapy, it has benefit, but there was no dramatic response, so it will probably be given in combination. It has a clear place in second or third line…Perhaps there are fewer side effects with this."

A poster reported on the combination of pivanex with Taxotere in Taxotere cell lines. There was sensitization, but not by the expected, prominent pathways. A Phase II trial of pivanex plus Taxotere vs. Taxotere is enrolling.

➢ **MERCK/ATON'S suberoylanilide hydroxamic acid (SAHA).** This small molecule is now in Phase I and II trials at several institutions. Rodent studies reportedly showed little to no toxicity. Parenteral administration has been tried in leukemia and prostate, breast, and colorectal cancer. Oral administration has been tried in breast adenocarcinoma and lung tumors. The company also is considering IV administration. A researcher said, "This targets HDAC 1+3, which are more tumor-specific, so there is reason to continue this even with the positive results of SAHA...We need to consider what is the best strategy to advance to Phase II and Phase III trials."

Efficacy. So far, as a single agent, anti-tumor activity has been seen in solid tumors and hematologic malignancies, including CTCL, diffuse large B-cell lymphoma, laryngeal cancer, and mesothelioma. Phase I oral trials showed good absorption (about 50% bioavailability). There was no PR or CR, but the average patient had stable disease out to 155 days (range 62-309 days), whether or not the patient fasted. The best response was obtained at 600 mg QD (with a similar response at 200 mg and 400 mg).

Dosing. Intermittent dosing appears to be the most promising with this agent. A researcher said, "This is not a cytotoxic agent...If the cell and animal studies mean anything in terms of humans, I would say they strongly suggest that a period of rest, so to speak, between doses seems to be most effective…Almost all animal data is with intermittent administration, given once-a-day IP…so there is a 12-hour period without adequate drug levels…Oral administration also was intermittent…So clinical trials followed that logic – a single dose. We are now exploring multiple doses during the day, and we don't have a complete answer in patients, but certainly we've seen a significant anti-tumor effect at well-tolerated doses given what I call intermittently (QD)…The side effects, while very variable as to the time of onset, generally occur after the patient has been on the drug for several weeks to a month…When we give a rest of three to five days and start again, there is no evidence of residual side effects. However, other patients have been on SAHA continuously for two years with no side effects."

Toxicity. Dose-limiting toxicities are non-hematologic – dehydration, nausea, anorexia, fatigue, and diarrhea – all of which are reversible when the drug is stopped for a few days. A researcher said, "In our studies, we have not seen any cardiac toxicity…I'm aware that other HDACs in clinical trials have shown cardiac toxicity, but so far SAHA has not. That may relate to the differences in the structures of the different agents." However, there was one arrhythmia with the QD dosing.

Combination therapy. Combination therapy trials are planned but haven't be done yet. A researcher reported that combining SAHA with Millennium's Velcade (PS-341, bortezomib) in colorectal cancer was highly synergistic. A speaker said, "We have not had any experience with combination therapy yet, though we have some animal models where SAHA was used in combination and some in vitro models where it was explored with radiation, with retinoids, with Gleevec (Novartis, imatinib) and with some cytotoxic agents…The bottom line is SAHA is either quite synergistic or additive…We have not yet seen one where SAHA interferes with a common anti-cancer agent. We are planning Phase II trials in combination therapy, but haven't initiated any."

Among the questions researchers hope to answer about SAHA are:

- What is the mechanism of the SAHA-selective effect on gene transcription?
- Why are normal cells relatively resistant to the effects of SAHA? A speaker said, "It takes up to a 10x dose to have an effect on normal cells. It looks like different cells may have different pathways which, in part, are responsible for the relative resistance of normal cells."
- What are the non-histone targets of SAHA?

➢ **NOVARTIS' LAQ-824**. A poster reported this to be additive to the VEGF PTK-787 on tumor growth and angiogenesis in vivo in breast cancer, and similar preclinical data was reported in prostate cancer last year. A Phase I monotherapy trial is underway at Dana Farber Cancer Institute.

➢ **FUJISAWA'S FK-228.** A poster reported, "For future combination therapy, FK-228 may not be suitable to pre-treat patients with anti-cancer drugs being Pgp (p-glycoprotein) substrates, such as paclitaxel and doxorubicin, due to the possible rapid induction of Pgp." Apparently, there is synergism with 5FU, but giving FK-228 prior to paclitaxel is antagonistic, and giving paclitaxel prior to FK-228 is synergistic. The researcher said, "Cardiac toxicity was not a big problem. It was an initial concern, and it was observed in dogs, but it is not a major problem in humans." FK-228, a bicyclic tetrapeptide, is currently in a Phase I/II trial.

➢ **ABBOTT'S Depakote** (valproic acid). This is a cheap HDAC, and some academic centers are experimenting with it. It reportedly works!

➢ **SCHERING AG/BERLEX'S MS-275**. The first human data (Phase I) was reported today on 31 patients, but the company needs to do more Phase I dosing and dose-schedule studies before proceeding to Phase II. The MTD was 10 mg/m^2 given once every 14 days. The drug has a half-life of 49 hours, which is much longer than the animal models predicted. There were no CR and no PR, but 15 cases of stable disease out to 62-309 days. DLTs were nausea, vomiting, anorexia, and fatigue, but no cardiac toxicity was reported. A dose of 2 mg/m^2 QD for 28 days was tried but found to be too toxic. A researcher suggested that the cardiac toxicity may be schedule-dependent and tolerable – related to high dose mono-therapy more than combination therapy.

The company also is considering an IV formulation to boost serum levels (which are only 25 ng/mL with 10 mg/m^2). The fact that this is more tumor-specific than SAHA makes it worth continuing to pursue, a researcher said.

Hypermethylation agents (DNMT and MBD2 inhibitors)

An expert said, "These agents are being reassessed for cancer therapy. Rather than empiric testing of more and more, researchers are working on dose de-escalation studies – adjusting doses downward but giving the agents longer…I think these agents will be combined with HDACs in the future."

SUPERGEN'S Dacogen (decitabine)

SuperGen reported the results of its pivotal Phase III trial of this DNA precursor in MDS in a conference with investors – during, but not at, the AACR meeting. Doctors all expected the results to be positive, and the drug did show that about 22% of patients did better with Dacogen, but side effects remain a problem, including nausea, vomiting, pneumonia, headaches, and insomnia. Dacogen reportedly is more potent than Pharmion's azacytidine.

PHARMION'S azacytidine

This competitor to Dacogen has FDA fast track status. An expert said researchers are looking at giving azacytidine, an RNA precursor, with sodium phenyl butyrate, then backing off the azacytidine to see how little azacytidine can be given.

Comparison of Azacytidine and Dacogen

Azacytidine	Dacogen
Goes through RNA first	Direct to DNA
Fast track status	Active at 1/10 of azacytidine dose

IGF (Insulin growth factor 1)

Several companies are working on these, though they are very early stage, including: Imclone, Schering Plough, and Pfizer. There wasn't any significant data at AACR on these, but they bear watching.

Other agents worth watching:

AMERICAN PHARMACEUTICAL PARTNERS' Abraxane (ABI-007)

Sources remain positive about this cremophor-free formulation of paclitaxel, and they expect FDA approval. Dr. Von Hoff said, "That is going to be great."

The FDA generally wants a non-inferiority trial to have at least 500-1,000 patients, and the pivotal Abraxane trial – a single Phase II study vs. Taxol (Bristol-Myers Squibb, paclitaxel) – had 460 patients. However, sources believe that the trial was close enough to this to pass scrutiny. Sources also were not concerned that the Taxol in this trial had a lower response rate (14%) than is listed in the label (28%). Dr. Von Hoff said, "The response rate was so much better (than the comparator), significantly better – 33% vs. 19% for Taxol, with a p-value <0.001…And with a low p-value, the FDA can allow a single trial…I don't believe approval will be a hurdle. Look what happened with Avastin (Genentech, bevacizumab) in colorectal cancer."

Asked how doctors will use Abraxane if it is approved, an expert said, "They will substitute it for Taxol, but I'm not sure if they will substitute it for Taxotere. But Abraxane doesn't need pre-medication to prevent anaphylaxis, and there is no cremophor in the material, and that will be attractive."

BAYER/ONYX'S BAY-43-9006, a raf kinase inhibitor

An independent researcher said, "I think this should be pursued in melanoma. It inhibits melanoma tumor development." Two Phase II melanoma trials are underway, one as monotherapy and one combination therapy. A Bayer researcher said, "The company has approved funding for a Phase III melanoma trial, but I'm not sure it will go forward."

Bay-43-9006 also is in an 800-patient Phase III trial for renal cell carcinoma at doses of 400 mg QD and 400 mg BID (depending on tolerability).

BAY-43-9006 Dose	Mouse Response
100 mg/kg	Toxic: 30% of mice died
50 mg/kg	No significant weight loss, no toxicity
10 mg/kg	No activity

BIOGEN-IDEC'S HMN-176, a stilbazole derivative. In vitro, it is synergistic with a number of chemotherapies, including 5FU. A researcher said, "Best is giving HMN-176 first, followed by 5FU at Day 21…Cisplatin plus HMN-176 should be given at the same time (on Day 0)…Scheduling is important and may not correlate with the in vitro data."

BRISTOL-MYERS SQUIBB:

- **BMS-501949.** This an androgen receptor antagonist for prostate cancer that has the potential, if it succeeds, to replace AstraZeneca's Casodex (bicalutamide), TAP Pharmaceuticals' Lupron (leuprolide), etc. Prostate cancer specialists have been asking for a drug like this – more potent and more specific hormone – and the company expects to start Phase I trials at the end of 2004 or early 2005 with a follow-on agent to BMS-501949. A Bristol-Myers Squibb researcher called it a "big break-through." No other companies are thought to have anything to compete with this.
- **SARM (**selective androgen receptor modulator)**.** Data was presented recently at the American Chemical Society meeting on this testosterone replacement therapy. It reportedly helps with bone and cognition – without inducing prostate cancer. The concern is potential for abuse or causing prostate cancer. However, Bristol-Myers researchers are very excited about it. A researcher said, "The concern is possible abuse."
- **BMS-354825.** A poster showed that, in a small Phase I study, this orally bioavailable, small molecule, ABL tyrosine kinase inhibitor overcomes Gleevec resistance in CML. It was dosed at 15 mg QD x5, followed by two days rest, but doses up to 52.5 mg BID will be tested. An estimated 10% of Gleevec patients are non-responders or become resistant. A researcher said giving BMS-354825 could allow the dose of Gleevec to be increased, and he said there has been no toxicity so far, with a "nice clinical response."

CELGENE'S Revlimid (formerly Revimid)

No new data.

GENTA'S Genasense (oblimersen, G-3139)

Genasense will be considered by the FDA Oncologic Drugs Advisory Committee (ODAC) on May 3, 2004. Sources were not sure how the panel would vote. An oncologist said, "Our melanoma folks don't know what to do about this data. Nothing has been shown to be better than the old (melanoma) drugs. I'm not very excited about Genasense."

The Genasense data to date raises questions about whether the FDA will approve Genasense, regardless of the panel vote. Among the issues with Genasense are:

1. Adverse events in the Phase III trial were worse than for placebo.

Measurement	Genasense	Placebo
Overall adverse events	40%	27%
Grade 3/4 adverse events	67%	43%
Discontinuations due to adverse events	6%	2%

2. The Phase III trial showed a statistically significant benefit in time-to-progression (TTP) and relative response, but not in the primary endpoint of survival, which was only about a month better than placebo. An expert commented, "Anything ≥5% with acceptable toxicity would have interest. In breast cancer 1% (efficacy) is enough." The FDA can approve a drug that misses its primary endpoint, but the hurdle is high. (*See Regulatory Issues on page 13.)*
3. The mechanism of action is not clear.

GPC BIOTECH AG'S satraplatin (JM-216)

A Phase III trial of this IV platinum began in September 2003 comparing satraplatin+prednisone to placebo+prednisone as second line therapy in about 900 hormone-refractory prostate cancer patients. A researcher said, "Androgen-insensitive prostate cancer cells are more sensitive to satraplatin than androgen-sensitive cells. The cytotoxicity is in the range of oxaliplatin (Sanofi-Synthelabo's Eloxatin) and cisplatin, but satraplatin is oral and less toxic." This agent also has shown activity in ovarian and NSCLC.

ZENTARIS GMBH/KERYX BIOPHARMACEUTICALS' KRX-0401 (perifosine)

This is a first-in-class, oral AKT inhibitor. Keryx has the U.S. marketing rights. In Phase I trial perifosine was given in combination with radiotherapy to patients with unresectable, locally-advanced tumors. Additional Phase I data is due at ASCO 2004. Nine Phase II trials of perifosine currently are underway in six cancer types.

GENENTECH'S pertuzumab (2C4)

A researcher said, "It is still too early to say how this will do."

GENENTECH/OSI'S Tarceva (erlotinib)

The results of the monotherapy trial of Tarceva in NSCLC are due in 2Q04, but no other information was available. Sources insisted that all details on the demographics of the participants – percent of women, smokers, etc. – remain sealed. However, most sources expect Tarceva to meet its primary endpoint and gain FDA approval.

If the trial meets its primary endpoint of a 33% improvement in survival, oncologists predicted it would have a role. How would they choose among AstraZeneca's Iressa (gefitinib), Imclone/Bristol-Myers Squibb's Erbitux and Tarceva? One researcher said, "It will depend on the patient. Overall, Tarceva seems relatively safe."

PFIZER:

- **SU-5416.** A researcher said this has not been dropped in malignant glioma – yet.
- **CP-31398**, a styrylquinazoline. A poster reported that this has chemopreventive potential against development of neoplastic lesion in genetically predisposed tissue and in chemically-induced colonic pre-neoplastic lesions. The mechanism is, at least in part, upregulation of p53.

PROLX PHARMACEUTICALS:

- **PX-478,** a transcription factor inhibitor (an inhibitor of hypoxia-inducible factor 1a). A poster reported on "marked activity, including regressions and cures against a number of human tumor xenografts." A Phase I trial will start in August 2004.
- **PX-12**, a thioredoxin redox inhibitor in Phase I trials.

SANKYO'S RS-5444

This PPAR-γ agonist may have utility against thyroid cancer, which typically is fatal in three to six months and has few chemotherapeutic options. RS-5444 is reported to have a 3-log higher affinity to PPAR-γ than rosiglitazone (GlaxoSmithKline's Avandia). It also may have anti-tumor activity in colorectal and breast cancer. A researcher said, "Sankyo and the Mayo Clinic discovered that, in rarer forms of thyroid cancer, there is a molecular signature that is different…These patients have a normal copy of a particular receptor, and it is that normal copy that may be susceptive to the drug they developed (RS-5444)…Other cancers with a rearranged copy of that receptor may not be susceptible…RS-5444 is well-tolerated orally…We've begun a number of studies on RS-5444 in combination with other therapies...and we are seeing in preclinical research an additive and sometimes a synergistic effect with these therapies."

SCHERING AG/BERLEX'S ZK-230211

This progestin receptor antagonist (PR-antagonist) is first in class. It has been shown to prevent carcinogen-induced breast cancer in rats. A researcher said, "By treating rats with PRA, we were able to block carcinogenesis and development of breast tumors nearly completely…We tried it in another (rat) model with nearly similar results…Then, we tested our PR-antagonist PRA vs. tamoxifen and AstraZeneca's Arimidex (anastrazole), and once again we found our PR-antagonist inhibits tumors and tumors also shrink and disappear after several weeks of treatment. The activity of this PR-antagonist is superior to both tamoxifen and Arimidex…In one model, there were 10 rats in each group, and out of these, only 1 rat (on PRA) developed a tumor, compared to the control where 10 of 10 rats got large tumors…and our one tumor was tiny… We haven't seen any serious side effects or any increased cancer risk in other organs (at six months)."

A breast cancer expert called this an exciting approach, "Everything today is focused on the estrogen receptor…and I think there is strong science behind the Schering approach…It is very compelling data…This is moving to a clinical setting and could be a very significant new agent in armamentarium in treating hormonally-regulated cancers…I would follow this story closely."

TELIK'S Telcyta (TLK-286)

Posters at AACR supported the continued development of this drug, indicating it is additive and/or synergistic with a variety of other agents, including Iressa. For the first time, Telik will have a booth at ASCO in June 2004.

- **Poster #1.** Researchers concluded: "There is non-cross resistance to paclitaxel in human ovarian cancer cells. There is increased sensitivity to paclitaxel in a paclitaxel-resistant ovarian cancer cell line…The implications are that combination therapy makes sense, and taxane-resistant patients might respond.
- **Poster #2.** Researchers found Telcyta works with Iressa – at least in human cancer cell lines. The drug also worked with Lilly's Gemzar (gemcitabine), oxaliplatin, paclitaxel, carboplatin, cisplatin, and doxorubicin, but not 5FU.

A Telik official said:

- The ovarian cancer Phase III trial should be ready by the end of this year, and the data will be submitted to the FDA in 2005. The company is hoping for FDA approval for third-line ovarian cancer.
- Follow-up data on combination trials will be at ASCO 2004.
- The company is starting to build its marketing team. The plan is for Telik to partner outside the U.S. and to market Telcyta itself in the U.S.
- The Phase III NSCLC is vs. Iressa.

VION PHARMACEUTICALS' triapine

This is a small-molecule inhibitor of ribonucleotide reductase under investigation to treat leukemia, lymphoma, and ovarian cancer. It has a half-life of one hour, and currently the 5 uM dose has to be given in a continuous infusion over two hours. A Phase II trial as monotherapy in lymphoma and a Phase I trial in ovarian cancer are underway. A researcher said, "I think this is promising, but the question is what serum level is achievable…We want to see if there is an effect in less than 48 hours. If so, it would be used as a sensitizer. We also want to see if we can make the effect last 48 hours in humans. Perhaps we could infuse for 48 hours, but that would be tough."

NEWS ON ALREADY APPROVED DRUGS

ABBOTT'S Nembutal (pentobarbital)

Researchers reported that Nembutal, a barbiturate with GABA-like effects, inhibited metastasis in colon and ovarian cancer cell lines. They suggested their findings may have therapeutic implications for the treatment of colon and other cancers.

ASTRAZENECA'S Iressa (gefitinib)

An AstraZeneca official commented, "We should have mandated biopsies, but it is difficult to do that in lung cancer. And it is very tough to require biopsies in colorectal cancer, too…We are not dropping Iressa for GI cancer, but we are trying to understand who might benefit. Without an identified subgroup, it is not worth pursing it (in GI)." He described the Iressa Phase IV post-marketing study as "accruing well," but he wouldn't say when it is likely to be finished. He also said, "There was nothing in the toxicology that indicated interstitial lung disease. The incidence is 0.2% worldwide, but it's higher in Japan – and compares to ≤10% with Taxotere."

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

A Bristol-Myers researcher reported on a validation study of preclinical markers, using samples from ongoing clinical trials. She said the study is looking for ways to identify responders, but it will be 18 months before the results are known and about three years before the test will have clinical use.

GENENTECH'S Avastin (bevacizumab)

Sources complained about the $44,000 price tag and predicted that would limit off-label use. One doctor summed up the sentiment this way: "Off-label use depends on the data in the other indications, and on their party payers. We will need published Phase II data to convince doctors and payers to use it in unapproved indications."

Doctors agreed off-label use will be determined by:

- Availability of Phase II data for off-label indications.
- Payer reaction to the Phase II data on off-label indications. Sources agreed there will be no off-label use without payer reimbursement, and they believe payers will insist on seeing published Phase II data.

A poster reported that on the results of giving Roche's Xeloda (capecitabine) on Days 0-6, followed by Avastin on Days 7 and 10. The researchers found the greatest tumor volume reduction was with the combination – longer than either alone and longer than the two given simultaneously. They concluded, "The combination of Avastin and Xeloda has greater (longer) tumor inhibition after cessation than with either alone."

Erythropoeitin (AMGEN'S Aranesp and JOHNSON & JOHNSON'S Procrit)

Canadian researchers reported on a study (funded by J&J and NCIC-Canada) which showed that giving erythropoeitin prior to radiotherapy can protect against the learning and memory impairment that can occur with whole brain radiation. Cognitive defects are often seen months or years after the radiation therapy, but once they develop, they are irreversible and often progressive.

A researcher said, "Performance in epo-treated animals was almost identical to control…Epo serves as a neuroprotector and can protect against radiation-produced CNS damage…We are looking for the best schedule to protect the brain in a fractionated radiation therapy setting…There are more than 200,000 brain tumors a year in North America, and many of these patients suffer long-term neurocognitive impairment due to the radiation…Epo has the ability to reverse neurocognitive impairment and improve the quality of life of brain tumor patients…The protective effect of epo on CNS is felt to have some specific effect on nerve and blood vessel cells in CNS, so this has no implications on anemia use of epo."

Asked if oncologists should consider using epo off-label now for this purpose, the researcher said, "In the experiments we conducted, we used a single dose to mimic fractionated radiation therapy…but radiation therapy is generally given as fractionated treatment over a number of weeks, so we want to see if there is a better way to deliver the dose of epo and to find the best schedule when it is delivered in this setting…We are also looking at whether epo can be given much later, after treatment is finished…For patients not at risk of tumor recurrence, with no tumor burden, could epo be given later but before cognitive decline, and still be neuroprotective?"

VACCINES

Just when many people thought vaccines had become passé, they seem to have risen from the dead. Again and again, sources pointed to vaccines as the most exciting thing on the horizon in oncology, as hard as that may be to believe. Researchers are increasingly excited about vaccines, and most of the major academic centers are working on them. An NCI official said, "The current Phase III vaccines were developed 10-15 years ago, and most are near misses…Vaccines are a work in progress…The newer vaccines will take five to 10 years for approval, but there will be a whole bunch – and it could be sooner."

A speaker offered this advice on cancer vaccine development:

1. It should not be conducted via a "shotgun" approach. Evaluate vaccine #1, then #2, then #3, etc.
2. Vaccines should be evaluated as part of an "immunologic platform."

3. Immune response is a very dynamic process, and the generation of an immune response against a tumor…A vaccine may not eradicate a tumor, either fully or partially, but it may arrest tumor growth and induce a stable disease state, leading to increased survival – where radiation and other therapies may be used.
4. Vaccines should be integrated with both radiation and chemotherapy, not one or the other.
5. The trend appears to be shorter intervals, not longer ones, between vaccinations.

Among the companies with cancer vaccines in development are:

DENDREON'S Provenge

This vaccine for prostate cancer may be the first commercial success, but most sources had mixed reactions to it. An NCI official said, "I'm not sure this is approvable. It only works in patients with a Gleason score of 7 or lower." A California doctor said, "There has been a lot of buzz about this."

LARGE SCALE BIOLOGY

This company is developing vaccines grown in the leaves of tobacco plants. One of these is a treatment for Fabray's disease that is expected to enter clinical trials in about 12 months. The larger indication is an HPV vaccine for cervical cancer, for which the company will initially seek orphan drug status to treat HPV-infected newborns, and then expand to their mothers and, finally, to the general population. This vaccine may have particular appeal in less developed countries because of the ease of large scale production and anticipated low cost. However, the vaccine is not expected to last a lifetime. Rather, it may be protective for four to 10 years, similar to a tetanus vaccine, so at least two inoculations are likely to be necessary.

Human clinical trials are expected to begin in about a year. The company will go after orphan drug/vaccine status initially by targeting pregnant women with an active HPV-11 infection and their babies. A researcher said, "These infants get growths in the trachea and often require multiple surgeries. It is a very small market, but vaccinating mothers with HPV would protect infants. We are interested in that because it would show the vaccine is effective. The vaccine also could be used for therapy of the affected babies…That would put it in an orphan drug treatment category…but proof of concept in that would perhaps allow us to move more quickly in larger trials." Another expert said, "I have been less enthusiastic about other vaccines. This is not the case with this approach…This is a very exciting approach…and while I understand the regulatory process for vaccines is more challenging, taking high risks and getting an answer quickly on the approach makes a lot of sense…So when clinical trials start, they should be able to develop an immune response in children in a few months and with short follow-up, meaning a year or two."

CELLGENESYS' GVAX

A researcher reported that this pancreatic cancer vaccine is synergistic with IV docetaxel in a melanoma mouse model. Survival improved a statistically significant (p=.014) 68% with the combination therapy (52 days) vs. either vaccine or docetaxel alone (both 24 days).

The company plans to initiate two Phase III trials of GVAX in hormone-refractory prostate cancer by July 2004:

- Survival in asymptomatic patients without cancer-related pain, comparing GVAX vs. docetaxel.
- Bone pain in symptomatic patient getting GVAX plus docetaxel vs. docetaxel alone.

THERION BIOLOGICS' CEA/Tricom

This altered smallpox vaccine delivers a gene that makes an anti-tumor antigen (CEA) that is found on many colon, pancreatic, lung, and breast cancer cells. In heavily pre-treated patients, no toxicity above Grade 1 has been reported yet. In Phase I/II studies Tricom increased survival by a statistically significant six to 12 months (p=.03). There will be additional data on Tricom at ASCO 2004. A speaker said, "I think the future is to use these vaccines in combination with selected drugs and local radiation of tumors."

DIAGNOSTICS

ARCTURUS' Paradise Reagent System

Hospitals are required to store tumor samples from surgical patients in case further testing is needed, and biopsy tissue and other tissue specimens are universally preserved by being fixed in formalin and embedded in paraffin, a process that was thought to compromise DNA and RNA integrity. Arcturus has developed a tamoxifen signature technology that allows RNA to be extracted from formalin-fixed biopsy samples that are up to five years old. Then, genetic analyses can be done to see if patients are tamoxifen-responders by matching two genes – HOXB13 and IL17BR. Many breast tumors fail to respond or develop early resistance to tamoxifen, but it has not been possible until now to identify which women will fall in these categories.

Using archived breast cancer biopsies, researchers identified 60 women treated with adjuvant tamoxifen only. Of these, 28 (46%) got distant metastases at an average of four years, classifying them as non-responders. The other 32 (54%) were disease-free at 10 years. The ratio of HOXB13 to IL17BR predicted which group the women were in. So, researchers believe that non-responders to tamoxifen can now be identified by this ratio in advance, allowing doctors to find other treatments for those women.

An AACR official called this "beautiful science." He said this test would be especially useful for women with primary breast

cancer, "If you know they will get a distant metastases in three to five years despite tamoxifen therapy, you may need to start more vigorous chemotherapy earlier…Women may want to know for prevention or surveillance. If they know they are not a tamoxifen responder, they may opt for more mammograms and more therapy. Early detection of a recurrence is better than later detection."

Most other experts questioned were equally enthusiastic. One of the reasons they like it is that they can see ways to apply it, particularly in determining which women should not be taking tamoxifen (~30% of women on tamoxifen are non-responders). Dr. Von Hoff is excited about this technology, but he wants a validation study before using it for clinical decision making. He said, "This is useful…I believe it is worth a prospective clinical trial, with patients randomized to tamoxifen or not, based on this. So now, there could be a trial of tamoxifen+Aromasin (Pfizer, exemestane) vs. Aromasin. But still, the critical piece is a clinical trial to validate the pattern. What the company has done is a training set, but it is not enough for me to make a decision on advising patients." A German researcher said, "This is an advance because…it is a good tool for validation, and it has clinical value. It is an advance in how to treat the patient."

Arcturus will sell an analyzer to labs or hospitals, then reagent sales will provide recurring revenue. For the tumor signatures, customers will need to purchase analytic-specific reagents (ASRs) and general purpose Paradise reagents for the RTPCR (real time PCR) assay. The company also could get revenue from assay licenses.

Arcturus is expected to begin human trials pretty quickly. Competitors include:

- **Genomic Health**, which is a CLIA lab that does its testing in-house.
- **Illumina**. While Arcturus' Paradise system looks at the whole genetic profile, the Illumina system looks only at a subset and uses PCR amplification, not RTPCR.

IMMUNICON'S CellTracks

Immunicon claims its automated tumor cell diagnostic test can find a single circulating cancer cell in several milliliters (7.5 mL) of blood. The test is approved for use in breast cancer, but an official said it could be used for all solid tumors. Three years ago, the AACR featured a competing product by CellWorks at a press conference. CellWorks was never commercialized, probably due at least in part to scale-up issues. Immunicon claims to have solved these problems and has high throughput capacity with its screening product. Johnson & Johnson's Veridex has the exclusive marketing rights to this and any other cancer test developed by Immunicon.

So far, only one CellTracks system has been sold and installed – at MD Anderson Cancer Center in Houston – but there are clinical trial sites at the Cleveland Clinic and at the Impath Lab in Los Angeles. The product won't officially ship until July 2004. In the meantime, it is being placed for research use only. An official admitted, "We do have an education effort with oncologists."

An Immunicon-funded clinical trial studied the role of circulating tumor cells in 41 patients with metastatic breast cancer who had just been diagnosed and were about to begin treatment. It found that the 24 women who had tumor cells circulating in the blood had reduced survival compared to those without circulating tumor cells.

Measurement	No Circulating Tumor Cells n=18	≥3 Circulating Tumor Cells n=24	≥50 Circulating Tumor Cells n=24
Median survival	24 months	13.6 months	3.8 months

Researchers found the presence of cancer cells in the blood predicted prognosis more accurately than the site of metastatic disease or the presence of estrogen receptor on the tumor cells. The principal investigator said, "The general consensus is that if a tumor is estrogen receptor positive, it is considered slower growing and less aggressive. Our study indicates that if cancer cells are present in the blood, the cancer may be more aggressive, regardless of estrogen receptor status."

However, this was a small study, and doctors questioned about it at the meeting said they want more data before embracing this test. A SWOG study is being considered, with a protocol under development.

Another poster reported on a study of blood from 37 metastatic prostate cancer patients. Researchers found that PSA was not predictive of survival, but circulating tumor cells were. A researcher said, "In prostate, I wouldn't change treatment with five cells, but in breast cancer I would."

Measurement	≥5 circulating tumor cells	<5 circulating tumor cells	PSA ≥10 ng/mL	PSA <10 ng/mL
% of patients	62%	38%	51%	49%
Median survival	0.7 years	>4 years	0.95 years	4.0 years

Experts at AACR were not very interested in this test. Every source questioned was either dubious about the technology or dismissed it outright, saying it would need (a) considerable validation, (b) proof that treatment after finding the cell(s) would prolong survival, and (c) a link to specific therapeutic options. A company official admitted that validation studies are needed and that there is no real evidence that a single circulating tumor cell is bad, but the official insisted that this test gives doctors more data than they have had in the past.

Comments about this technology included:

- An oncologist commented, "If it is predictive, people will use it…But we will need long-term data before it is useful."
- A Texas oncologist said, "This is conceptually great, and if the assay is proven sensitive, then it could be used to check mortality and survival."
- Dr. Von Hoff said, "It looks promising, but it really needs validation…There have been hints that circulating (cancer) cells correlate with prognosis or having a bone marrow assay could say who will progress. Three years ago, I didn't believe there would be enough measurement sensitivity for that to happen, but there will be studies in the next several months that show one can prognosticate and determine if you should continue a patient on therapy…Measuring circulating tumor cells could be used as the ultimate marker…Trials for validation are going on now. There are three companies with this technology, and many academic centers."
- Another oncologist said, "This is of no use unless it can directly predict a treatment – which it can't."
- An expert said, "We already treat patients aggressively. Would you save patients from the need for aggressive therapy? Maybe. But this is not useful until more testing has been done. I want to see in a large, randomized trial whether there is a correlation between patients who develop metastases and the tumor cell count." A lab company official said, "It may be another tool, but it is not a standalone diagnostic. It may have utility to measure response to treatment. But the sensitivity has to be sky high."
- Dr. Mitchell Gross of Cedars Sinai Medical Center in Los Angeles, a prostate cancer expert, said, "Without a 1,000-patient study looking at the survival difference, there is little utility…If I tested a prostate cancer patient and found one or two cells, I would do nothing…PSA-RTPCR is a poor prognostic indicator; it is associated with worse survival, but we don't know how to change the treatment. I don't see the Immunicon assay as very useful."
- An NCI official said, "People are skeptical."
- A biotech official said, "This would be very good for patients in clinical trials. It won't change the way a patient is treated until there is more data, but we've been pushing for years to incorporate something like this in clinical trials…To use this, centers will have to have a certain technical expertise. It would be difficult to use as a diagnostic tool. I can't see how you could easily do studies to prove that. You would need to follow normals to see if they get circulating tumor cells. And I'm not sure basing treatment on this test could pass ethics committees."
- A Pennsylvania doctor said, "If I were a patient, I would want to know this. But we need to figure out why circulating tumor cells are causing death, how to kill the circulating tumor cells, and whether there is a survival benefit to treating patients with circulating tumor cells."

Assay to Detect Recurrence of Ovarian Cancer

The National Cancer Institute (NCI) is developing an assay to detect recurrence of ovarian cancer. This protein signature assay appears promising in detecting the recurrence of ovarian cancer, and in time it could become a major (and routine) screening tool for the diagnosis of ovarian cancer. The test measures carrier albumin binders (CABs) in serum. Researchers used mass spectrometry and an artificial intelligence algorithm to successfully differentiate the ion signatures of patients with ovarian cancer from those of high risk normal patients. They assayed 127 high risk normals with 115 ovarian cancer patients over five years, and detected Stage 1 cancer with 100% specificity and sensitivity. A researcher said, "Some day this test for ovarian cancer may be as routine as a Pap smear."

The NCI holds the patents on this, and a researcher said industry has not licensed the technology, so the NCI itself plans to file a 510(k) application with the FDA, based on the results of an ongoing trial in resected ovarian cancer patients. That trial is now enrolling patients.

Blood Test for Liver Cancer

Researchers at Johns Hopkins Kimmel Cancer Center have developed a blood test that can predict some future cases of liver cancer in hepatitis B patients. The test is based on a biomarker that detects mutations in HBV that tend to speed up cancer development. To test this method, researchers monitored 120 people in China for 10 years. In that period, six people developed major liver disease: four with liver cancer, one with hepatitis, and one with cirrhosis. In all six, HBV mutations were found in the blood up to eight years before their diagnosis.

Angiogenesis Gene Linked to Biomarkers in Breast Cancer

Researchers at Johns Hopkins reported that the HOXB7 gene is linked to overproduction of tyrosine kinases – a family of the breast cancer markers. They also found that the gene is important in initiating cancer cells to metastasize. Their data showed that HOXB7 gene expression is low or undetectable in normal breast tissue but is expressed at a five to seven times higher rate in primary tumors and up to 20 times more in bone metastasis. The findings suggest that HOXB7 is important for the early development of breast cancer and may be a good target for detection and therapeutic agents.

New Breast Cancer Imaging Approach

Early mouse work by the NCI found that sentinel lymph node biopsies for breast cancer can be done more simply using micro-magnetic resonance mammo-lymphangiography with a nano-sized contrast agent. This experimental contrast agent is

more hydrophobic than other agents, washes out in two to three hours, requires only a local injection and a small amount of agent. It reportedly can detect breast cancer cells down to 300 microns in a mouse, though it may be less sensitive in humans. A researcher said that additional toxicology studies need to be done before this can move to human clinical trials – and it will need industry support. He said, "The big hope is to avoid biopsies…If we can identify the real metabolic markers, then we can use MRI because we can fine tune this with certain chemical shifts to just look at that region."

BREAST CANCER

Dr. Dennis Slaman of UCLA offered some tips on breast cancer therapy:

➢ The best test (for Her2/neu over-expression) is FISH. He said, "People argue about the expense of this – which is about $400 – but compare that to the cost of women without the alteration or to missing women who do have the alteration. The cost of the diagnostic pales by comparison."

➢ "A *Fortune* magazine article suggested we are losing the war on cancer…One thing blamed was the models we are using – saying they are not useful…To that I say, rubbish… Models are useful if they are used critically and evaluated comprehensively."

➢ "We need to link the right therapeutic to the right subgroup or subtype. There are clearly subgroups in lung cancer that have a spectacular response to a therapeutic…but that is only 10%…Had we taken Herceptin and developed it in overall breast cancer, the clinical benefit would have been zero…So, you really do have to know what patient population you are treating and that you have the right therapeutic link."

REGULATORY ISSUES

Dr. Richard Pazdur, Director of Oncology Drug Products for the FDA, spoke several times at the AACR meeting. Among the points he made were:

- The FDA "doesn't approve drugs. We approve marketing plans."
- "The approval process is not a screening process for drug activity…but there has to be a link to clinical benefit."
- He wanted to clear up any confusion over the idea that the FDA requires that efficacy be shown in isolation for every agent used in a combination treatment. He said, "The reality is that there has to be a demonstration of a contribution of the agent to the combination…What is needed to prove the contribution varies with the risk:benefit."
- The FDA relies heavily on response rate, which he called a "conventional" endpoint: "It is a unique endpoint, and the treatment entirely responsible for tumor reduction. It does not include stable disease."
- "TTP has not been a regulatory endpoint because it has a composite nature…Our fear is that when you use TTP, over time you get, in subsequent trials, a trade off of losing efficacy for more favorable toxicity…We prefer efficacy to remain a pure endpoint."
- "Surrogate endpoints must be correlated with clinical outcome, and they must fully capture the net effect of treatment on the clinical outcome, which is the sticky wicket. There are **few** surrogates I can think of even outside oncology that really satisfy this…(A statistician said) that surrogates fail because they are not in the causal pathway of the disease, the intervention affects only the pathway mediated through the surrogate."
- "At the end of the day, the drug's benefit will be marked by how it helps people. In oncology there is always an interest in getting drugs out there sooner…To make an impact on the War on Cancer or in battling diseases we know as cancer, we have to look eventually at hard clinical endpoints…As we move from hard clinical endpoints to biomarkers, it can't be because we want to; it has to be for a good reason."
- Asked if it is better to establish subgroups upfront, Dr. Pazdur responded, "It has to be done prospectively. One of the problems we get is people who 'fail' the primary endpoint and then want to redefine the population and look at non-specified subsets, which is a statistical quagmire."
- "When we meet with a sponsor, we want a comprehensive drug development program, not just a discussion of drug approval…A short-term approach may not succeed, given our desire to see Phase IV trials integrated into the overall strategy."
- With respect to combination therapy: "We don't demand single agent activity be shown, just that there is a contribution to efficacy – for example, a Phase II trial that showed no activity when given alone but a higher response rate with the combination."

Key points in FDA consideration of oncology drugs were described as:

➢ **Primary endpoint:** Dr. Pazdur emphasized that it is difficult – but not impossible – to get a drug approved when the primary endpoint is missed, "We take a very dim view of approving on a non-pre-specified endpoint." He explained that if a company has a reasonable explanation for missing the primary endpoint – e.g., the crossover rate was too high – the FDA might consider approval on secondary endpoints, provided they are all statistically significantly positive.

➢ **Trial bias:** "One goal in clinical trials is to minimize subjective bias. He said, "The lack of blinding has profound implications…We want to know if there is a true treatment effect."

➢ **The magnitude of the treatment effect:** "A p-value of 0.0001 is better than just under 0.05…A realistic estimation of the treatment effect should be used in powering trials. There is a tendency in oncology to underpower studies…We don't have an appreciation of how therapies will work, and there is a lot of guestimation on how well the drug will work, and this frequently results in a lower than necessary number of patients entered…This is a ***major*** problem in many oncology drugs we are dealing with."

➢ **Secondary endpoints: "**When a survival advantage is claimed, we look at secondary endpoints. Are the response rate and TTP going in the same direction? What happened with subgroups? What was the consistency of the secondary endpoints?"

➢ **External substantiation – one trial vs. two trials:** "There is an increasing tendency of sponsors to come (to the FDA) with one trial – perhaps to reduce the risk of drug development. Where there is some certainty of the drug working, sponsors may come in with big studies as in breast cancer, but where there is less certainty, sponsors often want to spread the risk, and so they do a trial in lung, one in colon, etc."

➢ **Assay sensitivity:** "Is there a true effect?"

➢ **Appropriateness of the clinical trial design and analytical method.**

➢ **Acceptability of the study conduct.**

➢ **The quality of data collected.**

➢ **Control of bias and confounding.**

Other regulatory issues that were discussed included:

Endpoints: Oncologists continued to argue that the FDA should accept progression-free-survival (PFS) as an endpoint in cancer trials. An FDA official said the agency is considering this, and may do it in the future. However, no decision has been made yet, and none appears imminent.

Comparison of the Clinical Trial Endpoints

Survival	Time-to-Progression
100% accurate	Less accurate
Assessed daily	Assessed every 2-6 months
Importance unquestioned	Importance uncertain
Reflects both safety and efficacy	Reflects only efficacy
Takes longer	Faster
Might be obscured by secondary therapy	Not obscured by secondary therapy
Reflects natural history of disease plus treatment effect	Reflects natural history of disease plus treatment effect

Accelerated approval: A senior FDA official and other sources all agreed that the FDA is not getting tougher on Phase II approvals. There does not appear to be any change in the FDA willingness to approve oncology drugs based on Phase II data. FDA and pharma officials agreed that a Phase II trial for accelerated approval needs 100-150 patients when randomized, and 50-100 if non-randomized. One pharma official commented, "It is very rare for a pivotal Phase II trial to have 50 patients." Another pharma official said, "I don't get the sense that the FDA is getting tougher on Phase II approvals. I think they are pragmatic. And the FDA is always willing to talk…The FDA does question the data harder if you don't do a randomized trial, but they recognize the difficulty of doing a randomized trial against placebo (in cancer)." A third pharma official said, "The messages from the agency reflect a concern with the difficulty of Phase II trials, but the agency hasn't gotten more restrictive. But they are insisting on better endpoints and trial designs."

Unproven mechanisms of action: Sources said this is not a bar to FDA approval. A pharma official said, "An unproven mechanisim doesn't stop approval, but you need some idea of the mechanism, and you need to prove safety. In the big picture, the mechanism doesn't matter."

Erythropoeitin: Surprisingly, there was no discussion at the meeting about the FDA Oncology Drugs Advisory Committee (ODAC) meeting to be held on May 4, 2004, on the safety of erythropoeitin in oncology.

CMS Reimbursement: There was no discussion or debate at AACR over CMS reimbursement issues in oncology. CMS reimbursement is less a research issue than an ASCO-type clinical issue, sources insisted.

Surrogates and Biomarkers: Dr. Pazdur said, "Validated oncology surrogates are few and far between…The agency has demonstrated flexibility, and we will continue to do so…The hallmark is a demonstration of clinical benefit…In oncology, we have interpreted that as a reduction in tumor-related syndromes or survival. Clinical benefit has to be clinically meaningful, not just a biomarker." An FDA GI advisory committee raised several concerns about using biomarkers in colorectal trials, including:

- **Chronic safety** – How long and how many patients would be needed?
- **Rebound** – The need to prove those patients stopping the active drug don't have a higher rate of new polyps than patients on placebo.
- **Resistance** – The need to know that the effect doesn't diminish over time.
- **Durability**.

Imaging: A speaker said there is a "lot of promise in imaging."

Off-label usage: Both the FDA and payers appear to be increasingly concerned with off-label use of drugs. A pharma official said, "The FDA feels there is significant off-label usage for some drugs without sufficient safety information, so they are trying to narrow off-label use. They want companies to file more INDs…I don't see the FDA doing anything in the next year or so, but there is more and more talk about it." ♦