Trends-in-Medicine

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by Lynne Peterson

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If there was any hot topic at this year's meeting of the American Association for Cancer Research (AACR), it was genomic signatures, which an AACR official estimated accounted for about 10% of the posters at the meeting. Small molecules, cancer stem cells, and therapies targeting smaller markets were highlighted. Doctors were also excited about the variety of VEGFR inhibitors, especially Genentech's Avastin (bevacizumab).

Among the comments about what's exciting this year were:

- "Avastin is the major cancer drug for the next five years. It can probably be added to the IV fluid. I think it will work to potentiate chemotherapy in any solid cancer. There is good science behind it, but it needs optimization. The broad activity tells you something."
- "Small molecules are at the forefront of excitement, and that will only increase."
- "We may develop a 'Lipitor for cancer.'" This source was suggesting a cancer preventive may be developed that could be taken as easily – and commonly – as Pfizer's cholesterol-lowering agent.
- "The lesson of Gleevec (Novartis, imatinib) is that a drug can be quite effective with a small market. The CML population is only 10% of the NSCLC market…If a drug can work in 5% of three cancers, it could do well. We need to change the way pharmas look at the market."
- "Cancer stem cells may exist, and that could make a new target. The cell of origin, I believe, is the originator cancer, and that's what maintains the disease. There is growing interest in this field recently. It is an old theory with new interest in solid tumors. Cancer stem cells could become dormant but reactivate causing later relapse."

There also is growing interest in more frequent administration of low doses of chemotherapeutic drugs with no holidays or prolonged interruptions. This was referred to as "dose-dense" chemotherapy, which is not necessarily "dose-intense" chemotherapy, or metronomic chemotherapy. One example cited was metronomic administration of American Pharmaceutical Partners' Abraxane (ABI-007), and a study was presented which found Abraxane was effective when dosed metronomically. However, the genomic signature research was almost all very early, investigational studies, without clear commercial potential or sponsorship. Last year, there was considerable excitement at AACR over Arcturus' Paradise test of tamoxifen responders, and Immunicon's CellTracks circulating tumor cell measurement system, but there were no noticeable data on either of these this year, and neither company had a booth.

The diagnostic companies that presented data at the San Antonio Breast Cancer Symposium in December 2004 were also noticeably absent from AACR.

Asked at what point in a drug's development doctors feel comfortable using a drug and obtaining reimbursement, sources cited several things they consider before using a drug – including reimbursement, toxicity, and peer-reviewed data. A West Coast oncologist said, "I'm comfortable using off-label drugs in trials. Outside of trials, it depends on the toxicity. If toxicity is low, then I'm more likely to use it off-label…SU-11248 (Pfizer's sutent) will be used more than Avastin (Genentech, bevacizumab) in lung because it has a shorter half-life. I hesitate to give Avastin to lung patients. With SU-11248, you just give a pill, and if you have to stop it, it is easier than stopping Avastin." A Texas doctor said, "I want to see peer-reviewed data before using something off-label."

Comparison of TKIs

Drug	Indication being tested	Status	Characteristics	Potential advantages
Abbott's ABT-869	Breast, ovarian, prostate, and endometrial cancer	IND has been filed	Multi-targeted	More potent
AstraZeneca's ZD-2171	Solid tumors, including ovarian cancer	Phase II in solid tumors; Phase I in ovarian cancer	VEGFR-1-2-3 (a VEGF-kdr)	Selectivity, potency
AstraZeneca's ZD-6474	Lung cancer bone metastases	Phase II	VEGFR-2, EGFR	---
Bayer's sorafenib (BAY-43-9006)	Renal cell, melanoma	Phase III completed, expected filing in 2005	Activity against Raf-I, VEGFR-2, and PDGFR-β	Raf inhibition
Bayer's BAY-57-9352	CML and solid tumors	5 Phase II registration trials underway	Targets VEGFR-2, PDGFR, and c-Kit	Potency, Src inhibition
Bristol-Myers Squibb's BMS-582664	All cancers	Phase I safety study	VEGFR-2/FGFR-1 (no PDGFR-β activity)	Oral, small molecule, inhibits whole pathway, easy to make (cheaper?), combinable with cytotoxics
Bristol-Myers Squibb's BMS-354825	Solid tumors, CML	5 Phase II registration studies underway	dual Bcr-Abl and Src kinase inhibitor	Src inhibition; works in Gleevec-resistant patients
Cephalon's CEP-7055	Refractory solid tumors	Phase I	VEGFR, KDR, VEGFR-1, Flt-1, and VEGFR-3, Flt-4	---
Chiron's CHIR-258	Solid tumors and hematologic cancers	Phase I	FGF, VEGFR-1-2-3, PDGFRb, Flt-3, and c-Kit	---
Exelixis' XL-647 (EXEL-647)	Solid tumors	Phase I	EGFR, VEGFR, HER-2, and EphB4	---
Exelixis' XL-999 (EXEL-999)	Solid tumors	Phase I (Phase II in late 2005)	KDR, FGFR-1, VEGFR, PDGFR-β, and Flt-3	---
GlaxoSmithKline's lapatinib (GW-572016)	Breast cancer	Phase III	Reversible inhibitor of EGFR and ErbB-2 (HER-2/neu)	---
GlaxoSmithKline's GW-786034	Solid tumors	Phase II	VEGFR-2	---
Novartis's AEE-788	Breast and perhaps other cancers	Phase I/II	EGFR, VEGFR, HER-2	---
Novartis's AMN-107	CML	Phase I/II	aminopyrimidine ATP-competitive inhibitor of Bcr-Abl	Effective in Gleevec-resistant patients
Novartis/Schering AG's vatalanib (PTK-787)	Colorectal cancer	Phase III	VEGFR-1 and VEGFR-2	---
Pfizer's sutent (SU-11248)	GIST	Phase III	VEGFR, PDGFR, Flt-3, c-Kit	---
Pfizer's AG-013736	Solid tumors, including breast	Phase II	VEGFR, PDGFR	---
Pfizer's SU-14813	All solid tumors	Phase I	---	Compared to SU-11248, this has: Lower volume distribution, no active metabolite, and a shorter half-life, but very similar selectivity profile
Pfizer's SU-6668	Solid tumors	Phase II	VEGFR, PDGFR, FGF	---
Schering AG's ZK-304709	Breast cancer	Phase I	Unknown	---

TYROSINE KINASE INHIBITORS (TKIS)

Numerous TKIs are in development, and the targets often differ, but the initial targets may not necessarily prove to be the best targets in the future, so it probably is appropriate to look at the class rather than the specific indications being sought. The furthest along in development are Bayer's sorafenib (BAY-43-9006) and Pfizer's sutent (SU-11248), but it was Novartis's AMN-107 that got the attention at AACR. AMN-107 was the only TKI to be featured at an AACR news conference or in AACR press releases. However, there were posters on many of the other TKIs in development. One pharma official with a TKI in very early development was asked why his company was continuing to develop a TKI in such a crowded field, and he responded, "We had a consultant analyze the field, and the consultant told us there is room for at least five to nine TKIs in the clinic."

CHRONIC MYELOID LEUKEMIA (CML): NOVARTIS'S AMN-107 and BRISTOL-MYERS SQUIBB'S BMS-354825 both effective in Gleevec-resistant CML patients

Both of these drugs are follow-ons to Novartis's Gleevec (imatinib) for CML and possibly GIST. Experts insisted that they are not, at least initially, designed to replace Gleevec but to offer potent alternatives for the 10% of advanced CML patients who are resistant to Gleevec. The AACR press conference only covered AMN-107, but researchers said BMS-354825 results were "equally impressive." One researcher commented, "Overall, the response rates look fairly comparable. The toxicity profiles have some difference that it will take time to tease out…There is no Grade 3-4 edema with AMN-107…It is way too premature to make a comparison with BMS-354825 right now."

NOVARTIS'S AMN-107, an aminopyrimidine ATP-competitive inhibitor of Bcr-Abl, retains half the chemical makeup of Gleevec, while the other half was engineered to assure a tighter link to Bcr-Abl, thus increasing potency and potentially overcoming resistance due to mutations in Bcr-Abl. Two studies were presented on AMN-107:

- **Cell-line study.** Researchers at the Oregon Health and Science University (OHSU) compared the potency of AMN-107 to Gleevec using a panel of cell lines expressing 16 different Gleevec-resistant, mutant versions of Bcr-Abl, and they found that AMN-107 was 23 times more potent than Gleevec against 15 of the 16 resistant mutants (all except T315I). A researcher commented, "AMN-107, at its least effectiveness, is comparable to Gleevec at its most effective."

- **Interim Phase I results.** M.D. Anderson Cancer Center researchers reported on updated results from an ongoing Phase I/II, international, dose-finding study of AMN-107. Interim results from this trial were presented at the American Society of Hematology meeting in December 2004. At AACR, researchers reported on 100 of the 109 patients enrolled so far. Final data from this trial are expected in fall 2005.

The new data reveals that >70% of advanced CML patients responded to AMN-107, and patients with the early form of the disease responded at a rate of >90%. The researchers noted that the response rate in >100 patients enrolled in the clinical trial to date continues to improve, as doses are rapidly increased. The first patients began treatment at 50 mg, but now all are taking 400 mg BID and have not reached the MTD. Dr. Francis Giles, the principal investigator, said, "We need to have all the patients on what we deem the highest safe dose to complete Phase I. That will be at least 400 mg BID and perhaps 600 mg BID…We need to run it long enough to see if a great majority of patients can tolerate it…so it could be mid-2005 or later…I doubt we will have definitive data at ASCO 2005."

Dr. Giles added, "This (trial) proves that sequential targeted drugs can be delivered and work…If you can take a pill and rescue people who failed the current standard of care, that is remarkable…The drug is very safe, and we are seeing a response that improves daily…Any physicians with a CML patient who is failing Gleevec therapy should try to get their patient into an AMN-107 clinical trial."

Researchers plan to launch a series of studies in the next month testing AMN-107 as a first-line therapy for CML patients, whether they have the early chronic stage, advanced "accelerated," or terminal "blast" stage of the disease. The high level of responses seen to date are classified as hematologic, but increasing numbers of cytogenetic responses are also being seen, and the number of molecular major responses is increasing. However, Dr. Giles warned, "We have to be careful. Gleevec is very, very effective…and I'm not sure we can say we know how to use Gleevec optimally, so displacing Gleevec will be a very difficult thing…There appears to be a synergy between the two drugs (AMN-107 and Gleevec), so we may look at combination therapy… Combining AMN-107 with BMS-354825 depends on proving that Src (which BMS-354825 targets) matters in CML. Whether Src inhibition matters or not is a question…but there are other targeted therapies, such as HDACs, for which there is a lot of very elegant preclinical data suggesting combination therapy may work."

Other interesting points made about AMN-107 included:

- Marrow suppression will probably be the DLT.
- There is some indirect hyperbilirubinemia, but it reportedly reverses itself in a couple of days with no dose reduction.
- A small subset of patients will not respond to either Gleevec or AMN-107.

Asked if AMN-107 is likely to have utility in solid tumors, Dr. Giles said, "I don't think you can reasonably expect that. With the high potency of AMN-107, you will see more activity in tumors sensitive to Gleevec. Will it work where Gleevec did not in a new tumor type? No. There, BMS-354825 will pose more questions because we don't know the

impact of having the Src activity. I don't expect AMN-107 to have an effect in solid tumors where Gleevec has not."

BRISTOL-MYERS SQUIBB'S BMS-354825. This agent, which is ~300-fold more potent than Gleevec, is in Phase I trials in solid tumors and Gleevec-intolerant or Gleevec-resistant CML. The company has no specific focus in GIST, and it is not being explored in renal cell carcinoma because it is a Src inhibitor, which is not active renal cell cancer. Five Phase II registration trials are underway. Another Phase I solid tumor trial is expected to start this month at M.D. Anderson Cancer Center, H. Lee Moffitt Cancer Center, and Sarah Cannon Cancer Center.

A researcher said the advantages of BMS-354825 over AMN-107 include:

- "AMN-107 is an analog of Gleevec, with the same liabilities and shortcomings. AMN-107 is better than Gleevec in some settings, but it won't avoid all Gleevec-resistance."
- "AMN-107 is less potent than BMS-354825."
- "AMN-107 is not a Src inhibitor."

A speaker noted:

- BMS-354825 may be used in a cocktail with Gleevec. He said, "The combination is more effective than BMS-354825 alone for cells expressing wild-type Bcl…There is a minor additive effect…BMS-354825 can target mutations in the presence of very high levels of Gleevec, and there is no antagonism or interference from Gleevec at levels that are well beyond clinically achievable doses."
- BMS-resistant mutations may be sensitive to Gleevec.
- Gleevec could be used as the front-line drug, and AMN-107 or BMS-354825 reserved for Gleevec failures.
- AMN-107+BMS-354825 might be an interesting combination.

Among the posters on BMS-354825 was a cell line study that found that BMS-354825 is active in NSCLC.

HEAD AND NECK CANCER

Oncologists were asked how they will use Imclone's Erbitux (cetuximab) in head and neck cancer, once it is approved. A California doctor said, "It will be a Medicare issue. If it's covered, we'll use it. I think it will be used with radiation. It's not better than cisplatin in efficacy and disease control, but it has a better side effect profile…I might switch entirely to Erbitux once it is approved because of the (lower) side effects – and I would consider adding chemotherapy to the Erbitux." He estimated this would be 80%-100% of all head and neck cancer patients.

Reimbursement is the main reason Erbitux is not currently used in head and neck cancer. One expert said, "Even Blue Cross/Blue Shield won't cover it. I tried."

The data on Erbitux in head and neck cancer is vs. radiation, not vs. chemoradiation, but that is not an issue for oncologists. One explained, "That's not a concern. The trial was Erbitux plus radiation. Looking at the data on two-year local control, Erbitux+radiation is comparable to cisplatin+radiation in terms of efficacy. The question is what the results will be of Erbitux+radiation+cisplatin."

What's on the horizon that looks promising in head and neck cancer? Sources pointed to:

- **LILLY'S antisense**. An expert said, "Lilly has an interesting compound down the road, and they are doing a solid program."

- **GLAXOSMITHKLINE'S lapatinib.** A California oncologist said, "In head and neck we see responses, but we haven't been able to find mutations…~10% of mutations in NSCLC are EGFR/ErbB-2. People found some patients respond well to Tarceva (Genentech, erlotinib) plus Iressa (AstraZeneca, gefitinib), but they couldn't find a mutation, so ErbB-2 may play a role…GlaxoSmithKline's lapatinib is very promising in head and neck cancer…I think it is a great compound…It is 'interesting,' but the outlook depends on the commitment of the company, and I heard it is a major focus for Glaxo in head and neck. I heard they were going for a breast indication…Two groups are using the Glaxo compound in trials; one is government-funded, and the other is investigator-led. Those trials are in female non-smokers; you see more EGFR mutations in those. SWOG did a Phase II of Iressa, and they are trying to push using the Glaxo compound in the same patients, but Glaxo withdrew its support."

LUNG CANCER

ASTRAZENECA'S Iressa (gefitinib). Oncologists continue to believe that Iressa should remain on the market. One expert commented, "Iressa has had a place. It should stay available. It is better tolerated than Tarceva, and it might be good for subgroups."

Researchers discussed the pre-planned, subset analysis of the ISEL trial. As presented at the FDA Advisory Committee meeting, all subsets favored Iressa over placebo. A speaker said, "This raises the confidence that the differences seen are due to the drug and not to chance…There was some improvement in survival with Iressa, but the difference did not reach statistical significance. There was a statistically significant improvement in survival in some planned subgroups – never smokers and patients of Asian origin."

An expert asked, "It is easy to understand the Asians and never smokers, but there was also a tendency for less effect the longer the patient was out from diagnosis. Does that also

correlate with EGFR mutations?" The researcher responded, "That is a possibility. There is a huge amount of interest by clinicians on EGFR mutations…One of the issues is whether mutational analysis or other biological analysis will give added help to selection of patients for this sort of treatment. It is a bit dangerous looking for slight changes within the datasets."

Compared to the BR-21 trial, ISEL patients were more refractory:

- 90% of ISEL patients were refractory to the most recent chemotherapy.
- Only 18% of ISEL patients responded to the most recent chemotherapy, vs. 40% in BR-21.
- 45% of ISEL patients had progressed on the most recent chemotherapy, vs. 21% in BR-21.

ISEL Trial Subset Results

Measurement	Iressa	Placebo
Median survival		
Never smoked	8.9 months	6.1 months
Ever smoked	5.0 months	4.9 months
Asian	9 months	5.5 months
Non-Asian	5.2 months (Nss)	5.1 months
Safety		
Rash	37%	10%
Diarrhea	27%	9%
Serious adverse events	19% (Nss)	17%
Withdrawal due to adverse events	5%	2%
Interstitial lung disease-like events	1%	1%

A Japanese study found that plasma levels of MIp-1β may be a useful predictor of skin toxicity with Iressa.

GENENTECH'S Avastin (bevacizumab). In a small Phase II lung cancer trial Avastin did not work. A speaker suggested some possible reasons:

- Crossover in non-responders.
- Bleeding.
- Non-squamous cell patients. He said, "If you take out the non-squamous patients, you get a statistically significant survival benefit."

However, the company announced the Phase III lung cancer trial was positive, and details of that trial will be presented at ASCO 2005. Experts said the issue to watch in that data will be the bleeding rate, but one speaker said the bleeding rates in the Phase III trial were not as bad as in the Phase II trial.

So far, Avastin does not appear to be affecting use of Tarceva. A California oncologist said, "Eventually Avastin will be used in lung, but not right now because of economic reasons. Patients are mostly elderly, and they are not covered for it – and it is expensive…I will also be looking at the side effects in the trial to be presented at ASCO 2005. We've seen efficacy, but not side effects – bleeding, hemoptosis, clot risk. So there are two barriers to use – safety and lack of Medicare coverage."

Vitamin D intake levels may predict successful lung cancer surgery. The successful outcome of surgery to treat early stage NSCLC appears to depend on the level of vitamin D present in a patient, which is affected by food, supplements, and even the season of the year during which the operation is performed. Harvard researchers, looking at disease-free survival (DFS) and overall survival (OS) in 456 early-stage NSCLC patients in Boston, found that patients with high vitamin D intake who had surgery in months with lots of sun were more than twice as likely to be alive five years after surgery, compared to patients with low vitamin D intake who had wintertime operations. The mechanism behind the link between vitamin D and surgery outcome is not known, but there have been other studies that hinted vitamin D may work to inhibit a variety of different cancers, and animal studies have shown anti-proliferative and anti-invasive properties to vitamin D. A researcher said, "This study in no way suggests that people should try to time their cancer surgeries for a particular season…but, if validated, it may mean that increasing a patient's use of vitamin D before such surgery could offer a survival benefit."

Vitamin D in NSCLC

Timing of surgery	5-year disease-free survival	5-year overall survival
Winter operations	54%	50%
Spring/fall operations	56%	57%
Summer operations	70%	59%
Winter operation + Low vitamin D intake	46%	30%
Summer operation + High vitamin D intake	83%	72%

MELANOMA

Researchers are excited about several investigational agents for melanoma, including:

MILLENNIUM'S Velcade (bortezomib):

- **Velcade plus Temodar (Schering Plough, temozolomide)** in advanced melanoma. A Phase I study found 3 MRs and 1 PR in 19 patients. An expert said, "I can't say this is it. It's not the cure for melanoma, but it is of some interest – and it is very active in vitro. As a single agent, Velcade has no effect in the clinic in melanoma." Phase II trials are planned.
- **A cell-line study** by Emory University researchers found that Velcade down regulates the androgen receptor and induces growth arrest and apoptosis in prostate cancer.

The cells rapidly underwent G2/M arrest at 24 hours followed by a dramatic increase in apoptotic cell death at 48 hours. [This did not appear as dramatic G2/M arrest as with Telik's Telcyta (TLK-286).]

BAYER'S sorafenib (BAY-43-9006). A source said this is something he wants to try, "I was impressed with the carboplatin+taxol+BAY-43-9006 data. I saw things I didn't expect. A number of patients are getting better, and I'm not used to seeing that in melanoma…BAY-43-9006 is not working through the Raf kinase pathway. In 30-40 patients it acts the same in responders and non-responders with ~60% inhibition."

GENENTECH'S Avastin (bevacizumab). A source also wants to try this in melanoma.

RENAL CELL CARCINOMA: Bayer's sorafenib (BAY-43-9006) and Pfizer's sutent (SU-11248)

During AACR (but not at the meeting), Bayer announced that, based on an interim data analysis showing a statistically significant improvement in PFS with sorafenib, all patients in the ongoing Phase III trial in advanced renal cell cancer will be offered sorafenib. The interim data from that trial will be presented at ASCO 2005.

At AACR, there were several sorafenib posters, including:

- A mechanism of action poster looked at the action of sorafenib in a murine model of renal adenocarcinoma, concluding that the drug exerted its anti-tumor effect primarily via inhibition of tumor angiogenesis.
- An *in vivo* study of the endothelial cell pathways found that sorafenib is likely to have effects on tumor endothelial cells in addition to tumor cells.
- A mechanism of action poster looked at sorafenib activity in AML cell lines and mice. Researchers said the study suggests that sorafenib may have biologic activity in AML patients with Flt-3 mutations.

Oncologists questioned at AACR about sorafenib (BAY-43-9006) were very optimistic about this agent. A Texas doctor said, "I'm fairly excited about this. They had good data for three months, but the question is what the response is at six months." Another expert said, "PFS and survival are more important than response rate."

In particular, they are excited about the ability to dose it continuously and what they perceive as a more favorable side effect profile compared to Pfizer's sutent (SU-11248). A Bayer official said a key advantage of BAY-43-9006 is that it can be given continuously and patients have to go off Pfizer's sutent for two weeks every four weeks, but he also indicated that the ability to combine BAY-43-9006 with other agents and a better side effect profile are advantages. A Texas doctor said, "If BAY-43-9006 is easier to give, that would make up for a little less efficacy." Another expert said, "I think the side effects of BAY-43-9006 are slightly better than SU-11248, but neither has much toxicity…Efficacy is greater with BAY-43-9006 because of the nature of the studies. How doctors choose between the two drugs may be on price, marketing, or who gets approved first."

Sources were uncertain how broadly combinable sorafenib might prove to be. An expert said, "It will be broadly combinable if the toxicity is okay, and it should be." Another source said, "We did preclinical studies of BAY-43-9006 in combination with each of these: Gemzar, paclitaxel, cisplatin, navelbine, and camptosar (Pfizer, irinotecan), and clinically, we studied BAY-43-9006 with carboplatin+Taxol. They all looked mostly additive. BAY-43-9006 is definitely combinable with no increased toxicity and no decrease in efficacy."

Sources are not convinced there are substantial efficacy differences between sorafenib and sutent. Preclinically, they are the same, a source insisted, adding, "The clinical data are what will differentiate the products in the minds of doctors." A sorafenib researcher said, "I think the efficacy of sorafenib and sutent are about the same, but even if sutent is slightly more efficacious, patients will tolerate sorafenib better and will prefer it." An oncologist said, "I'm not convinced that sutent is more efficacious than BAY-43-9006." Another expert said, "The data on sutent are too preliminary."

Sources were asked how they would view the two agents if PFS looked similar between them in renal cell carcinoma, but there were a difference in response rate. An oncologist said, "If PFS were the same, but one drug had a higher response rate in Phase I or Phase II, I wouldn't conclude one was more potent than the other, but if the same difference were shown in Phase III, then I would believe there is a difference." A Bayer official said, "Survival trumps progression. Crossovers will cloud our survival data, but we'll have progression-free survival data."

Patients who are rechallenged with BAY-43-9006 after progression on placebo may respond a second time. A Bayer official said preclinical studies were done on this – and reported two years ago, "In those studies, animals who got the drug for 10 days, stopped treatment, and had their tumors grow were then given a second course of BAY-43-9006. Tumor growth stopped again, even though there was larger tumor mass than when they were initially treated. The preclinical data showed that the mechanism is cytostatic, so you want to maintain treatment as long as possible. When you stop treatment, the tumor starts to grow again. If the drug is given for 10 days, there is a 10-day delay in tumor growth. When the drug is given for 20 days, there is a 20-day delay before the tumor grows." Another expert said, "If a patient progresses on BAY-43-9006, you might try a higher dose.

I'm not sure whether or not you should continue with the same drug, but increasing the dose is a possibility."

Final data on a human rechallenge trial will be presented at ASCO 2005. In this study, patients were given a 12-week run-in. Patients who progressed came off study, those with tumor shrinkage stayed on study, and those with stable disease were randomized to drug or placebo.

It may be possible to sequence sorafenib and sutent. A Bayer researcher said, "I can't say, but, in theory, there is no reason why you couldn't sequence them. Possibly, you could take BAY-43-9006 when you are off sutent, but why would you want to go off BAY-43-9006?" An oncologist said, "To an extent, it would be possible." Another expert said, "I'm not sure that will work. The drugs are reasonably similar. But people will try this with little information."

If sutent comes to market with an approved indication in GIST but with data in renal cell carcinoma, and sorafenib gets an approved indication in renal cell carcinoma, doctors said they will use sorafenib first in renal cell carcinoma. The preference will be for the approved drug, and part of that is due to expected reimbursement issues with off-label use of another drug when there is a newly approved drug with an indication. An expert said, "Doctors will probably use the approved drug first and reserve off-label drugs for backup." A Texas doctor said, "The approved medication would be used first; the other would be used second-line." A Midwest doctor said, "Physicians are prescribing more on-label because of reimbursement. In renal cell carcinoma, they will most widely use what is approved." Another source said, "Sutent will be cheaper than Avastin, but it is not inexpensive, so cost will still be an issue off-label."

Ovarian Cancer

Among the agents described by experts as promising in ovarian cancer are:

American Biosciences/American Pharmaceutical Partners' Abraxane (ABI-007). A source said this is likely to be tested in ovarian cancer soon.

Genentech's Avastin (bevacizumab) also is expected to have activity in ovarian cancer. There will be data at ASCO 2005. An expert said, "Animal models of Avastin plus Taxol show additive, and probably synergistic, activity."

GlaxoSmithKline's lapatinib. Several experts said they are excited about this agent. An ovarian cancer expert said this is the agent to watch. It is in Phase II and considered promising. A breast cancer researcher said, "Lapatinib looks exciting and is ahead."

Biomarkers

Dr. Judah Folkman of Harvard Medical School said his lab is working on three biomarker programs:

1. Urinary matrix metalloproteinases.
2. Circulating endothelial precursor cells.
3. Platelet angiogenesis proteasome. He said, "This is not yet in the clinic, but it is very sensitive and one of my favorites…Tumors have both angiogenic and non-angiogenic cells. The angiogenic cells can be measured in plasma, but not the non-angiogenic cells. The non-angiogenic cells activate in mice at about 133 days…The question is: What switches them on?…To validate our studies, we will start with CRC."

Dr. Folkman cited some ways platelet angiogenesis measurement might be used: "If you had three assays, and they remain flat, you wouldn't be worried, but if they are rising, why would you want to wait for the patient to get worse. Why not add Avastin?…Women with a breast cancer gene are now offered a bilateral mastectomy and oophorectomy, and many refuse…Why not do an angiogenic profile every three months …If it is rising, why wait to treat?" He also suggested the test could be useful in macular degeneration, and he compared it to cholesterol measurements to initiate and monitor use of Lipitor (Pfizer, atorvastatin).

Biomarkers that predict oral and breast cancer. UCLA researchers reported on a proof-of-principle study that found genetic biomarkers isolated in saliva, salivary transcriptomes, could successfully predict oral squamous cell carcinoma in about nine out of 10 cases. This follows a similar study published recently showing these biomarkers can predict head and neck cancer.

The UCLA team collected saliva and blood from 32 patients with primary oral squamous cell carcinoma and 40 breast cancer patients, and matched each with saliva and blood from normal subjects. They were able to harvest up to 10,000 types of human mRNA from saliva, setting up a comparison test between cancer patients and the normal subjects based on analysis of their genetic "profiles." A researcher said, "Both serum and saliva exhibited unique genetic profiles. The risk model yielded a predictive power of 95% by using only the salivary transcriptome samples and 88% by using only serum transcriptome samples for oral squamous cell carcinomas. For oral cancer, salivary transcriptome has a slight edge over that of serum transcriptome analysis."

Researchers predicted that robust, reproducible, high-throughput tests will be able to be developed using these biomarkers, though the results still need to be validated in a large, blinded trial. However, they noted that they still need to be sure that the test is not affected by a patient eating, drinking, smoking, or from diet or oral hygiene. An investigator said, "There is utility beyond the mouth. We've begun to look at breast cancer…The data look very good in breast cancer as well as oral cancers…This could be a high-

throughput and reproducible test…The National Institute of Dental and Craniofacial Research is working hard to turn saliva diagnostics into a reality. Our discovery that RNA is present is saliva…is a distinct advantage…It is potentially useful for individual profiling and for diagnostics."

Asked how promising this test is, an expert said, "Spitting is easier than giving blood or dragging a stool sample to the doctor…So, this is a very clever idea." The investigator said, "I don't know if saliva can be used to stage disease. Saliva is a filter of blood. What's in blood is known to be in saliva, but the level is lower, so proteins can't be detected with Elisa, but now with nanoparticles and nanotechnology-based biosensors, we are bound to see engineering creativity coming on board."

DIAGNOSTICS

Diagnostic tools in development include:

➢ Measuring plasma VEGF as a way of monitoring response to antibodies, even after a single injection.

➢ Mass spectrometry may be useful in diagnosing certain cancers, including lung, kidney, prostate, breast, liver, brain, and intestine. Proteins have been identified that are specific to particular organs, but they still need to be validated.

➢ The signatures of angiogenic neoplasia and cancers can be detected with homing peptides.

- They can distinguish normal from pre-malignant and malignant vasculature in an organ.
- They can be selective for the vasculature of a particular cancer type/organ.
- The lymphatic vasculature associated with tumors also has signatures that vary with organ and tumor type. The lymphatic vasculature appears to have a signature that discriminates one tumor type from another and tumor lymphatics from normal lymphatics.
- They can be used to:
  - ♦ Enable non-invasive detection of neoplasia and cancer.
  - ♦ Monitor response to therapy.
  - ♦ Detect recurrence in a neoadjuvant setting.
  - ♦ Deliver toxic payloads to the neoplasias and tumors, exploiting the fact that the signatures are there and not worrying about whether the signatures are functionally important.

➢ Angiogenic and EGFR signaling by molecular imaging may be useful for early and accurate diagnosis and tumor phenotyping. These would be a helpful tool for doctors to utilize the best therapies. They could monitor a patient closely for 48 hours, and if there was not response, move on to another therapy. They could also be used to decide whether or not to proceed with a specific targeted therapy and to help with optimal dosing in individual patients. A speaker said, "This method would basically replace taking biopsies. This allows you to do an imaging study quickly and see if drugs show efficacy very rapidly – and cheaper."

Three types of molecular imaging discussed were:

- Agents for imaging general cellular, biochemical, and physiologic processes (glucose utilization, etc.).
- Agents that target specific imaging.
- Surrogate imaging agents.

Researchers at Georgetown University are patenting a test to detect 17Kda cleaved caspase 3 in serum, which they say has the potential to be a minimally invasive surrogate marker for the efficacy of cancer therapy in the clinic. So, far there is no commercial partner.

Genomic patterns ("signatures") that predict cancer patient outcomes. Scientists reported on several sets of genes or "signature portfolios" from the Human Genome Project that describe a patient's chances for developing cancers, fending off malignancies, and responding to treatment, including:

➢ The "Death from Cancer Signature": A set of eleven genes can identify patients at much higher risk for metastatic complications and more severe cancer illness as the disease progresses. Patients with this set of genes are genetically less likely to respond to conventional therapies and might want to consider more novel therapies.

➢ A 40-gene signature may predict esophageal cancer patient response to chemoradiotherapy.

➢ A 9-gene signature that predicts survival in colon cancer patients.

➢ A 60-gene signature that predicts treatment outcome in melanoma patients.

NANOTECHNOLOGY

The Director of the National Cancer Institute (NCI), Dr. Andrew von Eschenbach, said that nanotechnology is not close, "This is still very, very early in development and evolution. There are a few things underway…but it is still very early…It won't be here tomorrow in a sudden magical moment." However, Anna Barker PhD had a different view, "The FDA ruled on and is reviewing several nanotechnologies …especially for delivery…I see multifunctional kinds of technologies coming…In five years we will see revolutionary changes. One thing NCI has done recently is help researchers build new teams with oncologists…We just put out a (nano-technology) request, and we got one of the largest responses ever…I think this is something that will move quickly."

Gene-silencing nanoparticles inhibit Ewing's sarcoma. Researchers have developed a novel "Trojan horse" delivery system to transport gene-silencing nanoparticles into tumor

cells, and the method was shown to inhibit Ewing's sarcoma – a rare and often deadly bone cancer – in an animal model of the disease. In recent years, scientists have been intrigued by the potential of siRNA to block the activity of genes that promote the growth of tumors, but there have been problems in delivering these bits of genetic material in high concentrations to specific tumor sites, while avoiding degradation.

Researchers at Children's Hospital in Los Angeles and the California Institute of Technology overcame these hurdles by using a sugar-containing polymer that binds to and condenses the engineered siRNA into nanoparticles that, in effect, form a protective shield around their genetic cargo. These nanoparticles, in turn, are attached to transferrin, a protein that typically carries iron molecules through the bloodstream until it meets up with a transferrin receptor on the surface of another cell. The transferrin binds tightly to a receptor on the cell's surface, where it is drawn inside and surrounded by a small vesicle. The vessels are acidified, causing the nanoparticles to release their contents – the siRNA.

Despite aggressive therapy, about 40% of Ewing's patients and 95% with metastases die from their disease. Researchers tested this novel technology in laboratory mice grafted with human Ewing's sarcoma tumors. After three consecutive days of treatment, there was strong, but transient, inhibition of tumor growth. When the mice were treated twice-weekly up to four weeks, the results were more striking. Future experiments will combine the novel delivery system with small molecular anti-tumor agents.

An investigator said, "This is the first study to demonstrate that systemic therapy can affect metastases. The delivery system is uniquely effective." Another expert commented, "This is a lovely study combining a whole lot of technologies."

EGFR and VEGFR Inhibitors

It is unclear whether there is any reason to believe that the specific profile of receptors that each drug hits makes it likely to be better in a given indication. An expert said, "There are no conclusions on this yet. We know in some cancers that high phosphorylation is not an indication of response to inhibitors of phosphorylation." Another source said, "I think blocking one receptor isn't enough." A third source said, "We really don't know that yet. BAY-43-9006 is a Raf kinase, but the importance of that is unclear."

EGFR

Which patients are currently getting EGFR inhibitors? A West Coast doctor said, "All (lung cancer) patients should get them because the mutation only predicts response rates, not necessarily survival." Another expert said, "Tarceva shows benefit in all patients, so most get it third line. Some are getting it second line, which is what I prefer, but most doctors only use it in 20%-30% of their second-line patients (mostly Asians and never smokers) in the absence of data. Tarceva is still finding its place."

Experts insisted that EGFR is the right target, but they noted that there are differences between antibodies and kinases, and the biologically optimal dose has not been determined for any of these. A speaker said, "The initial proposed mechanism of action was inhibition of cell proliferation or possibly an immune mechanism…Today, the actual mechanism, in my opinion is promotion of apoptosis, inhibition of angiogenesis, and inhibition of metastasis and local spread…Clearly, the EGFR receptor was not the right marker. The actual marker today that works clinically is skin rash. Many labs are working on finding the right marker. Is it a ligand product, P-EGFR, HER-2-3-4, P-MAPK, or P-AKT?"

The delay in clinical studies of markers was blamed on a variety of factors, including: the complexity of the problem, inadequate technology, disinterest, lack of any FDA requirement, expense, and lack of patient demand. A speaker called for a collaboration of industry, academia, and government – plus payors.

Among the interesting points that came out at AACR about EGFR inhibitors were:

- Mutations were the big story at ASCO 2004, but it is now clear that mutation is not the whole story in NSCLC.
- Dual therapy appears promising, with possible:
  - Synergy (3-10x) between Erbitux and Iressa in NSCLC.
  - Dual inhibition with Genentech's Tarceva and Avastin. Tarceva inhibits tumor cell growth and blocks synthesis of angiogenic proteins; Avastin inhibits VEGF. A two-site, Phase I/II trial has treated 40 lung cancer patients (all non-squamous cell) with this combination. That trial found no bleeding or other side effects, 20% ORR, and improvement in median survival (12.6 months vs. 6.7 months in the BR-21 trial). At one-year, 50% of patients on combination therapy were alive.
- HER-2 may influence response to tyrosine kinase inhibitors (TKIs). A speaker said, "While EGFR and HER-2 mutations are never present in the same tumors, HER-2 may be amplified/over expressed in some EGFR mutant tumors and cell line and may influence response to TKIs. Targeting both EGFR and HER-2 may result in improved clinical response."

HER-2 Positivity and EGFR Inhibitor Response in NSCLC Study

Measurement	Both genes FISH +	Either gene FISH +	Both genes FISH -
Response	54%	17%	2%
Disease control	76%	48%	25%
TTP	9.8%	4.9%	2.6%
Survival	20.8%	8.9%	7.3%

- K-RAS mutation is a better indicator for **non-responders** to EGFR inhibitors than an EGFR mutation is for a responder.
- EGFR mutations are only ***slightly*** indicative of response.
- A cell-line study by researchers at the University of Texas Southwestern Medical Center found EGFR, HER-2, K-RAS, and B-RAF mutations appear to be mutually exclusive, indicating that at least one activating mutation in the EGFR-RAS-RAF pathway is sufficient for the pathogenesis of lung cancers. Researchers suggested that there are different molecular pathways to lung cancers in never smokers and smokers.

Antibodies do not have the same characteristics in terms of responses to mutations, etc., as EGFR inhibitors do.

VEGF

Sources insisted there are differences between the anti-VEGFs. An expert said, "There is a difference in size of the antibodies that could translate into a difference in pharmacology." Another said, "Yes, there are differences. Look at the differences between Iressa and Tarceva." A pharma official said, "There is a difference between the antibodies and the small molecules. No small molecule is perfect." A fourth source said, "There is a difference, but we don't know if the Avastin dose is optimal or the schedule is optimal. Some anti-VEGFs block one receptor, and some block multiples, so there is a lot of variety."

They also agreed that targeting the VEGF receptor vs. the ligand is likely to produce meaningful differences. A pharma official said, "I believe targeting the receptor is more important than targeting the ligand." A West Coast doctor said, "Avastin is the only ligand…VEGF-3 may be involved in metastasis." Another source said, "It could be the small molecules hit other things."

Avastin is the anti-VEGF compound that sources believe is the most promising, but there are several others getting attention. A doctor said, "Avastin is No. 1, then Pfizer's SU-11248, which will be approved in renal cell carcinoma and in Gleevec-resistant CML." Another expert said, "BAY-43-9006, AG-013736, and ZD-6474 look especially promising – and so is the combination of Avastin+Tarceva in lung cancer."

NSAIDs and Cox-2 Inhibitors

Pfizer's Lipitor+Celebrex in CRC: Low doses better than high doses. Rutgers University researchers reported that combining a statin and a Cox-2 inhibitor at low doses dramatically limited the incidence of invasive and non-invasive colon adenocarcinomas in laboratory animals, inhibiting 95% of the tumors that developed in untreated animals. The low-dose combination – the equivalent of 40 mg/day of Pfizer's Lipitor (atorvastatin) and 120 mg/day of Pfizer's Celebrex (celecoxib) – was more effective than either drug alone.

Statins and Cox-2 Inhibitors in CRC

Measurement	Tumor incidence
40 mg/day Lipitor+ 120 mg/day Celebrex	Down 95%
80 mg Celebrex	Down 80%
60 mg Lipitor	Down 31%-41%

Pfizer's Celebrex (celecoxib). NCI researchers reported on an explanation of the mechanism by which Celebrex suppresses the formation of colon polyps. They found Celebrex alters a specific "signature" set of 173 genes in the mucosal lining of colons of patients at high risk for a rare, hereditary form of CRC (plus certain other cancers such as ovarian or endometrial cancer), and many of the genes, whose expression is changed, were tied to the immune system and the inflammatory response. Researchers also found that patients taking higher dose Celebrex (800 mg BID) had more dramatic effects than those on a lower dose (200 mg BID). The genes affected by Celebrex are involved with cell signaling, cell adhesion, response to stress, TGF-beta signaling, and the regulation of apoptosis.

A preclinical dose-finding study by UCLA researchers found that 800 mg BID Celebrex was the most effective dose to give with Tarceva in advanced NSCLC.

NSAIDs cut the risk of oral cancer among smokers. Norwegian researchers reported that NSAIDs – such as aspirin or ibuprofen – protect smokers against the development of oral cancer. Their population-based study of 908 people found that light-to-moderate smokers who took NSAIDs over extended periods of time had 65% less risk of developing oral cancer than smokers who went without NSAIDs. The protective effect was best for people who smoked ≤1 pack of cigarettes per day per year. The effect diminished for people who smoked more than that. All types of NSAIDs examined were effective at reducing the rate of squamous cell carcinoma of the oral cavity.

NSAIDs protect against intestinal tumors in mice. A mouse study found that using the NSAID sulindac was highly effective at eliminating the cancer-causing risks produced by a high-fat Western-style diet – even in patients without two key tumor suppressor genes (p27 and APC). Researchers from the Albert Einstein Cancer Center emphasized that the results do not ***yet*** have relevance for preventing human colon cancer, but the findings illustrate the interplay between genes and common nutritional and medicinal agents in development of cancer in the intestines.

NSAIDs and Oral Cancer and Heart Disease Risks

Measurement	Hazard ratio for risk of oral cancer	p-value
Overall NSAID use	0.47	<.0001
NSAID use ≤5 years	0.53	.044
NSAID use 5-10 years	0.68	.075
NSAID use 10-15 years	0.61	.015
NSAID use 15-26 years	0.30	<.0001
Acetaminophen use	0.79	.14
Hazard ratio		
NSAID	**For oral cancer**	**For CV death in long-term NSAID users**
Any NSAID	0.47	2.06
Aspirin	0.38	2.26
Naproxen	0.50	1.70
Ibuprofen	0.37	2.86
Indomethacin	0.41	2.26
Piroxicam	0.56	1.84
Ketoprofen	0.68	1.90
Acetaminophen	0.79	---

ONCOLYTIC VIRUSES AND VACCINES

Several oncolytic viruses are in varying stages of development, including:

BIOVEX'S ONCOVEX. This modified herpes simplex virus that expresses GM-CSF, is being tested in a variety of tumor types, including melanoma, breast, head and neck, and CRC, with the hope it will treat metastatic disease and reduce tumor recurrence. It is delivered subcutaneously directly to the tumor, though a researcher said it could be administered to other sites by catheter.

U.K. researchers reported on a Phase I/II trial of 26 patients (8 melanoma, 13 breast, 3 head and neck, and 2 CRC), OncoVEX showed "promise of causing necrosis of tumor cells" both clinically and in biopsies taken about two weeks after the final dose.

BioVex's chief scientific officer, Robert Coffin PhD, said, "Cell-Genesys's GVAX is similar…but we do it all *in situ* by directing the virus directly into the tumor. We have quite a lot of preclinical data suggesting the virus is effective…About 70% of tumors had a necrotic of inflammatory response…The necrosis was limited to areas of tumor tissue and areas associated with the herpes antigen." He said that in the Phase I/II trial, there were some cases of "tumor flattening" and some cases where there was an effect in tumors that were ***not*** injected. The company is now moving to a Phase II trial in individual tumor types.

Another expert asked about this technology said, "It is a very exciting approach. Using a virus to kill tumors is being studied in many ways…This is a very clever approach, and I think we will see more of this."

Modified measles virus. Researchers from the Mayo Clinic reported on cell line and mouse studies of a weakened measles virus, modified with a protein that normally takes up iodine in the thyroid gland, that is being studied to treat liver cancer. A researcher concluded, "IV treatment with this combination followed by injection of radioactive iodine into the mice…resulted in high uptake of the radioactive iodine at the tumor site. This provides the possibility of enhancing the therapeutic effect by co-treatment with therapeutic radioactive iodine." He said it will be another two years before this technology will progress to Phase I studies.

GENITOPE'S MyVax (GTOP-99). This lymphoma vaccine is designed for patients with follicular NHL who have had a clinical response to a CVP (cyclophosphamide+vincristine+prednisolone) chemotherapy regimen. It is custom-made from each patient's tumor cells. An investigator said the Phase III trial completed enrollment of 676 patients in April 2004, with follow-up continuing to relapse. The primary endpoint is time to relapse, and the next look at the data will be in about a year (2006).

Most sources did not know enough about the MyVax data to have an educated opinion or for it to give them confidence in MyVax, but those who did know the vaccine were very cautiously optimistic about it. However, an investigator said he thinks it will take time to show a benefit. Another source said the MyVax trial is double-blind, and there haven't been any anecdotal reports, but he is optimistic about it, "There is no efficacy data…But if I had lymphoma, I'd want to get this vaccine."

Two other similar Phase III trials are ongoing. An investigator said, "If one works, all probably will work, but there may be subtle differences…These are first generation idiotype vaccines. There is a lot of room to improve. The technology is old."

- An NCI-sponsored trial.
- Favrille's Favid. A Phase II trial is opening at UCLA of dendritic cell vaccination followed by Favid.

One of the concerns with idiotype vaccines is scalability, but a source said, "MyVax is scalable because PCR amplification is used, and it is efficient. The question is how active the vaccine is vs. what else is available. There has to be a substantial benefit to get it used…And someone will have to buy Genitope to commercialize MyVax."

MISCELLANEOUS

Statins lower the risk of advanced prostate cancer. A 10-year study of 34,428 U.S. men in the Health Professionals Follow-up trial (an ongoing, prospective study that began at the Harvard School of Public Health in 1986) found that men who used statins had half the risk of advanced prostate cancer and a third the risk of metastatic or fatal prostate cancer, compared to men who did not use statins. The risk of advanced prostate cancer fell with increasing duration of use of statins, but statins did not impact on prostate cancer that is confined within the organ. Researchers from Johns Hopkins University, the National Cancer Institute (NCI), and Harvard University stressed that confirmatory studies are needed. None of the participants had diagnosed prostate cancer in 1990, but 10 years later 2,074 men had been diagnosed with that cancer. Of these, 283 were advanced, and of those, 206 were metastatic or fatal.

Long-term calcium supplement provide long-term protection against colon cancer polyps. Dartmouth Medical School researchers reported that calcium supplements reduced polyp formation by 36% in the five years after the conclusion of a 930-patient randomized trial. This is the second major study to show the chemoprotective value of calcium, but the researchers did not recommend widespread use of calcium supplements – yet. These current findings come from the 822-patient observational phase of the Calcium Follow Up Study, which included 597 follow-up colonoscopies. The study found an even larger effect for protection against development of non-neoplastic hyperplastic polyps – a 48% reduction of risk. However, the study also found that the protective effect of calcium diminished over time. Over the entire follow-up period, which was as much as 10 years in some patients, the protective effect fell to a non-significant 19% in patients who had used the supplements in the study. Patients who used calcium supplements after the randomized trial had ended had a non-significant 15% reduced risk of developing polyps.

Estrogen. Although estrogen has been found to promote breast cancer in some women, researchers now are suggesting that there are women in whom estrogen may be a cancer therapeutic. A researcher said a Phase I trial is about to begin in which low-dose estrogen will be given to women (with breast cancer) who have failed two hormone therapies.

MORE INFORMATION ON SPECIFIC DRUGS

ABBOTT LABORATORIES' ABT-869. This is currently in preclinical development, but an IND has been filed, and the company hopes to start a Phase I trial soon in breast, ovarian, prostate, and endometrial cancer. Abbott researchers reported that all of the tested TKIs displayed inhibition of CSF-1R signaling, but ABT-869 appears to be more potent. A researcher said, "ABT-869 is more potent (than other drugs in this class), not only on the enzyme but in vivo. The PK allows the possibility of continuous dosing.

A cell-line study looked at the potency of several TKIs against CSF-1R (over expression of which occurs in a significant percentage of breast, ovarian, prostate, and endometrial cancers) and KDR Kinases. They concluded that a cell-based assay can confirm the inhibitory activity of lead compounds and drug candidates against the CSF-1R protein *in situ*.

Potency of Different TKIs Against CSF-1R and KDR Kinases

Drug	CSF-1R Cell	KDR Cell
Sutent	57	22
AG-013736	6	1
CHIR-258	40% at 100 nM	84
Sorafenib	24	56
Gleevec	16	>12,500
ABT-869	10	2

Another poster looked at the mechanisms of action of ABT-869 in a model of AML. Researchers concluded that ABT-869 has potent activity against AML cell lines with mutated kinases and "impressive" *in vivo* activity in xenograft tumors.

AEGERA THERAPEUTICS' AEG-33783. This is a neuroprotective which the company believes will reduce peripheral neurons from chemotherapy-induced toxicity. A poster was presented on preclinical data, and a Phase I trial is expected to start by the end of 2005. It may also be effective against diabetic neuropathy, but the company is looking for a partner to help develop that indication.

AMERICAN BIOSCIENCE:

- ***nab*-17-AAG.** American Bioscience may effectively "steal" this agent from Kos Pharmaceuticals. Kos has been working on development of 17-AAG, but the problem appears to be limitations on dose escalation due to the cremaphor. American Bioscience applied the same nanoparticle albumin-bound (*nab*) technology it used to get approval of Abraxane to 17-AAG, again eliminating cremaphor.
- ***nab*-028.** A cremaphor-free nanoparticle formulation of a novel taxane, which the company would not identify, except to say it is 100 times more potent than paclitaxel and docetaxel against CRC cells.
- ***nab*-docetaxel.** A cremaphor-free nanoparticle formulation of docetaxel.

AMGEN'S AMG-531. A PK/PD study of this novel thrombopoietic agent found AMG-531 alleviated thrombocytopenia in mice after a single injection. Researchers concluded that this may be a useful agent in chemotherapy patients for stimulating

platelet production and reducing the need for platelet transfusions. The serum half-life is ~6 hours. The first indication is expected to be TIP, and AMG-531 is in Phase III trials for that. A researcher said, "It works well in those patients. We plan to do more studies in chemotherapy patients this summer."

ARRAY BIOPHARMA:

➢ **ARRY-334543.** This is a dual inhibitor of EGFR+ErbB-2. The company expects to file an IND in June 2005 and start a Phase I trial of all comers in solid tumors in fall 2005. The advantages over lapatinib were described as:

- Comparable potency.
- Better solubility at a low pH.
- Better exposure (higher blood levels).
- Possibly dose reduction which could mean QD dosing without loss of efficacy – with the ability to titrate up if needed.

➢ **ARRY-333786.** This is a single-inhibitor of ErbB-2, which is currently being evaluated for development, would compete with Genentech's Herceptin (trastuzumab), an ErbB-2. An Array official said one of the potential advantages of ARRY-333786 over GlaxoSmithKline's EGFR/ErbB-2 inhibitor, lapatinib, is that it would be easier to find a patient population for this than for a dual inhibitor. A researcher said, "We are trying to figure out who the investigators will be, and that will influence the trial. Herceptin doesn't get into the brain, and, theoretically, ARRY-333786 should get into the brain, especially in breast cancer where brain metastases are a big problem.

ASTRAZENECA:

➢ **ZD-0530.** This oral, highly selective and dual-specific Src/Abl kinase inhibitor is in early clinical development. A rat study found that ZD-0530 inhibited tumor growth in a dose-dependent manner in nude rats, and complete inhibition was achieved with daily oral doses of 10 mg/kg.

➢ **ZD-2171.** This oral, once-daily VEGFR-1-2-3 inhibitor is in Phase II clinical trials in a broad range of solid tumors, and a Phase I trial in ovarian cancer will have data at ASCO 2005. Its potency and selectivity appear to be its advantages. A cell line study found it may have additional therapeutic utility in c-Kit-dependent diseases via a direct effect on tumor cells. A mouse study found that ZD-2171 reduced polyp growth in a model of intestinal adenomas. Its advantage may be greater potency for KDR.

➢ **ZD-4054.** This specific, oral endothelin A (ET_A) antagonist is in Phase II development for hormone refractory prostate cancer. A study in healthy male volunteers found that a single oral dose of ZD-4054 (10 mg or 30 mg) reduced forearm vasoconstriction in response to brachial artery infusion of ET-1, when compared to placebo, which researchers said provided clinical evidence that ZD-4054 antagonizes ET_A. In the future it may have utility in ovarian cancer, a researcher suggested. The advantage of this ET_A may be its specificity (it doesn't hit the ET_B receptor).

➢ **ZD-6126.** This vascular targeting compound reportedly destabilizes microtubules, causing a rapid rounding up of immature tumor endothelial cells, which stops tumor blood flow and induces tumor cell death. French researchers reported on a mouse study of ZD-6126+Iressa+radiotherapy (RT) in head and neck cancer. They found that ZD-6126 alone had no significant effect on tumor growth, but combining ZD-6126 with an anti-EGFR agent (Iressa) may lead to "supra-additive anti-tumor effects." However, the addition of RT to the combination of ZD-6126+Iressa did not enhance efficacy.

➢ **ZD-6474.** This dual-action agent, which targets both VEGFR-2 and EGFR, is in development to treat lung cancer bone metastases, which occur in one-third of lung cancer patients. Researchers reported several studies, including:

- A mouse study which found that ZD-6474 decreased bone tumor volume ($p<.01$) vs. control – and more than was achieved with paclitaxel or ZD-6474+paclitaxel (regardless of the order of administration of the two agents – ZD-6474 first, after, or with paclitaxel).
- A mouse study which found that ZD-6474 enhanced the anti-tumor effects of RT in a lung cancer model, and the efficacy of ZD-6474+RT was superior to that with paclitaxel+RT.
- A study of the effect of ZD-6474 as well as Iressa, Tarceva, Erbitux, and Avastin on NSCLC cell lines with exon-19 deletion mutations. This study found that ZD-6474 was more effective than any monotherapy with any of the other agents in tumors with the exon-19 deletion mutation.

BAYER:

➢ **Sorafenib (BAY-43-9006).** While Bayer prepares the FDA submission and waits for approval in renal cell carcinoma, it appears the company has slowed down other sorafenib trials. A Phase III trial in melanoma was scheduled to start shortly after AACR, but a researcher warned that the trial needs to enroll quickly because it will become difficult to enroll patients after sorafenib is approved in renal cell carcinoma. There will be data at ASCO 2005 on tumor biopsies from the 800-patient Intergroup trial (E2603) of sorafenib+carboplatin+Taxol (paclitaxel) in Stage 4 melanoma. This is a 2.5 year trial, with one more year of follow-up. A Phase III trial in hepatic carcinoma is ongoing.

➢ **BAY-57-9352.** This orally-active TKI is expected to be used in combination with the current standard of care for multiple cancers. It currently is in a Phase II clinical trial in breast cancer in combination with Doxil, and other trials are ongoing in CRC and NSCLC.

A preclinical study looked at combining BAY-57-9352 with either capecitabine or paclitaxel. Researchers concluded that BAY-57-9352 can be combined with either capecitabine or paclitaxel in future studies.

- In combination with capecitabine, researchers reported significant anti-tumor activity over a wide range of doses in a CRC model, both as a single agent and as combination therapy. There were added benefits to the combination: Responses were 30%-90% with the combination vs. 0-10% for either agent alone. The highest doses tested – 60 mg/kg BAY-57-9352 and 500 mg/kg capecitabine – resulted in 20% lethality.
- BAY-57-9352 was at least as efficacious as paclitaxel, researchers found that combining it with paclitaxel did not decrease the efficacy of either agent. The highest doses tested – 60 mg/kg BAY-57-9352 and 15 mg/kg paclitaxel – resulted in 20%-50% lethality.

BRISTOL-MYERS SQUIBB:

➢ **BMS-582664.** This dual VEGFR-2/FGFR-1 kinase inhibitor, is a prodrug of BMS-540215 and a potential competitor for Avastin. It is in Phase I in all cancers, looking at safety, not efficacy. A Bristol-Myers Squibb official offered these potential advantages over Avastin: It is oral, a small molecule, shuts down the whole pathway, is easier to make and, thus, likely to be less expensive. There is no PDGFRβ activity, so the company is not exploring it in GIST. A poster showed activity in a cell line selected for chemoresistance. It also reportedly can be safely combined with cytotoxics such as paclitaxel.

➢ **BMS-554417.** This inhibitor of both insulin-like growth factor receptors (IGIF-1R) and insulin receptors is still in preclinical development. A researcher commented that it "challenges the dogma that you can't inhibit the insulin receptor safely." A poster found it might be useful in colorectal, breast, lung, and ovarian cancer as a potentiator of chemotherapy.

CELGENE'S Revlimid (lenalidomide, CT-5013). In the pivotal MM-009 and MM-010 trials presented at the International Myeloma Workshop in Sydney, Australia, in April 2005, Revlimid was dosed at 25 mg/kg. However, an NCI study presented at AACR found a daily dosing MTD of 10 mg/day. DLTs were observed with daily dosing, but not when it was given 21 days on/7 days off (28-day cycle). NCI researchers recommend that dosing regimens in future trials be based on creatinine clearance because there is high inter-patient PK variability which is reduced when normalizing for renal clearance.

CELL THERAPEUTICS' CT-2106 (polyglutamate campto-thecin). The company is continuing to work on its polyglutamate delivery system, despite the failure of a pivotal lung cancer trial of Xyotax (CT-2103, polyglutamate paclitaxel) in March 2005. There was no excitement about the preclinical data – a xenograft study – presented at AACR in ovarian cancer that found CT-2106 (at doses from 13.5-40 mg/kg) was superior to oral topotecan, producing "a large number" of complete and partial tumor regressions with a long response duration. CT-2106+cisplatin was found to be superior to cisplatin+paclitaxel, with potential synergy and no significant signs of toxicity, suggesting CT-2106 may be useful either as a single agent or in combination with cisplatin. The MTD is 27 mg/kg. Another study indicated that CT-2106 will be tried in cell lines that are resistant to CDDP.

CHIRON'S CHIR-258. This agent is currently in Phase I trials for the treatment of solid tumors and hematological malignancies, including a dose-finding study in solid tumors and another study in AML.

- A poster was presented on the PK and PD profile of this oral agent. Chiron researchers said the "relatively prolonged 'effect' compartment $t_{1/2}$ values suggest considerable flexibility in selecting the appropriate dosing regimen with CHIR-258," and the study is being used to guide the selection of dose and dosing regimen for CHIR-258.
- A poster presented PD assays that are currently being evaluated for use in clinical trials of this agent.

CHROMA THERAPEUTICS' CHR-2797. A poster on this oral aminopeptidase inhibitor found that 30 mg/kg/day statistically significantly decreased tumor burden, tumor weight, and colony numbers in rodents with subcutaneous breast cancer tumors. There was a clear dose-response curve, and doses of 50 mg/kg/day and 100 mg/kg/day showed more effect than 30 mg/kg/day. Researchers expect CHR-2797 will be dosed QD.

CLAVIS PHARMA'S Elacyt (CP-4055). This agent is still in Phase I, but a Phase II is planned. At AACR, researchers reported on two Phase I studies conducted at seven European centers.

- **Trial 1** was a dose-finding study. With 30-minute IV doses of 30-200 mg/m^2 for five days every three weeks, there were frequent treatment delays due to Grade 3-4 neutropenia, and dosing was changed to Q4W at 240 mg/m^2. The MTD was 200 mg/m^2/day on Days 1-5 Q3W (but this schedule is not a recommended schedule because of late Grade 4 neutropenia) and 240 mg/m^2/day on Days 1-5 Q4W. The DLT was Grade 4 neutropenia.
- **Trial 2** is an ongoing study of three intermittent weekly schedules (100-800 mg/m^2). The intermittent dosing improved the toxicity profile, with no Grade 4 neutropenia. Dose escalation is continuing to 440 mg/m^2/week. In the first 30 patients, the OR was 3% (6% for melanoma patients), with one confirmed PR and 11 SD (lasting 6 weeks to 13 months).

GENENTECH/OSI PHARMACEUTICALS:

➢ **Tarceva (erlotinib).** Tarceva was approved by the FDA in 2004 for the treatment of NSCLC. Shortly after AACR, Genentech filed an sNDA for the first-line treatment of advanced or metastatic pancreatic cancer, following positive results in a pivotal Phase III trial of Tarceva in combination with Lilly's Gemzar (gemcitabine). This study was a randomized, double-blind, placebo-controlled trial in 569 pancreatic cancer patients.

Results of Phase III Trial of Tarceva in Pancreatic Cancer

Measurement	Tarceva+ Gemzar	Gemzar+ placebo	p-value
1-year survival	24%	17%	.025
Median survival	6.4 months	5.9 months	---
Progression-free survival	9%	8%	.003
Rash	72%	28%	---
Diarrhea	51%	36%	---
Interstitial lung disease	2.1%	0.4%	---

A study presented at AACR found that pancreatic tumor xenografts and cell lines respond (with varying degrees) to Tarceva. Researchers plan to further analyze xenografts that responded to Tarceva to see if they can identify biomarkers that can distinguish responders from non-responders.

An OSI researcher reported on the effect of smoking on the PK of Tarceva. Plasma samples were taken on 485 patients per-treatment and monthly. Of these, 133 patients had a "reliable" steady-state median trough (≥3 samples and no dose change within 5 days). The data suggested that the dose might need to be increased in smokers – or decreases in non-smokers. OSI is designing a study now to determine whether dosing needs to be adjusted for smoking status.

The researcher reported:

- Adverse events were not statistically associated with Tarceva exposure, but there was a trend to increased rash and diarrhea with increased Tarceva exposure.
- Of baseline characteristics, only smoking status was associated with clinically-relevant differences in Tarceva exposure.
- There was a dramatic decrease in plasma concentration of Tarceva in smokers vs. non-smokers.
- Tarceva exposure is significantly decreased in healthy male volunteers who smoke ≥10 cigarettes/day.
- Tarceva plasma profiles are consistent with the hypothesis that decreased exposure results from induction of CYP1A enzymes. This is the first time that an interaction of Tarceva with CYP1A compounds has been examined.

Another study characterized the molecular determinants of Tarceva sensitivity in NSCLC cell lines. Researchers concluded that EGFR mutations alone can't explain the

Effect of Smoking on PK of Tarceva

Measurement	All Tarceva patients	Population PK	Patients with reliable median trough levels
Duration of treatment	9.6 months	16 months	32 months
Dose (mg/m^2)	150	148	149
Survival	6.74 months	10.48 months	14.26 months
Progression-free survival	9.71 months	16.14 months	31.57 months

response to Tarceva. They found that the ability to inhibit AKT signaling was critical, and tumors may differ by patient in their AKT signaling, "If EGFR is driving the AKT signaling, then cell-lines are more likely to respond to Tarceva…Tarceva-sensitive cells express increased e-caherin and are not non-responsive. Non-responders express vimentin, and responders don't." Now, they said, it remains to be shown whether the same holds true in humans. If so, it suggests a potential diagnostic marker for Tarceva responders.

The combination of Avastin + Tarceva is gaining attention, but cost is limiting off-label use of this combination – in any cancer. A California doctor said, "Avastin+Tarceva is being used off-label by doctors familiar with the side effects because there is so little to offer in head and neck." Another source said, "Phase Ib studies of Avastin+Tarceva are coming soon, perhaps at ASCO 2005." A Texas doctor said, "I'd like to try Tarceva and Avastin together, but cost is an issue. I can't get it (the combination) covered."

➢ **SGN-30.** This antibody is in Phase I trials at M.D. Anderson and other cancer centers in refractory Hodgkin's lymphomas, ALK, and ALCL. In vitro it doesn't appear to work in multiple myeloma. In animal studies, it has shown marked tumor reduction, but there is some discordance in the data: In animals, it shows an effect in Hodgkin's and ALK, but *in vitro* it only shows an affect in ALK, not in Hodgkin's.

GLAXOSMITHKLINE'S GW-572016. A poster indicated this drug inhibits proliferation of prostate cancer cell lines more potently than Iressa. It inhibits both EGFR and HER-2, while Iressa inhibits only EGFR.

INCLONE'S IMC-1121b, a fully human antibody targeting VEGFR-2, just started a 33-patient, two-center Phase II trial in solid tumors.

JOHNSON & JOHNSON'S Zarnestra (tipifarnib, R-11577). On May 5, 2005, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted 7-4 that Zarnestra should not be approved to treat elderly patients with newly diagnosed AML who have a poor survival prognosis. Panel members were concerned with trial data showing that only 11% of patients responded to Zarnestra, and it was not possible to identify who

would be a responder. The median duration of response for responders was 275 days.

KOS PHARMACEUTICALS' 17-AAG. At the International Myeloma Workshop in April in Sydney, Australia, 17-AAG was identified as one of the promising drugs to watch in myeloma. At AACR, a Kos source said, "We are really excited about 17-AAG in melanoma, and we would like to do a Phase 1 trial in that."

A poster was presented at AACR showing that 17-AAG down-regulates the MAPK pathway in melanoma patients. A Phase II melanoma study is ongoing in unresectable Stage 3-4 patient who've had ≤1 prior chemotherapy, with response the primary endpoint. Patients, are divided into two groups – mutated BRAF and non-mutated BRAF – and are given 450 mg/m^2 of 17-AAG weekly for 6-8 weeks. A researcher said no DLT has been found yet. So far, eight patients have been enrolled, and there were no responses in the first seven patients on whom there are data after Cycle 1. A researcher said, "I think this will be a very good drug for melanoma, but the optimal way to give it has not yet been determined. Possibly, patients need a higher dose, but that is limited by the cremaphor." *(See American Biosciences' nab-17-AAG, page 12.)*

Another researcher said a Phase I/II trial is planned of 17-AAG + exemestane (Pfizer's Aromasin) in breast cancer patients who previously failed to respond to tamoxifen or a non-steroidal aromatase inhibitor."

LIGAND'S Targretin (bexarotene). Dr. Ivan Uray of Baylor College of Medicine discussed his study which found:

- Bexarotene acts through the RAR/RXR heterodimer to regulate IGBP-6 gene expression.
- LGD-268 (a highly specific rexinoid) fails to affect IGBP-6, suggesting that the ligand RXR alone is not sufficient to active the IGBP-6 promoter in human epithelial cells.
- LXR and PPAR are not involved in the up regulation of IGBP-6 by bexarotene.

A poster reported on a cell line study which found that bexarotene can prevent and even reverse resistance to paclitaxel in NSCLC cells. Researchers noted, "Treatment with bexarotene in combination with paclitaxel leads to re-sensitization."

Mutation Rates

Drug	Without Targretin	With Targretin
Paclitaxel	7.8 x 10^{-8}	1.9 x 10^{-8}
Doxorubicin	8.8 x 10^{-8}	2.3 x 10^{-8}
Cisplatin	5.4 x 10^{-8}	1.2 x 10^{-8}

A poster on Targretin in advanced prostate cancer also found it inhibited resistance to other agents.

Resistance Factor of Targretin in Advance Prostate Cancer (IC_{50} of resistant cells/IC_{50} of parental cells)

Drug	Paclitaxel	Vincristine	Doxorubicin	Cisplatin
Paclitaxel	33.2	24.5	14.5	1.1
Paclitaxel+Targretin	1.0	1.0	1.0	0.9
Doxorubicin	15.6	23.1	20.0	1.0
Doxorubicin+Targretin	1.1	1.1	1.0	1.0
Cisplatin	0.9	1.1	1.0	17.9
Cisplatin+Targretin	0.9	1.1	1.1	1.1

Three different data sets are expected at ASCO 2005:

- A subset of responders in NSCLC.
- Third-line monotherapy NSCLC data.
- Phase I/II trial in third-line NSCLC with Tarceva.

Ongoing studies include:

- A second-line study in combination with taxotere in NSCLC.
- A combination study with Avastin that is due to start by mid-2005. This is being started because of positive results from a cell-line study that showed Targretin decreases VEGF directly.

MEDIMMUNE'S Vitaxin. This humanized monoclonal antibody is in clinical trials to treat melanoma and prostate cancer. A study in rabbits and hamsters suggested Vitaxin is unlikely to have any negative impact on wound healing in patients following surgical procedures. Phase II data on Vitaxin in melanoma will be presented at ASCO 2005. A poster at AACR showed no delay in healing in a hamster or rabbit model of cutaneous wounds. A Phase II study in prostate cancer has just gotten underway.

NEOPHARM'S NEO-6002 (a gemcitabine-cardiolipin conjugate). A mouse study found NEO-6002 had less toxicity and better survival in a pancreatic cancer model than Lilly's Gemzar (gemcitabine).

NOVARTIS:

➢ **AEE-788.** This drug inhibits binding to EGF, HER-2, and various VEGF receptors (including HER-2, EGFR, and VEGFR). A researcher compared it to a combination of lapatinib and vatalanib (PTK-787). A Phase I/II trial is about to start at five sites worldwide. In a breast cancer cell-line study shown at AACR, researchers showed that, in combination with either letrozole (Novartis's Femara) or tamoxifen, AEE-788 may provide "superior" anti-tumor activity to single agents.

➢ **Vatalanib (PTK-787).** This is currently in two Phase III trials in CRC, CONFIRM-1 and CONFIRM-2. The drug was expected to be filed this year, but it is delayed a year or longer because of an interim analysis of CONFIRM-1, in which the drug missed its primary endpoint. However, experts outside Novartis as well as company officials insisted PTK-787 is ***not*** dead yet. One expert said, "It may not be dead, but it may take a long time to get it approved – probably the end of 2006." But it has slipped down the rope. It has been delayed a year or a year and a half." A Novartis official said, "PTK-787 is not dead. The next interim look at the trial is in early 2006. There were two statistical analyses of the CONFIRM-1 trial; one was positive, and the other was negative."

➢ **everolimus (RAD-001).** This oral immunosuppressant continues to look promising in cancer. A Novartis official called the results of a trial of everolimus+Femara in breast cancer "very impressive," and the preclinical data are expected to be published soon. A trial of everolimus in lung cancer is in Phase I, and the company's scientific advisory board reportedly is "very excited about that."

A poster looked at combining everolimus and vatalanib (PTK-787). A researcher explained, PTK-787 and RAD-001 both affect CD31, which is a marker of endothelial cells, but RAD-001 also affects smooth muscle cells, so there is a more potent anti-angiogenic effect when the two are combined…RAD-001 has an additive effect on angiogenesis. It affects smooth muscle cells, which is unique. There is good efficacy against primary tumors, and the effect on metastases is increased with the combination."

Novartis is working on a PET-based imaging system that its researchers believe will be able to differentiate responders from non-responders. A researcher said the system looks very good, "Two to four days after you give RAD-001, you can determine if a patient is a responder. The system is not yet ready to be presented, but it reportedly will be tried out clinically soon.

Everolimus also is being tested on drug-eluting stents. A Novartis researcher offered an interesting comment: "It is difficult to control the PK of oral everolimus. That is the issue with restenosis."

NERVIANO MEDICAL SCIENCES' PHA-680632. This Italian company is not taking this aurora kinase into the clinic; it was an advance candidate. However, the company has another unnamed aurora kinase that is in Phase I which would compete with Vertex's VX-650, Boehringer Ingelheim's Hersperadin, and AstraZeneca's ZM-447739.

PFIZER:

➢ **AG-013736.** This is a small molecule VEGF/PDGF/RTK inhibitor. In Phase I there were "numerous" examples of "ghosting," where the tumor appeared to become less dense on imaging, even if the tumor didn't shrink.

A poster on a mouse study found that:

1. AG-013736+low dose taxotere had greater anti-tumor efficacy than either agent alone, greater survival than either agent alone, and greater reduction in tumor bioluminescence.
2. AB-013736+carboplatin had a significant increase in anti-tumor effect and was well tolerated.

A Phase II trial in all solid tumors, including breast, is enrolling. There may be some data at ASCO 2005, but not from this breast trial.

➢ **CP-24,714.** This is a selective HER-2/neu kinase inhibitor which has shown significant activity in breast cancer and appears synergistic with Herceptin in cell-line studies. Studies include:

- **Single agent.** A Phase II study in Herceptin-naïve patients started recently outside the U.S.
- An **all-comers** Phase I in Herceptin refractory patients. This trial has not yet started.
- In **combination** with Herceptin. This study has not yet started either.

SCHERING-PLOUGH'S Sarasar (lonafarnib, SCH-6636). The only data on this agent, which reportedly is in a Phase III trial in thrombocytopenia, were a mechanism of action cell-line study and a PD marker study. The PD study suggested that Sarasar+paclitaxel may be effective in ovarian cancer, and determining PFTase enzyme activity in peripheral blood nuclear cells (PBMCs) may be a useful marker to assess the effect.

SEMAFORE PHARMACEUTICALS' SF-1126. SF-1126 is a targeted prodrug, a pan-PI3 Kinase (PI3K) inhibitor that doesn't activate until it reaches the tumor, which may lessen the side effects that have made PI3K inhibitors difficult to develop. SF-1126 sensitizes cancer to standard therapies as well as having its own unique effect. Preclinical data presented at AACR indicated SF-1126, which would be a first-in-class drug, is safe and effective, and it showed activity against all three distinct isoforms of the PI3 kinase pathway. Semafore hopes to file an IND in early 2006 for studies in brain, breast, prostate, and ovarian cancer. An official said, "SF-1126 does what Avastin does plus it sensitizes the tumor to chemotherapy or radiotherapy. The question is what SF-1126 does in humans in terms of toxicity, but we believe it is not as toxic as people expect with a PI3K."

SRI INTERNATIONAL'S SR-13179. This small molecule flavanoid, which inhibits metalloproteinase-2 (TIMP-2), is in development for the long-term treatment of non-hormone-

dependent breast cancer, androgen-resistant prostate cancer, and colon cancer.

SUNESIS'S SS-595. This cell cycle modulator, which was in-licensed from Dainippon, showed biological activity in preclinical tumor models. It is now in Phase I trials.

TELIK'S Telcyta (TLK-286). Telik presented three posters at AACR, but they were typical Telik posters: They reported preclinical research to support or explain clinical data; the work was all done by Telik, not outside researchers; and there were no copies of the posters handed out.

- A poster on preclinical data. An official said, "There is a clear signal that in platinum-resistant cells, Telcyta is synergistic with platinum. We are not trying to understand why, and we will say that actively. We are filling in the gap on mechanism when we have time, and that is what we are doing at AACR."
- Another poster looked at an irreversible prodrug of Telcyta to better understand how Telcyta works in different cell lines.
- A third poster looked at triplet therapy with Telcyta+ carboplatin+Taxol in ovarian and lung cancer cells. Researchers concluded that Telcyta is a synergistic inhibitor of both doublets and triplets, and the effect is more than the sum of each agent.

At ASCO 2005, Telik will have a poster on Telcyta in NSCLC.

Ongoing trials include:

- ASSIST-1, an ovarian cancer trial for which accrual has finished.
- ASSIST-2, a NSCLC trial.

Doctors are cautiously optimistic about Telcyta. An ovarian cancer expert said, "Clearly, there are responses. The challenge is with data interpretation. TLK-286 is generally given with doxorubicin or platinum, so it is hard to tell whether the effect is from the TLK-286 or the doxorubicin. But people are responding to the combination of TLK-286+doxorubicin. What's appealing is the mechanism singles out hypoxic cancer cells, and that might give it greater impact than other agents." Another expert said, "My level of enthusiasm is low to medium because the work hasn't gotten out broadly. Not a lot of my colleagues are talking about it." A Midwest doctor said, "TLK-286 looks interesting. Everyone is excited about it because of the potential of platinum potentiation, but it probably won't work. I'd like it to, but I don't think it will." Another source said, "The preliminary (survival) data are interesting. If there really is a 54% response in refractory ovarian cancer, that would be terrific, but the response will drop in the Intergroup study or a real-world study, but 54% is still remarkable in Phase II." However, this expert suggested GlaxoSmithKline's lapatanib may have more utility than Telcyta.

The *in vitro* studies do not give a clear signal that this is a potentiator of platinum agents, but they are strongly suggestive. An expert said, "I don't hang my hat on preclinical models, but it looks as if we are seeing something here."

Telcyta+Carboplatin+Taxol in Ovarian and Lung Cancer Cells

Variably dosed drug	Sum of all three as singlets	Triple therapy	Increase with Telcyta
Ovarian			
Carboplatin 22 µM + Telcyta 2.0 µM			
0.26 µM paclitaxel	~40%	~58%	1.4
0.18 µM paclitaxel	~38%	~57%	1.6
0.12 µM paclitaxel	~38%	~50%	1.5
Paclitaxel 0.6 µM + Telcyta 0.8 µM			
1.9 µM carboplatin	~42%	~68%	1.5
0.94 µM carboplatin	~38%	~64%	1.9
0.47 µM carboplatin	~33%	~53%	1.6
Paclitaxel 0.35 µM + Carboplatin 1.0 µM			
1.4 µM Telcyta	~32%	~52%	1.7
0.89 µM Telcyta	~18%	~38%	2.0
0.56 µM Telcyta	~17%	~36%	2.0
Lung			
Carboplatin 5.0 µM + Telcyta 2.5 µM			
0.56 µM paclitaxel	~22%	~65%	2.9
0.40 µM paclitaxel	~11%	~62%	4.9
0.28 µM paclitaxel	~8%	~58%	6.6
Paclitaxel 0.6 µM + Telcyta 3.0 µM			
7.6 µM carboplatin	~42%	~48%	1.8
4.8 µM carboplatin	~38%	~62%	2.4
3.0 µM carboplatin	~33%	~61%	2.5
Paclitaxel 0.35 µM + Carboplatin 1.0 µM			
3.0 µM Telcyta	~25%	~77%	2.7
1.80 µM Telcyta	~18%	~70%	4.8
1.0 µM Telcyta	~18%	~66%	4.6

VION'S cloretazine (VNP-40101M). There was no real enthusiasm or buzz about this at AACR. A study of cloretazine (a sulfonylhydrazine alkylating agent) plus Ara-C found the DLTs with 1500 mg/m^2/day Ara-C were ileus and colitis. The MTD was 50 mg/m^2. The most common non-hematologic toxicities were Grade 1-2 infusion-related hypotension, dizziness, and headache. Among the 30 evaluable patients at doses 400-600 mg/m^2, CR/CRp was 33%. The ORR for all dose cohorts was 27%. Researchers concluded that cloretazine contributes to Ara-C activity.

Ongoing trials include:

- Phase III trial of cloretazine+Ara-C to Ara-C alone in AML first relapse.

- Phase II trial of monotherapy in AML.
- Phase I trial in combination with temozolomide looking at AGT depletion in advanced hematologic malignancies. If AGT is low, patients are more likely to respond. The expectation is that temozolomide, which decreases AGT, will potentially sensitize patients to cloretazine.
- Phase II trial as a single agent in gliomas.

DATA TO EXPECT AT ASCO 2005

There will be a wealth of data on clinical trials at ASCO this year, including:

ASTRAZENECA'S ZD-2171 – Phase I data in ovarian cancer.

BAYER'S BAY-43-9006 – Phase III results in renal cell cancer plus rechallenge data and tumor biopsy data from the Intergroup trial (E2603) of sorafenib+carboplatin+Taxol (paclitaxel) in Stage 4 melanoma. This is a 2.5 year trial, with one more year of follow-up. A Phase III trial in hepatic carcinoma is ongoing.

CELGENE'S Revlimid (lenalidomide) + Thalomid (thalidomide) – Data on 40 patients with this combination therapy.

GENENTECH'S Avastin (bevacizumab) – Data in lung cancer, in breast cancer, and in ovarian cancer. Plus data on the combination of Tarceva and Avastin in lung cancer.

LIGAND'S Targretin (bexarotene) – Three different data sets are expected at ASCO 2005:

- A subset of responders in NSCLC.
- Third-line monotherapy NSCLC data.
- Phase I/II trial in third-line NSCLC with Tarceva.

MEDIMMUNE'S VITAXIN – Phase II data in melanoma.

NOVARTIS'S PTK-787 – More Phase III data in renal cell carcinoma.

PFIZER'S AG-013736 – No Phase II breast cancer data, but perhaps some other solid tumor data.

TELIK'S Telcyta (TLK-286) – A poster on Telcyta in NSCLC.

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