Trends-in-Medicine

February 2005
By Lynne Peterson

SUMMARY

Doctors are very excited about Genentech's Avastin, making the outlook tougher for Novartis's valatanib (PTK-787) and Amgen/Abgenix's panitumumab. Avastin failures in CRC are going on to other therapies, not more Avastin. ♦ Doctors do not believe AstraZeneca's Iressa should be withdrawn from the market, but most new patients are going on Genentech's Tarceva. ♦ Doctors want to use combinations of two targeted therapies (e.g., Avastin and ImClone/Bristol-Myers Squibb's Erbitux), but will be limited by cost for the near future. ♦ Millennium's Velcade works in multiple myeloma, and perhaps in some lymphomas, but doctors doubt it will be effective in solid tumors. ♦ Doctors are dubious about the outlook for Telik's Telcyta, cautiously optimistic about Ligand's Targretin, and fairly optimistic about Cell Therapeutics' Xyotax. ♦ Osteonecrosis is emerging as a problem with high dose, long-term bisphosphonate use. ♦ Dendreon's prostate cancer vaccine, Provenge, is likely to need additional trial data for approval.

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INTERNATIONAL CONFERENCE ON ANTI-CANCER THERAPY (ICACT)

February 1-4, 2005
Paris

Little or no new trial data were presented at this European cancer meeting, but there was a good review of recent data in various cancers and updates on treatment recommendations. In addition, ICACT provided a good opportunity to talk with leading oncologists about the outlook for drugs in development.

GENERAL

Europe vs. U.S.

Asked what is different in Europe from the U.S., doctors cited:

- **Speed of drug approval.** ICACT President Dr. Gabriel Hortobagyi of M.D. Anderson Cancer Center said, "I expect in Europe many new drugs will – because of clinical data – be approved, but with a gradual phasing in because of the inability of governments to handle a quick phase in."
- **Treatment approaches.** A Dutch doctor commented, "Americans are more aggressive, and European doctors tend to treat more on an individual basis. American doctors are more afraid of lawsuits, afraid to undertreat.
- **Side effect toleration.** A source said, "Americans like treatment despite side effects more than European patients, who care about the side effects."
- **Profit on infusions.** European doctors do not make money by infusing chemotherapy drugs.

United States

Among the predictions doctors made about the outlook in the U.S. if CMS further cuts physician fees and oncology drug markups:

- **Reduced patient access to care.**
- **Less in-office chemotherapy infusions.** Some physicians will stop administering chemotherapy in the office, sending patients to the hospital instead.
- **No significant increase in oral medications.** While it might seem logical that doctors would prefer oral medications if they no longer can make money on infusion products, that does not appear to be the attitude of doctors. For example, most sources do not plan to use more oral Xeloda (Roche, capecitabine) as a result of reimbursement changes. A U.S. doctor explained, "There is zero evidence it works in the adjuvant treatment of breast cancer. We can't expand Xeloda without that data. Those trials will take another

three to five years before we know the treatment value." Another U.S. doctor said, "We'll use Xeloda more if Medicare pays for it because it is better for patients…We use Xeloda exclusively. When it came out, we stopped using 5FU." A New York doctor said, "Roche just finished a trial comparing FOLFOX+Avastin (Genentech, bevacizumab) to Avastin+CAPOX, and it will look at efficacy, safety, and patient satisfaction. This will help settle whether there is a benefit to orals."

BISPHOSPHONATES

Several sources – at ICACT and contacted independently of ICACT – confirmed reports from dentists that they are seeing osteonecrosis, particularly serious dental issues (cavities, jaw problems, etc.), in patients on bisphosphonates. A Novartis sales rep said that Novartis is recommending that doctors have patients check with a dentist before using Zometa (zoledronate) in cancer patients. She said, "I don't understand how Zometa could cause this, but I know of several cases of osteonecrosis of the jaw. I don't know if Zometa is causative or coincidental." This issue suggests that Novartis could have trouble getting Zometa approved as a once-a-year infusion for osteoporosis.

Among the other comments on the issue of osteonecrosis and bisphosphonates include:

- *New York #1:* "The matter of jaw necrosis with bisphosphonates is very unclear. It seems most likely to occur in the setting of intravenous bisphosphonates – Zometa or Novartis's Aredia (pamidronate) – when used in patients with cancer. Patients get higher doses or are treated at more frequent intervals under these conditions. So, high dose and frequent use of very potent bisphosphonates seem to be key ingredients. In addition, many of these patients have very poor dental hygiene and/or have undergone tooth extractions. The reports of this happening in patients being treated with these bisphosphonates for osteoporosis are rare. As for oral use of bisphosphonate, I don't know if a case has yet been well documented."

- *New York #2:* "The rumors appear to be correct. The issue was first raised by a Florida dentist about a year ago. He described about 30 cases of ischemic necrosis of the jaw in patients with cancer being treated (mostly) with zoledronate and pamidronate. The doses used were very high (for zoledronate about 4 mg/month, compared to the 5 mg/year being evaluated for osteoporosis)…Apparently…about 500 cases were described at ASCO (2004). Again, this was mostly zoledronate and some pamidronate, but one or two following oral alendronate (Merck's Fosamax)…If it were just cancer patients, we might argue that because they are sick and on multiple meds, it remains to be proven that it's really the bisphosphonate, and I think that at present the benefit in this population still outweighs the risk. If I were using zoledronate at those doses, I'd probably get a pre-treatment dental evaluation, though, and have the patient see a dentist regularly during the course of treatment."

- *Austria:* "There is no good explanation for the osteonecrosis in the jaw."

- *Oregon:* "There have been a number of anecdotal reports and a small series of 'osteonecrosis' described in patients who are on high dose bisphosphonate therapy, almost always in patients with cancer. Unfortunately, our understanding of this problem has not yet matured. Osteonecrosis of the jaw frequently follows tooth extraction that is complicated by an infection that interferes with the healing of bone. Patients with cancer who have undergone radiation or chemotherapy are in a compromised state and are at increased risk of experiencing this problem, even in the absence of bisphosphonate therapy. Since no careful study has been performed, we cannot know whether or to what extent bisphosphonate therapy is, in fact, a risk factor for this problem.

"There have been a handful of cases with osteonecrosis of the jaw described in patients receiving other types of bisphosphonates, including Fosamax. However, whether there is a correlative relationship is even more uncertain. Most of the bone experts think that there is not a relationship between these jaw findings and the doses of therapy used for the treatment of osteoporosis. Recall that the doses of IV bisphosphonates used in the treatment of patients with cancers that have spread to bone are very much higher than the doses used to treat osteoporosis.

"The first of the anecdotal reports was described about two years ago. However, there is a very large and long-lived literature about what oral surgeons call osteonecrosis in patients with cancer even before bisphosphonates were widely used.

"I think it unlikely that these findings will have an important impact on the use of bisphosphonates in cancer. That treatment is very valuable as a way to minimize the progression of bone metastases and to limit other skeletal complications. If there is a lesson to be learned, it would be that tooth extraction should be done only under the most important circumstances in these patients…In summary, this will be an important clinical issue to pursue, and Novartis is being very aggressive (in a good way) of exploring these issues and attempting to understand both the nature of the clinical problem and its relationship to bisphosphonate therapy."

SMALL MOLECULES

Small molecules have been disappointing so far. There is no consensus that monoclonal antibodies are better than small molecules, but it is getting tougher for small molecules to prove their efficacy. A Dutch doctor said, "Some people are

biased in favor of one or the other. I've worked with both, but to me there is no difference and no consensus." A U.S. doctor said, "It's not true that monoclonal antibodies are better than small molecules." A Swedish doctor said, "So far, the monoclonal antibodies have proven better than small molecules, but in the end, I think we will combine them in some way."

Should both the ligand and the receptor be targeted at once? A Dutch doctor said, "Maybe that is what we are seeing with the combination of Avastin and Tarceva (Genentech, erlotinib)."

ASTRAZENECA'S Iressa (gefitinib)

Iressa use has suffered a severe blow as a result of the ISEL trial results which showed no survival benefit to Iressa over placebo in lung cancer (5.6 vs. 5.1 months) or in adenocarcinoma (6.3 vs. 5.4 months). An expert said, "Iressa use front-line is difficult at this time…and Iressa is in jeopardy in the second- and third-line settings." Another expert said, "There is still a place for Iressa in front-line therapy, but Tarceva is the choice in second- and third-line. The drug (Iressa) is real, but we need to know how to give it. It is now a me-too drug, and it will be hard to start with a me-too drug. It will probably come to an end." A Dutch doctor said, "People have stopped using it and they are waiting to see what the FDA does formally." A U.S. physician said, "I won't stop Iressa if it is working unless it is withdrawn from the market, but I'm not putting any new patients on it." A Swedish doctor said, "We use little Iressa; it requires a special license. But we won't stop using it. It is very good for some lung cancer. And Tarceva is not available in Sweden." Another source said, "Both small molecules and monoclonal antibodies are promising. I expect a lot of new developments in the next 10 years, making it possible to treat patients in a more individualized basis, based on tumor characteristics. Small molecules will work eventually. There have been some disappointments, but I'm sure some, in the end, will induce improvement."

However, doctors at ICACT insisted Iressa may still have a role and said they hope the FDA – which is holding an Oncology Drugs Advisory Committee (ODAC) meeting on Iressa on March 4, 2005 – does not withdraw it from the market, at least not for the time being. A U.K. doctor said, "Iressa failed, but we all have some patients who responded – almost magically…The Japanese are very worried about Iressa and pulmonary fibrosis, but they didn't withdraw it. I have one patient who was dying of lung cancer at Christmas 2004. She started Iressa just before New Year's, and in three days, it transformed her life. She was still alive and feeling well in mid-January, which is a surprise. There are still patients on Iressa for 1.5 years fourth-line…There have been some spectacular responses in pre-terminal patients. Not many, but how many do you need?"

Several speakers speculated on why Iressa has failed to show a survival benefit in ISEL. Among the possible explanations:

- **Interaction with chemotherapy.**
- **Dose.** A higher dose (750 mg or 1000 mg) might have had a different effect. A U.K. doctor wondered, "Is there a place for 500 mg Iressa? That question is more important post-ISEL…Iressa 700 mg is comparable to the Tarceva dose, but the 700 mg dose of Iressa was quite a tough treatment...700 mg might be a better option, but it is too toxic…The future of Iressa lies with the licensing authorities."
- **Smokers.** There were more heavy smokers in ISEL and fewer Asians than in the BR-21 trial of Tarceva. A speaker said, "If you look at the details of the (ISEL) study, which is not yet published, there is a significant survival benefit in Asians and in never-smokers (9.5 vs. 5.5 months and 9 vs. 5 months, respectively)."
- **Transient blockade of PI-3K pathway signaling** in mutant or other exquisitely sensitive tumors may have occurred with the Iressa dose (250 mg) used in ISEL.
- **Wrong endpoint.**

What will happen to ongoing Iressa trials, such as the NCI-Canada adjuvant trial of Iressa vs. placebo and the SWOG trial in locally-advanced NSCLC? One researcher said the IRBs are questioning continued use of Iressa, "We need to give more information to the IRB to accept continuing Iressa trials…but I think we need to complete these trials because they may tell us more than we know now."

GENENTECH'S Tarceva (erlotinib)

This is the only small molecule to show definite efficacy in colorectal cancer (CRC), but use does not appear to be getting a huge benefit from Iressa's problems. How is Tarceva being used after the ISEL trial? A U.S. doctor said, "We're using Tarceva second- and third-line." A U.K. doctor said, "Tarceva is being prescribed for compassionate use in Europe. When it is licensed, the uptake will depend on funding." However, a Dutch doctor said, "I won't use cetuximab (ImClone/Bristol-Myers Squibb's Erbitux) in NSCLC. I'm more likely to use Tarceva." A U.S. doctor said, "A Phase II study was done indicating that Tarceva and Avastin can be combined. Probably a Phase III will be done, but it hasn't been set up yet."

Skin toxicity

The clear message was that skin toxicity is related to EGFR efficacy, but that doesn't mean patients without a skin reaction shouldn't be treated. The rashes generally go through several stages. A U.S. speaker said, "When there is no skin toxicity, survival looks shorter…Skin toxicity occurs early on…And by that time you have response rate…so I wouldn't stop if you don't see skin toxicity…EGFR in tumors is aberrant…The

skin receptor is different than the receptor on a cancer cell…I would wait for more objective evidence that the EGFR inhibitor is or isn't working." A Dutch speaker said, "The question is how reliable a biomarker is rash? I think it is lousy. Almost all patients get rash. Do you dose to rash? I don't think so. Certainly, we need a better biomarker than dose to rash." A Belgian doctor said, "My experience-based advice – not evidence-based advice – is that the maximum rash is at three weeks, then the rash improves spontaneously, and then it can fluctuate a little." Another speaker stated, "Rash correlates with both response and survival." A fifth speaker said, "Skin rash is extremely predictive of activity."

The European EVEREST study is looking at dose escalation to rash in ~160 metastatic CRC (mCRC) patients refractory to irinotecan (Pfizer's Camptosar, CPT-11) who are given Erbitux+irinotecan.

EGFR Skin Rash Stages *(in order of appearance)*

Description	Treatment option
Acne-like	Anti-acne creams
Post-inflammation effects	Pulse dye laser
Dry skin	Emollient
Fissura	Hydrocolloid dressing or propylene glycol ± acetylsalicylate
Paronychia	Antiseptic soaks

Mutations

At the American Society of Clinical Oncology meeting in May 2004, researchers reported a correlation between mutations and EGFR efficacy in lung cancer. A speaker at ICACT predicted that mutations also will be found to play a role in EGFR efficacy in lung cancer.

EGFR testing

Immunohistochemistry (IHC) EGFR testing was strongly discouraged in CRC. A U.S. expert said, "The general feeling now is that IHC is probably not the best way to assess the receptor's presence or absence…There are IHC negative patients who respond. It could be that FISH would work or even a more molecular test…An article in the ***Journal of Clinical Oncology*** (JCO) recently looked at Erbitux in EGFR negative CRC patients. No trend was seen in terms of increased activity with increased EGFR staining. It does not seem necessary or appropriate to continue the IHC practice…Some third party payers have threatened not to reimburse for the drug in negative stains. I don't know of any specific cases of payers refusing to pay that, but I've heard of threats…There is a lack of correlation between EGFR staining and response. EGFR negativity should not be used to exclude patients from EGFRs...and EGFR+ should not be used to determine treatments…It is a non-issue…EGFR staining as determined by IHC has no prognostic significance. It is a completely useless test and should not be done in clinical practice." A U.K. doctor said, "I don't think IHC testing will solve it. Testing needs to be more complex – FISH or molecular analysis – but most molecular analyses only predict for response, which is not a good indictor of benefit."

Monoclonal Antibodies

Genentech's Avastin (bevacizumab)

This anti-VEGF is being studied in a wide variety of cancers, from ovarian, to breast (with taxanes), NSCLC, pancreatic [with Lilly's Gemzar (gemcitabine)], and renal cell (with interferon). It was approved in Europe in January 2005, and doctors are grappling with paying for it. A Dutch oncologist said, "People will have to use it. Some governments (like the U.K. and Holland) will hiccup, but you have to use it in colorectal cancer."

ImClone/Bristol-Myers Squibb's Erbitux (cetuximab)

A topic that came up repeatedly at the meeting was practical advice on what to use first-, second-, and third-line today, after the 300-patient Phase II BOND trial showed an overall response rate of ~23% with Erbitux monotherapy in EGFR-positive CRC, refractory to irinotecan. A U.S. physician contended that irinotecan has no advantage in second-line therapy; he recommended Option 2 in the chart below.

CRC Treatment Recommendations

Option	First-line	Second-line	Third-line
1	FOLFOX	Irinotecan (5FU/FA)	Erbitux+irinotecan
2	FOLFIRI	Erbitux+irinotecan	FOLFOX6 or 8
3	FOLFIRI	FOLFOX	Erbitux+irinotecan

Other Agents

Cox-2 inhibitors

A speaker described these as "an even more endangered class than EGFRs…Celebrex (Pfizer, celecoxib) has even more modest activity than Iressa in some cell lines. The combination of Celebrex and Iressa is more effective than either alone. I think candidly this is the way to go, whether it is IFN+retinoids or a Cox-2+EGFR…I think combination chemoprevention is the way of the future." Another expert said, "Celebrex is in trouble, but you can probably give it for a short period of time."

Cox-2 Activity in CRC

Drug	Mean delay in progression
Celebrex	39.2 days
Iressa	51.4 days
Iressa+Celebrex	69.3 days

Retinoids

A Dutch speaker said, "The National Cancer Institute (NCI) blocked the last two isotretinoin trials. The retinoids are fairly dead in head and neck cancer. They were unable to be given at high doses, and at low doses, they are ineffective in the prevention of secondary and primary head and neck tumors…In a Phase II trial of bioadjuvant therapy…39 of 44 patients were able to complete one year of therapy, so the therapy is surprisingly well tolerated…Is this a panacea? No. And we've had trouble accruing patients…Only people with substantial experience in the field can convince patients we don't know the answer (so they should participate)."

Rexinoids

These appear to be more promising than retinoids, but the jury is still out. (See Ligand's Targretin under NSCLC on page 10).

Breast Cancer

Aromatase inhibitors are growing in popularity, but tamoxifen is not down and out in breast cancer. A speaker said, "Italian researchers are very vociferous about wanting to look at low dose tamoxifen. And there is reason to do that, but it is a really difficult study to do. We know high dose tamoxifen works. Does anyone really want to look at low dose with the possibility of getting negative results? That trial is ongoing but floundering because of fewer women taking HRT."

If tamoxifen is used for prevention, how does that affect treatment if the woman develops breast cancer? An expert said, "It doesn't make much sense to offer tamoxifen for treatment (in that case). You would probably go on to an aromatase inhibitor if the woman is ER+, but a greater proportion of tumors that develop will be ER(-), and then you will have to consider chemotherapy."

At what age should chemoprevention for breast cancer begin? A speaker said, "That is a difficult question. My general feeling is late pre-menopause is the best time (~age 45). Aromatase inhibitors look best, but they can only be used postmenopause. So, then as soon as a woman becomes postmenopausal, you can give them…I think long-term late pre-menopause is an important time to try to prevent breast cancer."

Could chemoprevention be started in a high risk woman 10 years before the age at which breast cancer appears in her family history? An expert said, "An attractive option in young high risk women is to add back enough estrogen to prevent meno-pause…That is an exciting prospect, but it would be difficult to test that. That could be the ultimate solution for younger, high risk women."

American Pharmaceutical Partners' Abraxane (ABI-007, albumin-bound paclitaxel)

European doctors don't even have Abraxane on their radar screens. A U.K. doctor said, "We need more mature data first." A Swedish doctor said, "We need more studies before we will use it."

U.S. doctors at ICACT appeared to be taking a cautious approach to Abraxane. A U.S. doctor said, "The new taxanes need study, particularly the nanoparticle taxane (Abraxane). You can't substitute that in the adjuvant setting. If you are using docetaxel, there is no substitution data. Each regimen needs explicit testing…I just had to do the (hospital) formulary application for Abraxane, and, the truth is, if you practice evidence-based medicine, you have to look at the data, and the only randomized clinical trial is 175 mg once every three weeks. You can defend replacing that with Abraxane, but it is arguable whether you can replace weekly paclitaxel. Abraxane appears safer, doesn't require any pre-medication or IV tubing, but those (dosing schedule) comparisons have not been made. We will certainly replace 175 mg Q3W paclitaxel, but we are not giving many patients that. The other place where we will use Abraxane is in patients who have had a hypersensitivity reaction to paclitaxel or who have significant steroid contraindications." A New York doctor said, "There will be a lot of Abraxane trials now. There are a lot of reasons for patients to prefer this drug. You can treat patients, and let them go back to work."

Aromatase inhibitors:

Novartis's Femara (letrozole),

Pfizer's Aromasin (exemestane),

AstraZeneca's Arimidex (anastrozole).

Issues with aromatase inhibitors that were identified as deserving attention included:

- **Cardiovascular risk** of Femara and Aromasin. A speaker commented, "There is an increased risk with letrozole and some with exemestane, but no excess with anastrozole…Strokes are actually up with letrozole, but down a striking 29% with anastrozole."
- **Bone fractures** with all aromatase inhibitors. A speaker said, "We should have known about this…It is nothing new…We've been causing this for years…There are international guidelines to routinely screen women >65 for osteoporosis and women <65 with risk factors…So, in my mind, this is not something we need to learn, we should already have learned it." Another expert said, "Bone density goes up with IV bisphosphonates more than with oral bisphosphonates but there is still a little concern this may become brittle bone, not strong bone."
- **Sequencing with tamoxifen.** Dr. Hortobagyi said, "Until I see clear proof of the sequential approach (tamoxifen followed by an aromatase inhibitor), I think the burden of proof is on demonstrating that sequential therapy is better.

In the ATAC trial, 5% of patients on tamoxifen had recurrence compared to ~3% on Arimidex. Once a patient has a recurrence, that is not a curable condition. So I think it is better to start with an aromatase inhibitor." A U.K. doctor said, "I don't think tamoxifen sensitizes a patient for aromatase inhibitors."

- **How long to give an aromatase inhibitor.** A speaker said, "Right now we don't have full data for five years…We made an arbitrary decision in trials like BIG, ATAC, MA17 to give an aromatase inhibitor for five years because of reasons of symmetry. That is not based on any scientific data, and we eventually will have to do studies to see the optimal duration of AI therapy, but for the time being that is what I advocate."

Dr. Sandra Swain, Chief of the Cancer Therapeutic Branch at the National Cancer Institute, urged doctors to use Adjuvantonline.com, a website that helps doctors determine the appropriate treatment for breast cancer patients. In the 10 years since it was first developed, Adjuvantonline.com has been supported by funding from personal, foundation, governmental, and industrial sources. In 2004, it received educational grants from AstraZeneca and the Greenberg Breast Cancer Research Foundation. Dr. Swain said, "We use this on all our new patients."

A study presented at the St. Gallen Primary Therapy of Early Breast Cancer conference in January 2005 compared adjuvant online recommendations and Genomic Health's Onco*type* DX results in 668 patients – and the correlation wasn't very good. Dr. Swain said, "Adjuvantonline.com is over predicting risk in low risk patients and under predicting the risk for patients identified as higher risk by the Onco*type* DX, so it didn't have the best correlation. It was a relatively weak correlation. Onco*type* DX appeared to correlate more strongly with outcome than Adjuvantonline.com. Adjuvantonline.com is going to try to incorporate the Onco*type* DX scores… Adjuvantonline.com (currently) appears to under predict risk, especially in high risk patients."

Diagnostic tests

Speakers reviewed several diagnostic breast cancer tests. While doctors are optimistic about these tests, several speakers pointed out that they still need further refinement and prospective validation. ICACT President Dr. Hortobagyi warned, "Don't go home saying chemotherapy doesn't work in ER+ breast cancer. Don't go home and under treat patients. These are strong hypothesis-generating results, and they force all of us to rethink ongoing clinical trials and trials in development. We need to act on this, but it will take validation studies in the near future to decide which patients should be treated with hormones alone, which with chemotherapy alone, and which with both." Dr. Swain called these tests "the best opportunity for translation research in all of cancer medicine."

The tests discussed at ICACT included:

- **GENOMIC HEALTH'S Onco*type* DX** (a real-time PCR 21-gene assay). Dr. Hortobagyi said, "Studies suggest this 21-gene assay not only predicts prognosis but also predisposes to additional treatment in ER+N(-) breast cancer. But if it were that simple, we would go home and order this test. But the assay costs $3,500-$3,700…It has great interest, but I would like to see validation, especially in independent hands." Dr. Swain said, "High and low risk are well predicted by Onco*type* DX. The intermediate group is less clear. Tumor size didn't seem to make a difference to the prognostic ability of the test…The Kaiser data, Study B-20, and Study B-14 all correlate on the results of this test. In the Kaiser study, tumor size and grade did predict which patients would recur but not as well as the Onco*type* DX recurrence score. The major impact of using this kind of test is that you take out about 40% of patients who shouldn't be treated, and we know we are treating 70% of women who should not be treated." A Dutch doctor said, "My personal opinion is that Onco*type* DX is not adequately validated. It looks promising, but they need hard data. It is too early, with all the gene profiling tests, to put them into daily clinical practice."

The PACT Intergroup trial of ER+N(-) patients is using the Onco*type* DX test. Low risk patients will get hormone therapy alone, intermediate risk patients will be randomized to hormone therapy vs. chemotherapy plus hormones, and high risk patients will get chemotherapy plus hormone therapy. Dr. Hortobagyi said, "This will tell us what the test means in terms of utilization of resources. This is an equivalence trial, assuming no decrease in recurrence or overall survival."

- **The Amsterdam test** (a 70-gene prognostic signature) in node negative untreated breast cancer. An interim analysis on this test, presented at the San Antonio Breast Cancer Symposium in December 2004, found the correlation of predictive risk and survival was not as good as expected. Dr. Hortobagyi commented, "Enrichment of the high risk group is still modest…We would like to predict 50%-60% of the 10-year recurrence rate, so these tests still need work."

TRANSBIG, an EORTC trial, is using the Amsterdam test and may validate that. This is a 5,000-patient trial, with the adjuvant therapy decision based on the test.

- **A U.K. 74-gene test** that has been developed and validated. Dr. Swain said, "My impression is that there is a greater number of gene changes in responders than in poor responders. There does seem to be evidence that tumors which are responding to chemotherapy after three weeks have a greater change in gene expression than those that don't…But there is no consistency in which genes these are so far."

Trials to watch in breast cancer

- STAR, a 19,000-patient trial comparing tamoxifen to Lilly's Evista (raloxifene) in breast cancer patients. Recruitment is complete, and data are expected in 2006.

- The Phase III AVANT adjuvant trial, which just started, comparing FOLFOX4 vs. XELOX+Avastin vs. FOLFOX4+Avastin. The aim of this study is to find out if adding Avastin to the chemotherapy regimens FOLFOX4 or XELOX can prolong survival and reduce the chance of the cancer returning in patients who had surgery for colon cancer.
- NSABP-C08 trial which began September 15, 2004. This is a study of FOLFOX6 followed by either Avastin or no treatment. The primary endpoint is three-year disease-free survival. So far, ~200 of the planned, 2,632 patients have been randomized, and a researcher said accrual is "really starting to pick up. We expect randomization sooner than the 2.5 year period predicted."
- The five-year, European IBIS-II prevention trial in 6,000 high risk postmenopausal women comparing placebo to Arimidex (1 mg). So far, ~600 patients have been enrolled.

COLORECTAL CANCER (CRC)

GENENTECH/ROCHE'S Avastin (bevacizumab)

Oncologists are very excited about the potential for Avastin, which was approved by European regulators to treat CRC a week before the ICACT meeting, and that has taken the blush off enthusiasm for both Novartis's valatanib (PTK-787) and Amgen/Abgenix's panitumumab (ABX-EGF). A U.S. expert said, "Single agent Avastin is not very active in CRC, but I think it is a potentiator. You get better drug delivery to the tumor with the addition of Avastin."

Speakers also warned doctors not to forget that Avastin can have side effects, including hypertension, GI perforation (1%-2%), arterial thrombotic events (5%), including MI, cerebro-vascular accidents, angina, and stroke. A Dutch oncologist said, "We know little about Avastin with aspirin or NSAIDs …So, when we combine these drugs with steroids, etc., we are affecting hemostasis and need to be alert. The fact that Avastin is now approved, is a reason for me to put more attention on it…The hypertensive effect can be managed by conventional treatment…My advice is to treat the hyper-tension. Stop the drug for a moment if it is severe. If it is slight, treat and continue. And a few patients have been observed with perforation of the bowel, which is something you have to be alert for." A U.S. doctor said, "I present it to patients this way: Avastin is not a freebie. It doesn't make people sick or nauseous, and there is no rash, but every now and then it does something bad – 1:400 die of gut perforation and arterial thromboembolic events. There is no free lunch, but you are better off with Avastin than without it. That's why I use it pretty frequently first-line."

The results of the 880-patient, Phase III ECOG-3200 Avastin trial in second-line renal cell carcinoma was presented at ASCO GI in January 2005 and reviewed at ICACT. The primary endpoint of duration of survival, was superior with FOLFOX+Avastin to FOLFOX alone (12.5 months vs. 10.7 months, p=.002). Researchers concluded that there is benefit to adding Avastin to naïve patients front-line.

The question is what to do if patients relapse after front-line treatment with Avastin for renal cell or CRC. Most sources agreed that Avastin should not be continued once a patient fails it first-line, but a few doctors said they would continue it. A speaker said, "Right now, I'm not persuaded that it is the right thing to do to continue the Avastin. I only add it to second-line if patients didn't get it first-line. The continuation issue is unsettled right now." A Dutch doctor said, "I'll start with Avastin+irinotecan front-line, and then go to Xeloda+oxaliplatin. I don't think there is a reason to give Avastin second-line. There is no data yet, so we can't do that in Europe, but some U.S. doctors will do it."

Various Options for Avastin First-line CRC Failures

Option	First-line	Second-line	Third-line
1	FOLFOX7 or XELOX	EGFR or Avastin	Irinotecan+Velcade
2	FOLFOX+Avastin	Irinotecan+5FU	Irinotecan+Erbitux
3	FOLFIRI+Avastin	Irinotecan+Erbitux	FOLFOX
4	Irinotecan+Xeloda+Avastin	Oxaliplatin+5FU	Irinotecan+Erbitux
5	FOLFOX±Avastin	FOLFIRI	Irinotecan+Erbitux
6	FOLFIRI±Avastin	FOLFOX	Irinotecan+Erbitux

The lack of a platinum in the Avastin label is not stopping European doctors from adding a platinum to Avastin therapy. A doctor said, "We are just doing it anyway." Another commented, "It's not an issue. We don't read the label."

There was also a buzz about a Phase I/II study presented at the ASCO GI meeting in January 2005 on the combination of Avastin and Erbitux ± irinotecan in refractory CRC. A Belgian doctor said, "The data seem to suggest there may be at least an additive effect or maybe a synergy between Erbitux and Avastin."

Avastin+Erbitux in CRC

Measurement	Erbitux+Avastin+irinotecan n=39	Erbitux+Avastin n=35
CR+PR	38%	23%
TTP	8.5 months	6.9 months
Diarrhea Grade 3-4	26%	0
Grade 2 rash	18%	17%
Grade 3 rash	54%	67%

AMGEN/ABGENIX'S panitumumab (ABX-EGF)

A Phase III trial comparing panitumumab vs. best supportive care in third-line CRC is underway. The trial has completed enrollment with 300-400 patients. The primary endpoints are overall survival and quality of life. Secondary endpoints are TTP, response, and toxicity. A speaker said some skin

toxicity has been evident, indicating the drug is active. A U.S. doctor said, "The only difference between panitumumab and Erbitux is panitumumab is less likely to be immunostimulating. If there is a response, it will be a tough sell. The only way the company can make it in this market is if it is given less frequently (which it is) or if it is superior. I doubt it will be cheaper (than competing drugs)." A U.K. doctor added, "The company is behind in its recruitment targets because of Avastin…U.K. centers are reporting a 16% response rate in small trials."

If ABX-EGF is approved, sources predicted it would find a role. A French doctor said, "It is every-other-week, and it is completely humanized, so there is less allergic reaction. It will be used. But we need to try it with chemotherapy and Avastin."

ImClone/Bristol-Myers Squibb's Erbitux (cetuximab)

Usage is increasing, not declining, doctors insisted. A U.S. doctor said, "I'm using a lot, but the question is when to use it. Avastin+Erbitux with no chemotherapy may be better, but we need to figure out which patients and how to pay for it…I am not using Erbitux off-label." Another U.S. doctor said, "The combination is costly, so we need to wait and see if the combination works first."

Studies looking at Erbitux as first-line therapy in CRC include:

- A four-arm U.S. trial in which patients are first randomized to four arms – FOLFIRI, FOLFOX, CAPOX, and CAPIRI – and then randomized to three arms (Erbitux, Avastin, and Erbitux+Avastin).
- **COIN**, a three-arm U.K. study in which patients get oxaliplatin+fluoropyrimide (OxFp) until progression, cumulative toxicity, or patient choice. Then patients are being randomized to chemotherapy (OxFpP)+Erbitux or intermittent OxFpP. This trial is expected to begin soon.
- **Intergroup Study No. 147**, in which patients are randomized to either FOLFIRI, FOLFOX6, or FOLFOX6/FOLFIRI. Each is then re-randomized to either Erbitux or no Erbitux. The primary endpoint is overall survival.
- **CRYSTAL**, an ongoing, 540-patient, Phase III trial comparing Avastin±Erbitux in mCRC. The primary endpoint is progression free survival (PFS). A Merck official said, "Maybe Avastin doesn't have any activity, but it may facilitate Erbitux."

Lilly's Alimta (pemetrexed). The value of Alimta in mesothelioma appears undisputed, but use in other cancers is growing slowly. A Swedish doctor said, "We use little cisplatin, so Alimta won't change what we do. I prefer carboplatin even though it is more expensive. Cisplatin is much more toxic than carboplatin, and the benefits over carboplatin are small." A U.S. doctor said, "Alimta use is increasing. It is finding niches."

Novartis's valatanib (PTK-787)

There was surprisingly little excitement about this oral anti-VEGF agent at ICACT for two reasons: (1) It is a small molecule, and so far the small molecules have been disappointing, and (2) Avastin was recently approved in the U.S. and Europe. In fact, some experts are concerned that PTK-787 will have a difficult time doing trials or marketing with Avastin available. One doctor said, "It is not clear that PTK-787 is superior. We already have an anti-angiogenesis agent. If the difference is only incremental, it will be more of a marketing (price) issue than anything." Another U.S. expert said, "It will be a harder hurdle because of Avastin. Avastin+Erbitux is the next step. We wanted to try PTK-787, but we need Phase III data first…The question for this and for panitumumab is how to configure a study in advanced CRC to transpose the results to the adjuvant setting – or should we start an adjuvant trial while there is a window – but we need the Phase II or Phase III advanced CRC data first…If there is no window to do these trials, then it would have to be a company-sponsored trial, not an Intergroup trial."

Sources had no predictions on the outcome of the two Phase III trials of PTK-787 – CONFIRM-1 and CONFIRM-2. They do expect the data from both at ASCO 2005. A U.S. doctor said, "We really need to see the results. There is a good basis for use, but perhaps this is not the optimal compound yet. The concept of targeted therapy is good, and the bar is not higher because of ISEL."

If PTK-787 is approved, how would doctors choose between this and Avastin? Doctors insisted it is just too early to predict this. First, they want to know whether PTK-787 works, what the thromboembolic event rate is, and the side effect profile. A U.S. doctor said, "Even if the data are positive, it is not clear where it will fit in. I'm not convinced an oral will be quite as useful as a conventional IV – unless there is a safety benefit. I'm happier giving chemotherapy once every three weeks than worrying about patient compliance. And patient preference is to get everything altogether. Since they are getting an IV anyway, adding a half hour infusion lets them avoid pills." A French doctor said, "It's an oral, so it would be a choice, but it has to work." Another U.S. doctor said, "PTK-787 is oral but dizziness is an issue. Everyone assumed Xeloda would be the preference (over competing IV drugs), but it is still a minority."

Head and Neck Cancer

ImClone/Bristol-Myers Squibb's Erbitux (cetuximab)

Erbitux was described as "an excellent sensitizer" for other agents in NSCLC. One doctor said, "Erbitux improves the

effect of XRT…Erbitux is probably good for rectal cancer, but it is not impressive in head and neck."

A trial is underway of Erbitux in head and neck cancer, but it is already being used off-label when doctors can get it reimbursed. Other doctors are waiting for the trial results.

A Merck KgA official doubted that Erbitux will have a problem with regulators because different radiation regimens were used in the trial. He said, "Americans tend to use a more aggressive regimen of XRT than in Europe. It was speculated that in a subgroup, different regimens would impact results, but if we look at patient selection, that is more important. Any differences are not due to the XRT regimen but to patient selection. There is a significant difference in the inclusion of patients with J4J3 stage in Europe, and in the U.S. there is more T2…We know Erbitux and CT are synergistic, but in head and neck cancer, we are also seeing synergy with XRT."

MULTIPLE MYELOMA

CELGENE

➢ **Thalomid (thalidomide).** Transplantation is the standard of care in multiple myeloma patients fit for it. Until transplantation or in patients ineligible for transplantation, thalidomide is widely used – even in Europe, where the S.T.E.P.S. program (which is designed to assure that women do not become pregnant on the drug) is not required. An Austrian physician said, "The beauty is the time to response is quite short with thalidomide – 1.5 months…The problem is the increase in thromboembolic events, especially when you combine thalidomide with corticosteroids and, particularly, with cytostatics. Arrhythmia in a few elderly patients causes discontinuation. Thal/Dex/CT (thalidomide+dexamethasone+ chemotherapy) may have a high rate of thromboembolic complications…Most complications occur at the beginning of treatment, so you need to use prophylactic LMWH or therapeutic doses of Coumadin (warfarin). Some groups use aspirin, but that is still controversial." Another doctor said, "Thalidomide is widely used in Europe, but the pharmacists make it; we don't buy it from Celgene." A French doctor said, "Thalidomide use is up in Europe, but Velcade (Millennium, bortezomib) can be used in heavily-pretreated patients. I will use Velcade instead of thalidomide more and more." A fourth doctor said, "At a European multiple myeloma specialists meeting, doctors were asked if they had ever had a multiple myeloma patient who became pregnant, and the answer was, 'No.' So, I don't see what the (S.T.E.P.S.) fuss is all about."

➢ **Revlimid (lenalidomide).** A French doctor said he is optimistic about Revlimid and believes it will be better than thalidomide, especially in heavily-pretreated patients." Another doctor said, "I'm excited about Revlimid." A third expert said, "In multiple myeloma, there is a study ongoing, and we should have received an alert if there is a problem (with deaths), so that is reassuring – unless something is hidden…The company promised to open a compassionate access program at the beginning of the year, but I haven't heard more about it."

Revlimid was described by speakers as having:

- **Convenient oral dosing.**
- **Activity in thalidomide-resistant patients.** An Austrian doctor said, "Revlimid is active in thalidomide failures. I'm not sure if it works the other way around…In Europe because of the cost issue, we may start with thalidomide and reserve Revlimid for thalidomide failures, but if there is pre-existing neuropathy, we may start with Revlimid."
- **Manageable toxicity** – no significant neuropathy, DVTs, somnolence, or constipation.

➢ **Actimid (CC-4047).** A U.K. doctor predicted this won't be developed "because it is teratogenic, but it isn't known if Revlimid is teratogenic."

MILLENNIUM'S Velcade (bortezomib)

Velcade is the new drug on the block for multiple myeloma, and doctors are excited about it. An Austrian doctor said, "This is the most effective treatment ever reported…You could start with it as a single-agent, and if the patient relapses, add dexamethasone, and if the patient relapses on that, add doxorubicin…The neuropathy, unlike thalidomide, is reversible. It is mainly sensory, mainly Grade 1-2 and resolves after a couple of weeks or months in two-thirds of patients…Velcade has remarkable activity in heavily pre-treated patients...and has excellent toleration."

A panel on Velcade sponsored by Johnson & Johnson, which markets Velcade in Europe, answered several questions about Velcade, including:

➢ *Can patients be re-treated with Velcade?* **Yes.**

➢ *Are you seeing efficacy in other cancers* (besides multiple myeloma)? **Yes.** There is also clinical efficacy in T-cell lymphomas in clinical practice.

➢ *Isn't it expensive?* **Yes.** A French doctor said, "This is the first time we've encountered such a high response rate." Another speaker said, "It is likely the price will progressively come down with wider use."

➢ *Can you use it for maintenance therapy?* **Yes.** A speaker said, "Eight cycles are probably not enough, so maintenance therapy is under evaluation. We know you can give Velcade longer. Some patients have gotten ~30 cycles."

➢ *What is the outlook in solid tumors?* **Uncertain.** A speaker said, "Preclinically, it was synergistic with irinotecan…It is too early to draw conclusions, but it is promising….The Phase I study in AML shows promise." However, most other sources were not very optimistic about the outlook for Velcade in solid tumors. An Austrian doctor said, "The data are not very promising.

I'm not so enthusiastic. Patients still relapse, but it could avoid transplantation in ***some*** patients." A French doctor said, "What's most promising is Velcade in combination with other drugs in solid tumors."

- *How significant is the neuropathy?* A speaker said, "If you discontinue the Velcade or take a break with it, you can restart it and lower the dose. With thalidomide you have to stop some patients indefinitely."

NON-SMALL CELL LUNG CANCER (NSCLC)

Most speakers said they use carboplatin rather than cisplatin in doublets to treat NSCLC, but a U.S. expert urged them to use cisplatin. He said, "A cisplatin doublet is better than a carboplatin doublet in advanced lung cancer, and you probably should use it over carboplatin in adjuvant therapy…Adjuvant chemotherapy should be standard of care, but platinum-based therapy for Grade 3-4 NSCLC is optional." Another doctor said, "There is an almost religious debate going on: Which is better – carboplatin or cisplatin? Cisplatin has a higher response rate than carboplatin, but there is no survival difference, though a subgroup analysis of another trial found a survival advantage to cisplatin."

CELL THERAPEUTICS' Xyotax (polyglutamate paclitaxel)

Doctors were optimistic about this agent. One expert said, "There is a lot of enthusiasm in the U.S. for it. It is very promising." Data on the two key Phase II trials are expected at ASCO 2005:

- **STELLAR-3** – a trial of Taxol+carboplatin vs. CT-2103.
- **STELLAR-4** – a trial of gemcitabine or vinorelbine vs. CT-2103.

GENENTECH/ROCHE'S Avastin (bevacizumab)

The Phase II trial data of Avastin in NSCLC were described as "interesting." The key trial of Avastin in lung is the ECOG-4599 trial, and sources all expect the data at ASCO 2005, but no one could confirm that definitively, and there were no hints at what the data may show. Sources were unaware of any treatment-related fatalities in ECOG-4599. A U.K. doctor warned that squamous cell cancer patients were not included in this trial, "A significant percent of NSCLC patients have squamous cell lung cancer – ~40% in the U.S. and ~60% in Europe…Small cell patients were left out because the early work showed fatal pulmonary hemorrhages in small cell because of the rapid Avastin effect."

The minimum survival threshold doctors want to see in ECOG-4599 varies by country. Europe – particularly the U.K. – wants to see survival extended by Avastin for at least two months, but sources said U.S. doctors may accept less. A U.S. doctor said, "I'm a doubter. The results may be statistically significant, but not clinically significant."

Concern has been raised about hemoptosis (bleeding in the lung) with Avastin. A U.S. doctor said, "Hemoptosis was seen in squamous cell cancer (with Avastin) but there is no reason to suspect it won't occur with adenocarcinoma as well."

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

Erbitux definitely stole the show in NSCLC from Tarceva and Iressa at ICACT. A U.K. doctor said, "In terms of practicality, Erbitux is less convenient. And we don't know if it is better than Tarceva." A Swedish doctor said, "Erbitux came to Europe six months ago, so it is too new to say how it will do. The two patients I gave it to were a success."

One of the key questions doctors are grappling with is whether or how to combine Erbitux and Avastin. A speaker said, "There is no clear data on the advantages or disadvantages of combination therapy…In early Phase I/II results…toxicity seems not too high, and the conclusion was that it is feasible. So, we have to wait for the results on efficacy."

The cost of using two targeted therapies is a concern, especially in cost-conscious Europe, but not as much as might have been expected. A French doctor said, "The price will decrease in 15 years…We will have to stick with very clear indications to argue for the money…but we have to be conscious that all these trials are proof of concept and steps on the way to cure patients…Within 15 years the drugs will be at a lower price. I remember when my hospital was very anxious about cost of Zofran (GlaxoSmithKline, odansetron), and it is no longer an issue. The problem is how to get money for the very good indications…Only large Phase III trials can prove we have to use the combination of two targeted therapies." A Dutch doctor said, "It's feasible (to use two targeted therapies), but whether it is possible to get paid is another story. The benefit has to be quite striking in Europe to justify the cost of two targeted therapies." A Swedish doctor said, "I could do it if I wanted to, but it is costly, and that must influence me." A U.S. doctor said, "It's very expensive. It makes sense in theory, but the hope is there is synergy, not just an additive effect." A French doctor said, "Two targeted therapies are feasible. Cost is not the issue. In 20 years, the cost will come down."

LIGAND'S Targretin (bexarotene)

Two Phase III trials – SPIRIT-1 and SPIRIT-2 – with a total of ~260 patients are underway and nearly completed looking at oral Targretin added front-line to cisplatin/vinorelbine or carboplatin/paclitaxel in advanced NSCLC. Sources said the data analysis will not be completed before the end of March 2005, but they expect the data at ASCO 2005. The primary endpoint in the SPIRIT trials is overall survival, powered to

show a 30% improvement. The secondary endpoint is projected two-year survival. The trigger for analysis is the 456th death or 18-month follow-up, whichever comes ***later***. This is a change from the original 456th death or 12 months, and was done with the agreement of the FDA. No interim analyses are being done. The starting dose in the trial is 400 mg/m^2 QD. The company has said the top-line data will be released ~2 weeks after start of data analysis, and that both studies will be analyzed concurrently when the trigger is met in ***both*** trials.

- **SPIRIT-1** – Targretin added to cisplatin/vinorelbine. Enrollment was completed in August 2003 with 623 patients, 34% of whom were enrolled in the last six months of the 24-month accrual period.
- **SPIRIT-2** – Targretin added to carboplatin/paclitaxel. Enrollment was completed in September 2003 with 612 patients, 61% of whom were enrolled in the last six months of the 18-month accrual period.

Among the side effects with Targretin are hyperlipidemia, nausea, vomiting, and lipid empyema. Empyema is an accumulation of pus in the pleural space.

A source said the perceived survival benefit in the early stage trials is not an epidemiological phenomenon. He said he is not yet using Targretin off-label in NSCLC but that it holds promise: "I think there are some long-term survivors. There could have been selection bias, but there is bioactivity...I won't predict how the trials will come out, but I think you should follow them."

Median survival curves in NSCLC are shifting right and are now 10 months for Americans. Median survival is longer for Japanese patients – 14-15 months – because they metabolize drugs differently, an expert explained. A U.S. doctor said, "This is due to better supportive care and better second-line therapies. We may be misguided by targeted therapies. Are the mutations real? We need more than mutations. The retinoids are not promising, but the rexinoids are not determined yet."

Ovarian Cancer

Overall five-year survival in ovarian cancer today is 46.4%, but 71.9% of patients present with advanced disease. The improvement is due, in part, to the introduction of platinum compounds. A Belgian doctor said, "The standard of care is paclitaxel+carboplatin, but the backbone is the platinum compound…If we could catch the disease earlier, it would have a major impact on outcome. Unfortunately, screening for early ovarian cancer is extremely difficult...It is doubtful that screening the entire population with color doppler flow will be feasible. What is more impressive is proteomics – looking for a specific protein profile...The plan in the GYN cancer intergroup is for a focus on proteomics, but it will take years and years before we know the outcome."

However, paclitaxel+carboplatin was described as a "far from perfect" regimen. Median TTP is 15-18 months, and median survival is <3 years. A speaker said, "So far, adding a third drug to paclitaxel+carboplatin has shown no benefit…The expectation that an additional cytotoxic will lead to major improvement is not likely."

The role of surgery also should not be forgotten. A French doctor said, "The role of surgery is a critical point. We have known for 30 years that there is no doubt that in patients in which you achieve very good surgery, there is a better prognosis…Today, the data show that, with few exceptions (e.g., liver metastases), an attempt should be made to operate. It is a big mistake in ovarian cancer to give up on surgery."

Will targeted drugs improve survival in ovarian cancer? A speaker said it is too early to tell.

Among the drugs being investigated for ovarian cancer are:

- **Johnson & Johnson/PharmaMar's Yondelis (ET-743, ecteinascidin),** a sea snail toxin derivative. European regulators found this not approvable in 2003, but development is continuing. An expert said, "It will be tested in coming years in randomized clinical trials. That is the only drug at the moment that is appealing because the high response rate in platinum-sensitive disease is in the same range as platinum compounds, on the order of 50%."

- **Celgene's Thalomid (thalidomide).** A speaker said there is no conclusion yet that the combination of thalidomide and carboplatin is promising. He commented, "It is very doubtful indeed." A trial also is ongoing in Stage 3 patients comparing thalidomide to tamoxifen. Then, if tamoxifen is the winner, another trial will compare tamoxifen and Avastin. If thalidomide is the winner, it may then be tested against Revlimid.

- **Cell Therapeutics' CT-2103 (polyglutamate paclitaxel)**, which is in Phase III development. Doctors were optimistic about this agent. An expert said, "It can be given in a short period of time without pre-medication, so the incidence of hypersensitivity is quite low, and it doesn't cause alopecia. But the response is not too impressive (14% in platinum-sensitive patients, and 7% in platinum-resistant patients). Although the significant toxicity is 15%, it is still a drug of interest." A U.S. doctor said, "Patients have been seen in complete remission in the trial, which is powered for survival." A U.K. doctor said, "I can't predict the outcome, but I think this will be useful. It could miss the endpoint, and still have an effect."

- **Genentech**
  - **Avastin (bevacizumab).** A U.S. expert described Avastin as "probably the most interesting agent." The Phase II GOG-170-D trial of single agent Avastin is ongoing in the U.S. The trial is measuring six-month PFS, objective response, and overall

survival. Responses reportedly have been seen in that trial, and the results are expected this year. GOG-218, a three-arm, placebo-controlled, Phase III trial comparing Taxol+carboplatin+Avastin to Taxol+carboplatin is expected to start soon, enrolling ~500-600 patients.

- **Omnitarg (pertuzumab, 2C4)**

➢ **MILLENNIUM'S Velcade (bortezomib).** This is in Phase I in combination with carboplatin, and a speaker described it as "promising," with 8 of 12 patients responding in a Phase I trial.

➢ **SANOFI-AVENTIS'S Eloxatin (oxaliplatin).** A Dutch doctor said, "Oxaliplatin has come a long way…This agent, which was barred from the U.S. market for so long, has found a place." A Belgian doctor said, "Don't underestimate the neurotoxicity (with Eloxatin). There is ~20% neurotoxicity. Sanofi is working on a neuroprotective agent, and should have data in one or two years. The company is not pursuing Eloxatin in ovarian cancer because the data are not strong enough."

➢ **TELIK'S Telcyta (TLK-286).** TLK-286 was described as "of major interest." A source said, "It is tolerable (with the side effects fatigue, dysuria, and urinary frequency)…and the Phase II response rate was 15%."

- *Will Telcyta work in any of the three ongoing trials?* Doctors are dubious. A U.S. doctor warned, "The bar is set very high. They are looking for a huge difference." A U.K. investigator said, "It is promising, the concept is interesting, and we are seeing CA125 responses, but it is too early to tell if the drug will work in any of the three ongoing trials…But the bar may be too high. The drug may work but the trial fail. We all agree on this." A Belgian doctor described Telcyta as "very promising," saying, "I want to see the outcome with platinum, which is not in the Phase III trials. I wonder why the Phase III trial was designed the way it was…The drug is reasonably well tolerated…It could miss the primary endpoint and still be valuable."
- *What is the method of action?* One expert said, "TLK-286 works by inhibiting chemoresistance." Another said, "TLK-286 mainly overcomes platinum resistance – that's the reason for interest in it."
- *When is the data expected?* A Belgian doctor said, "The data won't be available for 1.5 years – until the end of 2006."
- *Will the ultimate use be monotherapy or combination therapy?* Sources generally believe it will work in combination with a platinum.

➢ **Anthracyclines.** A French doctor said, "Anthracyclines are not dead yet (in ovarian cancer). It is too early to say that."

➢ **Epothilones:**

- **Bristol-Myers Squibb's BMS-247550**
- **Novartis's NVS-906.** A speaker described this as interesting, but noted there has been some GI toxicity.
- **Kosan/Roche's KOS-862**

➢ **Small molecules – Iressa, Tarceva, and PFIZER'S CI-1033 –** in combination with chemotherapy. A expert said, "In preclinical studies there is a clear indication that combining these agents with chemotherapy has an increased effect. In small studies in the clinic, when combined with traditional ovarian cancer agents, we can draw no conclusions about them besides the fact that they are tolerable and show the typical side effects (skin, diarrhea, etc.)…Combining them with hormones (tamoxifen) also might be useful for some patients."

Among the small molecule studies planned or underway is a Phase II trial of Taxol+Erbitux x 6 which has started. Investigators expect to see a response, but the concern is whether there is any added toxicity from Erbitux. This trial is a prelude to a randomized clinical trial.

➢ **Matrix metalloproteinase inhibitors,** including Bayer's BAY-129566 which showed no improvement in overall survival. A speaker said, "These are not very promising yet, though there is still hope…but even in consolidation and maintenance therapy, they don't seem to have an impact."

➢ **Vascular toxins,** such as combrestatin.

PANCREATIC CANCER

LILLY'S Gemzar (gemcitabine)

A speaker emphasized, "Doublets improve survival, but there is no benefit to adding a third drug (triplets)…But there is evidence in a meta-analysis (of ~4,500 patients from 13 trials) to be published soon in JCO that found no significant survival difference using modern drugs like gemcitabine without platinum vs. platinum containing combinations."

Japanese Study Presented at ASCO 2004

Endpoint	Gemcitabine+ cisplatin	Irinotecan+ cisplatin	Paclitaxel+ carboplatin	Vinorelbine+ cisplatin	p-value
Median survival	14.8 months	14.2 months	12.3 months	11.4 months	Nss
One-year survival	59.6%	59.2%	51%	48.3%	Nss

GENENTECH'S Tarceva (erlotinib)

About 75% of pancreatic cancer patients go on to second-line therapy, and that is generally irinotecan+docetaxel. Pancreatic cancer is highly thrombogenic, and heparin is one strategy being discussed to reduce the added thrombogenic risk from the addition of targeted therapies. A California doctor said, "We are doing a trial with heparin in ~50 patients to get a good assessment of DVT – if we see it, and whether there is any increase in bleeding complications." Another U.S. doctor said, "I think the addition of heparin will lower morbidity and mortality as well as DVTs."

A new target for therapy of pancreatic cancer is Hedgehog (Hh) signaling. Researchers found that Hh signaling is active in human pancreatic adenocarcinoma cell lines. Synthetic inhibitors of Hh are in development.

Data presented at the ASCO Gastrointestinal Cancer Symposium showed that Tarceva+chemotherapy improves survival in patients with locally advanced or metastatic pancreatic cancer, but there was no excitement about this at ICACT. A U.S. doctor said, "I hope it is a positive effect, but the difference is so small as to not be clinically meaningful. The value of the drug may be more in combination with an anti-angiogenesis agent (e.g., Avastin) rather than gemcitabine …Perhaps a regimen of gemcitabine+Avastin+Tarceva or gemcitabine+Avastin+Erbitux…Tarceva will be explored with other agents in pancreatic cancer. Tarceva has the same target, but I'm not sure the same treatment effect. We learned from Iressa that it is very difficult to identify the right patient. It is good for some patients but not all patients." Another U.S. doctor said, "There is a small incremental response (to Tarceva in pancreatic cancer), but is it worthwhile to buy a small amount of time without changing overall survival in a disease with such a poor prognosis?"

PROSTATE CANCER

DENDREON'S Provenge

There was no discussion of this investigational vaccine at ICACT, but since the Phase III data from the D-9902-A trial is expected to be presented at the ASCO 2005 Prostate Cancer Symposium in Orlando on February 19, 2005, a discussion of the outlook for this product is being included here. This vaccine may eventually gain FDA approval through the Special Protocol Assessment (SPA) when Study D-9902-B is completed, but it appears unlikely that the company can get approval based on Studies D-9901-A and D-9902-A.

There are three key trials of Provenge:

- **D-9901-A.** In 2001, Dendreon announced that this 129-patient Phase III trial missed its primary endpoint, TTP at six months. Final three-year results were reported in October 2004, and they will be presented at the ASCO 2005 Prostate Cancer Symposium. With ~100% follow-up, there was a statistically significant benefit in overall survival at that point (3 years) in the intent-to-treat population. Survival was ***not*** a pre-specified secondary endpoint in that trial, but the FDA did require the company to follow patients for three years. At three years, TTP for patients with a Gleason <7 was also statistically significantly better with Provenge than placebo ($p<.05$).
- **D-9902-A.** This was a double-blind, placebo-controlled, Phase III trial in asymptomatic, metastatic, androgen-independent prostate cancer. When the six-month results of Study D-9901-A were reported, enrollment in this trial, which had been intended as a confirmatory study to the D-9901-A trial, was stopped (in 2002) at 98 patients, instead of the planned 125 patients. In January 2005, Dendreon announced that this trial also missed its primary endpoint – time to disease progression – in both the overall group and in the Gleason score subgroups (e.g., Gleason <7). Overall survival was a secondary endpoint, and there was a trend to survival, but it was not statistically significant. There was some concern that this trial was underpowered because enrollment was stopped early.
- **D-9902-B.** Enrollment in this trial is nearing completion with ~125 patients with a Gleason <7. There are three primary endpoints: TTP, time to bone pain, and overall survival. This trial is being conducted under an FDA Special Protocol Assessment (SPA). Dendreon amended the D-9902-A protocol to become this pivotal Phase III study.

Even though survival generally trumps everything, there are three key issues that lead to the conclusion that Dendreon will need Study D-9902-B or another study for approval of Provenge:

1. The survival analysis in D-9901-A was not pre-specified. Post-hoc analyses, no matter how well done, are viewed skeptically by statisticians and the FDA. Since there is additional data coming shortly (D-9902-B), the FDA can afford to wait for that.
2. This is a first-in-class product.
3. The FDA does not consider TTP at six months as a valid surrogate endpoint for survival. The survival data itself are more important, and there was no statistically significant survival benefit in D-9902-A. So, the positive survival data in D-9901-A are not confirmed. This means there is, at best, one trial with survival data. The FDA is rather adamant that data be replicated to be validated.

According to Rajeshwari Sridhara, Ph.D., Team Leader, Division of Biometrics 1, Office of Biostatistics, CDER, FDA, if there are two endpoints in a clinical trial, they are considered as co-primary endpoints. "Allocation of type I error rate for each of the test of hypotheses is necessary to maintain an overall type I error rate not to exceed a set limit.

One may consider closed testing procedure which generally does not require this type of adjustment."

Renal Cell Carcinoma

Bayer/Onyx's BAY-43-9006

Doctors described BAY-43-9006 and Pfizer's SU-11248 as fairly comparable. Sources believe BAY-43-9006 will show both a TTP benefit and a survival benefit.

Pfizer's SU-11248

Shortly after ICACT, Pfizer confirmed that the Phase III trial of SU-11248, an oral FLT3 inhibitor, in gastrointestinal stromal tumors (GIST) was halted seven months early because it showed both safety and efficacy. Pfizer said patients on the placebo will now have the option of taking SU-11248.

Data to Watch

Late breaker Phase III trials expected to be reported at ASCO 2005:

- **Cell Therapeutics' Xyotax** – STELLAR-3 and STELLAR-4.
- **Genentech's Tarceva** – single agent trial in NSCLC. (The presenter will be Dr. Thierry Le Chevalier of France.)
- **Genentech's Avastin** – ECOG-4599.
- **ImClone/Bristol-Myers Squibb's Erbitux** – Intergroup Study No. 147. This study in Stage 3 CRC compares FOLFOX vs. FOLFIRI vs. FOLFOX followed by FOLFIRI – all ± Erbitux. This trial started in April 2004, and so far 345 of the planned 4,800 patients have been randomized. Researchers are concerned the trial will be affected by the results of PETACC-3. A speaker said, "PETACC-3 could cause one arm to be dropped and another to be reconsidered."
- **Ligand's Targretin** – SPIRIT-1 and SPIRIT-2 trials.
- **Novartis's valatanib (PTK-787).** Sources said the CONFIRM-1 and CONFIRM-2 trials are complete, and the data will be presented at ASCO 2005.
- **Pfizer's SU-11248.** Doctors at ICACT said they are expecting more details from a Phase III study in GIST.
- **Sanofi-Aventis's Eloxatin** – NSABP-C07. This is a study of LV5FU ± oxaliplatin (FLOX) in 2,492 CRC patients randomized into this study. Researchers expect 675 events, and by the end of December 2004 had >600. The trial has 89% power to detect a 5.4% improvement in disease-free survival at three years.
- PETACC-3 (the Pan-European Trial in Adjuvant Colon Cancer), which compares LV5FU vs. FOLFIRI. A speaker said, "The results will be important if they meet the primary endpoint."

Other data to watch:

- **Genentech's Avastin**
  - NSABP-C08 trial. The trial should be complete in 2007.
  - AVANT trial BO17920 in Stage 2-3 disease. Patients are randomized to FOLFOX4 vs. FOLFOX4+Avastin vs. XELOX+Avastin. This trial opened in January 2005, and 20 of 2,450 patients have been enrolled so far.
- **Genentech's Herceptin (trastuzumab).** A speaker said, "In the U.S. one-third to 40% of node positive women (with breast cancer) are getting dose-dense paclitaxel right now. If the Herceptin trials are positive, what clinicians then have to face is a difficult choice because the trials all use Q3 chemotherapy, and they will have to (1) be conservative and use standard chemotherapy with Herceptin, (2) use dose-dense paclitaxel and deny Herceptin, or (3) put them together in the clinic and assume that is okay, which is the least favorite choice. You can't assume that."
  - The HERA trial in Europe is nearly finished, and data are expected soon.
  - NSABP B-31 and NCCTG-9831 trials should finish accrual in May or June 2005…The NCI reportedly plans to combine these two trials for analysis.
  - Pilot study of dose-dense paclitaxel and Herceptin. This study started January 15, 2005, and eight patients of the 70 planned have been enrolled so far. Patients get standard ACPCL every two weeks and then Herceptin for 52 weeks. Researchers will be looking at cardiotoxicity, and even one cardiac death would make the trial a failure. An investigator said, "When you give an anthracycline and monitor ejection fraction (EF), there are asymptomatic EF declines."

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