Trends-in-Medicine

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By Lynne Peterson

SUMMARY

- Oncologists raised questions about the efficacy of AstraZeneca's Iressa, but most believe that it will be approved.
- Doctors are dubious about the outlook for Genta's Genasense in melanoma, multiple myeloma or CLL.
- Novartis, Kosan Biosciences and Schering AG all have promising epothilones, but Bristol-Myers Squibb appears to have toxicity problems with its epothilone.
- Anti-angiogenesis agents are still alive, with the small molecules looking more promising than the antibodies.
- Farnesyl-transferase inhibitors also are alive but perhaps not well, with Schering Plough's Sarasar in the lead.
- New formulations of Taxol got a lot of attention, but the field is getting crowded and doctors are not sure yet of the clinical value of these agents.

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The most exciting agents are "interventions that are mechanistically-based, like (Novartis') Gleevec," the new head of the National Cancer Institute told delegates. He believes the best endpoints for cancer trials are "biologic correlates," saying, "We need to move to an approval process based on efficacy in altering critically important pathways in disease, so we don't have to wait for survival data -- like the Gleevec approach – as long as safety is shown. Efficacy is the real driving factor." He also favors a "Systems Biology" approach to future drug development, with heavy dependence on bioinformatics.

Regulatory Issues

The current FDA is being very strict on the use of single-arm trials, a speaker warned. Another source said, "The FDA loves patients as their own control, so I see that increasing." An FDA official said, "It is no secret that for the past six or seven years, initial approval of a lot of cancer drugs has been on single arm, Phase II studies, with the patient the control, looking at tumor growth. We've been willing to approve drugs in that setting based on the tumor response rate. We declared quite a long time ago that we thought it reasonable to make that an endpoint for refractory disease, and we are prepared to approve drugs on the basis of response rate. There is no minimum required response, just what is medically meaningful. In some cases that is about 10%. The bigger the better, but 10% in CRC can be enough."

Promising New Agents

Allos Therapeutics' RSR-13, a synthetic allosteris modifier of hemoglobin, which raises the ability of red blood cells to release oxygen, especially to tumors. This radiosensitizes the tumors, strengthening the therapeutic impact of radiation in solid tumors, where pockets of hypoxia would otherwise decrease the effectiveness of radiation. The drug has attracted some negative press due to illicit use by athletes hoping to improve their endurance. He described this as "a fascinating drug that may sensitize for chemotherapy and platinum, too."

American Bioscience/American Pharmaceutical Partners' ABI-007, a new formulation of an established agent – a cremophor-free formulation of nano-particle paclitaxel encapsulated in human serum albumin. The speaker said, "I never thought I would see this because new formulations of established agents are very, very difficult." In a Phase I trial it was dosed either q3w or weekly, and the DLT was neutropenia. No pre-medication was necessary.

Reportedly, there has been good response in patients with metastatic breast cancer. The speaker said, "Our experience was dramatic. We had a man with breast cancer and tremendous liver mets, and the liver mets cleared up, and he is alive

and well a year later. We also had a woman with lung cancer who had a very dramatic response. This drug has a long way to go, but the results so far have been pretty dramatic…(Initially) I wasn't anxious to take this into trials, but I was surprised that it worked in 8-cycle taxane-refractory patients. We need to watch the peripheral neuropathy with this agent."

AstraZeneca's Iressa. A speaker said, "While most people say cytostatic agents can't shrink tumors, every cytostatic agent we are working with can shrink tumors, and sometimes rather dramatically, with time."

BioChem Pharma's Troxatyl (troxacitabine, BCH-4556), a dioxolane nucleoside analog, still appears to be alive.

Eli Lilly's Alimta (LY-231514) Phase II data at ASCO is expected to be positive.

GlaxoSmithKline's GW-506U78 (nelarabine), an analog of guanasine, for pediatric lymphomas. The DLT in a Phase I trial was described as "disturbing" – coma, seizures, somnolence, encephalopathy – but apparently that has been reduced via dosing changes. In very refractory patients, there was 31% OR in T-ALL, 54% OR in adult T-ALL, and 18% OR in other T-cell diseases as well as "some miraculous responses."

Ilex's Clofarex (clofarabine, an adenosine analog), which has shown activity in pediatric and adult acute leukemia. He said, "It is a little tough to make, but it is incredibly specific for CRC in animals. Pediatric oncologists like it because it can be given IV or oral. I'd like to do a Phase I trial in CRC."

Johnson & Johnson/PharmaMar's ET-743. He said this clearly has been shown to have activity, "It is the only transcriptive factor to work so far."

ProlX Pharmaceuticals' PX-12. This is in early trials in Pittsburgh and Tucson, and he recommends keeping an eye on this.

Telik's TLK-286 and its competitor, **Pharmacia's PNY-166196** (brostallicin). He pointed to a documented partial response in NSCLC. He also said, "Daily times 5 dosing is an easy regimen. There is some cystitis, so that's not the best schedule. Weekly at a three-times higher dose is better. There has been enough hint of activity with this agent to continue development."

An expert predicted that some unnamed, large Phase III trial "will fall flat." To determine which one, he suggested looking at the Phase II endpoints used in a trial, with particular attention to:

- The criteria used to measure stable disease.
- Whether the trial was multi-institutional.
- Response rates, which should be >20%.
- Percent of non-progressors at four months.
- The number of patients in the trial, with a minimum of 55 preferred.
- How long the stable disease lasted. "If it is 30%-40% for more than four months, then it is starting to be interesting. Cytostatic agents in need to show 30%-40% SD at four months. Cytotoxic agents need to show >20% SD in ovarian cancer, but 5%-7% might be okay in CRC."

Three other agents also were mentioned as promising, but perhaps not quite as promising as the ones listed above:

1. Antigenics' Oncophage (HSPPC-96), an autologous melanoma heat shock protein vaccine. He said, "The company is doing a nice trial. The downside is the time this trial is taking."

2. Aphton's Gastrimmune, a vaccine made from an immunogenic form of gastrin-17. He described this as "a clever immunizer against growth factor." He also said, "We want to try this at our center (with or without gemcitabine). The animal data is fascinating – aging animals don't get tumors (though 30% should get them). Gastric and pancreas studies are underway, and maybe we will do a CRC study. One study was stopped for skin problems, but it is back on track now."

3. G-Quadruplexes. These got a big push at the last two AACR meetings (March and October 2001), but there was little discussion of them at this meeting. A speaker said, "Telomastatin from Japan is incredible. It is a fabulous molecule. This is a hot field, but there is no intellectual property around this." G-Quadruplexes are specialized DNA sequences (3-D knots) that may be able to down regulate the expression of the cancer gene, c-myc. The lead compound was thought to be an agent licensed to **Cyternex,** a privately-held biotech firm, which was expected to start clinical trials in the spring of 2003.

Challenges to Drug Development

The two key challenges to drug development going forward were identified as:

1. Developing drugs targeted at mutated genes. A speaker said, "Not many investigators are paying attention to deleted or mutated genes. An approach that may have great results is a synthetic lethal screening methodology."

2. Obtaining a lead against a new target without screening the entire Amazon jungle. One answer is using a TRAP assay, which is "affinity fingerprinting" and only requires evaluating about 200 compounds. This method uses a "training set" of 60 compounds against the protein target (using the lab's current assay system) to identify a starter molecule.

Increased Pharma Focus on Oncology

Several companies are increasing their efforts in oncology, particularly Eli Lilly and AstraZeneca. AstraZeneca had a

recruiting booth within its exhibit space and was actively seeking oncology researchers, particularly medicinal chemists, who officials said are in short supply right now. They were passing out a brochure with a picture of the company's new research facility near Boston on one side and job postings on the other. Officials said the company is increasing its R&D in oncology.

Anti-Angiogenesis

In contrast to the very negative attitude at last fall's AACR meeting in Miami toward anti-angiogenesis agents, researchers here emphasized that these agents are still alive, though they are likely to work only in combination with other chemotherapeutic agents. There are more than 200 research programs going on with at least 80 agents in clinical trials. A researcher said, "I like the anti-VEGFs. There is some hint of activity with the antibodies, but verdict is still out on the antibodies; the small molecules may be better...Some people have become negative about anti-angiogenesis. We need to be quite selective and ask key questions early on to narrow the field before clinical trials are initiated…We are taking this approach: adding an anti-angiogenic agent to chemotherapy and treating to maximal response. Then, we use the anti-angiogenic agent as maintenance therapy. If this works, it would be an important advance."

Small molecules	Antibodies
AstraZeneca's ZD-6474	Genentech's Avastin
Novartis' PTK-787	Genentech's rhuMab2C4
Cephalon's CEP-7055	Celgene's Thalomid (thalidomide)
Pfizer's CP-547632	
Pharmacia/Sugen's SU-6668	

Aeterna's Neovastat, which is made from the spine of the dogfish shark, is in Phase III trials.

AGO13736, which entered a Phase I trial this month.

Entremed's Endostatin. A speaker said the expectations for this agent were too high, but development is continuing. Two different forms of administration are currently being investigated – continuous infusions and subcutaneous injections.

Genentech

> **rhuMab2C4.** A Phase I trial started about five months ago.

> **Avastin.** This antibody reportedly is associated with hypertension, proteinuria and bleeding. A combination trial of Hoffmann-La Roche's Xeloda (capecitabine) and Avastin in breast cancer completed enrollment in December 2001.

Pfizer's CP-547632, which targets VEGF, is in an ongoing Phase I trial.

Pharmacia/Sugen's SU-6668. An expert made some comments suggesting there may be a PK problem with this, but he didn't elaborate.

TAP Pharmaceuticals' TNP-470. There was only one response in 270 patients tested in Phase I trials with this IV agent, and the drug had toxicities, but researchers have found a synergistic effect when administered with cyclophosphamide and Taxol. A speaker said, "Now, we were planning an advanced lung cancer study of chemotherapy+TNP, and we were excited that this would go to Phase III, but in October 2001, TAP made a business decision not to pursue the drug any further because the field is moving to oral agents. Some effort is being made to get NCI to take it back."

Antisense

Genta's Genasense (G-3139) is the key agent in this category. The announcement that Aventis is joint venturing with Genta on this came after the AACR meeting. Genta has three Phase III Genasense trials underway – one in melanoma, one in multiple myeloma and one in CLL, but most sources were not optimistic that it will prove effective in any of these. All three trials were expected to be completed by May 2002, but enrollment in the melanoma trial has been expanded from 270 patients to 450 patients, so that trial may take longer. There also were rumors at the meeting that the CLL trial has been having trouble enrolling and that one major cancer center participating in the trial has turned away patients.

- A Genasense researcher said, "If there is any role for Genasense, it will be in combination therapy. I heard it is not working in melanoma. It may be more effective as a sensitizer for Rituxan, particularly in AIDS patients and transplant lymphomas. We're about to launch a trial in low grade lymphoma patients who fail after two to four cycles of Rituxan."
- Another Genasense researcher believes European regulatory officials are dubious about this agent, "The MCA went so far as to make Genta prove that airline flights don't hurt the drug during shipping. Genasense is made in Scotland and in the U.S., and the U.K. trial is using a U.S. batch. The thinking is that it may show some benefit, but definitely not a lot. Investigators are really upset with the company because of (a) the data, and (b) inviting them to meetings and not telling them the meetings are cancelled until after they get there."

In addition, doctors at the meeting were very concerned about the company's statement that it will release only the results of the best of these three trials, keeping the others confidential. One called that "unethical."

Genta officials have claimed that Genasense works by immune modulation, not BLC2 down regulation, and a study by an Austrian researcher not connected to the company appeared to support that. In his study, mice were given a modified Genasense (with a methyl group was substituted for

a CPG motif), standard Genasense and saline. In the saline group, BCL2 was not affected, but in both the modified and unmodified Genasense groups, BCL2 was reduced by 60%. So, the effect does appear to be immunostimulation.

This same Austrian mouse study also showed spleen enlargement with Genasense, but the researcher said that should not be a problem in humans. He explained, "In mice the immune response is greater than in people, so I don't expect a problem in humans – and it never has been a problem in humans."

Aromatase Inhibitors (AIs)

Novartis' Femara (letrozole, CGS-20267) and AstraZeneca's Arimidex (anastrazole). AstraZeneca announced just after the AACR meeting that the FDA granted Priority Review (fast-track status) for its application to use Arimidex to treat early stage breast cancer (adjuvant setting) in postmenopausal women. Arimidex already is approved as a first-line therapy for advanced or metastatic breast cancer in post-menopausal women. Novartis' Femara (letrozole, CGS-20267) also is approved as a first-line treatment for postmeno-pausal women with hormone receptor positive or hormone receptor unknown, advanced or metastatic breast cancer.

The basis for AstraZeneca's sNDA filing was an interim (30-month) analysis of the five-year, 9,300-patient, multi-center (US and international) ATAC (Arimidex and Tamoxifen, Alone or in Combination) trial of postmenopausal women with early breast cancer. AstraZeneca released the interim data from ATAC at the San Antonio Breast meeting in December 2001, and the company filed a supplemental New Drug Application (sNDA) with the FDA in March 2002 based on that data. ATAC started in 1996, and patients were followed for a median of 33.3 months, with a median duration of treatment of 30.7 months. The trial compared tamoxifen alone (20 mg qd), Arimidex alone (1 mg qd) or a combination of the two therapies. Patients entered the trial after surgery, radiation and/or chemotherapy. The primary endpoints were disease-free survival and safety.

ATAC researchers reported a 17% reduction in the risk of breast cancer recurrence with Arimidex treatment compared with tamoxifen. In the Arimidex group, 10.1% of women relapsed or died, compared to 12.2% in the tamoxifen group, a statistically significant difference (p=.0129). The reduction in the risk of recurrence was a statistically significant 22% in women with confirmed hormone-sensitive tumors with Arimidex, compared to tamoxifen. On the secondary endpoint of contralateral breast cancer, there was a 58% reduction with Arimidex over tamoxifen. The study found no difference in efficacy between tamoxifen alone and the combination of Arimidex and tamoxifen.

Novartis also is pursuing an indication for Femara in the adjuvant setting, which it considers "a big deal because of the Arimidex data." However, Novartis is significantly behind AstraZeneca. It has started a Phase III trial of Femara in the adjuvant setting, but that trial is still accruing patients. A key official said, "There is no way for us to rush the data. We just hope we can pick up some off-label use and then get marketor other share back later, after we get the indication." The earliest there is likely to be any preliminary data from the second interim analysis of this trial will be the San Antonio Breast meeting in December 2003, but Novartis is planning for a 2004 filing and launch of the adjuvant use of Femara.

Some sources think AstraZeneca is rushing its program in the adjuvant setting. There was some criticism of the use of interim data for the sNDA. For example, a National Cancer Institute (NCI) researcher commented, "I don't think AstraZeneca should have submitted Arimidex for adjuvant use based on the ATAC data. I think they should have done more trials first."

Novartis officials admitted Arimidex has been taking some market share from Femara since the ATAC data came out, and they expect that to continue for some time. They predicted that Femara would begin to regain market share through off-label use once its adjuvant data is presented at a major medical meeting, and they expect Femara to become the market leader once Femara also gains FDA approval in the adjuvant setting. A Novartis official said, "The ATAC – data has already increased Arimidex sales, and it has caused people to switch from Femara to Arimidex. We expect that to continue."

Even before data or FDA approval of Femara in the adjuvant setting, there is some reason to believe that Femara will be used off-label in lieu of Arimidex, based on "class effect" attitudes. Many doctors currently prefer Femara to Arimidex in advanced and metastatic breast cancer.

- A California oncologist said: "I prefer Femara to Arimidex. I currently use it for all tamoxifen failures, and I've used it in some adjuvant cases."
- A New York oncologist said: "In six months, 70%-80% of ER+ breast cancer patients will be on aromatase inhibitors because the side effect profile and efficacy are better than tamoxifen (AstraZeneca's Nolvadex). I prefer Femara because to date it has shown better results. Usually the duration of response to these agents is 8-10 months, so I use one, and then the other. I'm more likely to start with Femara because studies have shown its superiority, and there is no difference in side effect profile, but I may use Arimidex when patients stop responding to Femara."
- A Georgia oncologist said, "I use both Arimidex and Femara. In the metastatic setting, they are very equivalent. In the adjuvant setting, there is more data for Arimidex, so it may be superior to Femara in the adjuvant setting. Right now, my use is pretty even, but Arimidex may take the lead in the adjuvant setting, but stay the same in metastatic breast cancer."

- A New England oncologist said, "I use Arimidex mostly and not much Femara, but I haven't started using either in adjuvant. It is very tempting, but most of the recommendations are to hold off. We were part of ATAC, and that data is still preliminary, very early, and many studies look good early and then converge at another year. Also, there is a little concern of Arimidex side effects – like serious osteoporosis – with long term administration. If the FDA approves Arimidex, then it will rapidly become used."

EGFRs

There are numerous EGFRs in development, and they can be divided into two categories – small molecules and monoclonal antibodies. An expert said, "There is no question that all the EGFR's have activity, but quick and dirty trial designs hurt the whole field. Iressa and Tarceva have very good trial designs. Even if their trial designs are negative, you have to stay with these agents."

Leading Small Molecules

Leading Small Molecules	EGFR specificity and Reversibility	Status
AstraZeneca's Iressa (ZD-1879)	Specific and reversible	Phase III completed
OSI's Tarceva (OSI-774)	Specific and reversible	Phase II completed
Wyeth's EKB-569	Specific and irreversible	Phase I completed
Novartis' PKI-166	Specific and reversible, oral	Phase I
Pfizer's CI-1033	PanHER-irreversible	Phase I
GlaxoSmithKline's GW-2016	PanHER-reversible	Phase I

AstraZeneca's Iressa (ZD-1839) took the lead position when the FDA refused to accept the filing for Imclone's Erbitux (C-225). Most sources said they would like to see Iressa approved, and none were concerned about relying on quality of life data, but questions have been raised about its approvability. Several experts – including Iressa researchers – have said the efficacy rate is really about 10%, not the 18.9% reported in the Phase II European/Japanese IDEAL 1 trial in monotherapy in non-small cell lung cancer (NSCLC).

The data from a Phase II trial being run by the National Cancer Institute (NCI) in head & neck cancer and data from the Phase II the U.S. IDEAL 2 monotherapy NSCLC trial will be presented at ASCO 2002. There have been rumors that the efficacy in IDEAL 2 will be ~12%, but most experts at the meeting said they believe that the drug is approvable even if the efficacy is only 10%. However, many sources said it might not be approvable if the efficacy in the Phase III trial is less than 10%. An investigator disagreed, saying, "If IDEAL 2 is more than 10%, then I think it is approvable even if the Phase III trial doesn't show a benefit. Maybe then we use it in Stage 1, 2 or 3 disease."

Sources believe the Phase III INTACT 1-2 data will be critical to Iressa's approval, even though the FDA filing was based on the Phase II IDEAL 1 and 2 data. AstraZeneca's decision not to present any data Phase III at the Society for Clinical Oncology (ASCO) meeting in May 2002 raised a lot of questions about that data and became a big topic of discussion among doctors at the meeting. ASCO had accepted an AstraZeneca abstract on INTACT, the 2,135-patient Phase III combination therapy trials in head & neck cancer, for presentation at a plenary session. INTACT 1 was a US trial, and INTACT2 a rest-of-world trial. An AstraZeneca official defended the decision, saying the data was not ready yet, "We had a blank (place) holding spot, but that data won't be ready. We still don't have that data. INTACT1-2 are on same schedule." An ASCO official said, "It is a specious argument. AstraZeneca should have presented." An investigator said, "The data was due to be analyzed when a certain number of deaths – 750 or so – had occurred, and they haven't had those yet. So, presenting the data would mean stopping the trial early. The idea to present was ambitious. They were hoping to see the events. They wanted to try, but ASCO let them withdraw. To give the data would break the blind. They didn't stop the trial at the last stopping point, so the results are not overwhelmingly positive, but I am still very hopeful."

Furthermore, AstraZeneca has not yet completed its filing for Iressa; the manufacturing data still has not been filed. This is raising questions about whether there is a manufacturing – or other – problem.

Iressa also is being tested in combination with Herceptin in a Phase III trial. A Canadian researcher said, "There is no synergy and no additive effect in this model. We are lowering the dose to see if we will find the additive effect other trials found." Another expert said, "Combining Tarceva and Herceptin will not lower Herceptin use. They are additive, not synergistic."

OSI/Genentech's **Tarceva** (OSI-774) is in Phase III trials. A Phase II trial also is underway combining it with Herceptin in breast cancer (and one site is Henry Ford Hospital). An investigator said, "OSI774 seems to be enrolling pretty quickly. I predict that enrollment will finish in the next three to four months."

Monoclonal Antibodies

Abgenix's ABX-EGF, which has a binding affinity 40x higher than C-225. This translates to lower doses and less frequent dosing. Reportedly, 90% of patients get a skin rash at 2 mg/kg, compared to 70% of patients who get a rash with C-225. ABX-EGF also is reported to have a better safety profile than C-225. Currently, five Phase II trials are under-way including trials in NSCLC, renal cancer, CRC and hormone refractory prostate cancer.

EMD Pharmaceuticals' EMD-7200.

Imclone's Erbitux (C-225). A reporter with The Cancer Letter insisted that his publication did not get the FDA's Refusal to File (RTF) letter on C-225 from an FDA staffer. An investigator said, "C225 is already coming back. There is not a single investigator who worked with it who doesn't believe it works. The company cut corners and is paying the price, and it has to get its act together."

Medirex's MDX210 and **MDX-447.**

Farnesyntransferase Inhibitors (FTIs)

An expert said, "The FTIs are a fascinating story. This was an incredibly rational way to go about drug development…but we need to better understand how they work." Another researcher said, "It is clear these won't work for everyone. We need to find which patients will respond." A third source said, "FTIs definitely have activity in leukemia, but I'm not sure what else. They all have some myelosupression – we saw that in the Phase I trials. They are alive, but I'm not sure how well they are."

Three agents dominate this area, ranked by sources in order:

1. **Schering Plough's Sarasar** (lonafarnib, SCH-66336).
2. **Johnson & Johnson's Zarnestra** (R-115777), an oral agent. In mice, this Phase III b.i.d. agent looked wonderful – shrinking tumors without serious toxicity -- but reportedly there is a 15% incidence of myelosuppression. A speaker said, "In every patient who took the drug, the molecular target was hit. Farnesyltransferase was inhibited regardless of response, but only 30% of patients responded." Another source said, "Myelosuppression is the main toxicity, but it is reversible." The issues to watch are QT prolongation and myelosuppresion.
3. **Bristol-Myers Squibb's BMS-214662**. A Bristol official suggested that this agent "may be a little disappointing."

Epothilones

Issues	Bristol-Myers Squibb's BMS-247550	Bristol-Myers Squibb's BMS-310705	Novartis' EPO-906	Kosan's KOS-862	Schering AG's 2K-EPO
Type	Epothilone B	Epothilone B	Epothilone B	Epothilone D	Epothilone B analog
Natural	Partially	Partially	Yes	Yes, fully	No, totally synthetic
Distinguishing featurs	Has a nitrogen ring instead of one oxygen ring.	Reportedly more water soluble and fewer side effects than BMS-247550.	N/A	Has no nitrogen, but has a methyl group in an open position.	
Status	Phase II at ASCO 2002. Phase III was due to start in 2002 but additional Phase II trials may be required or this may be dropped for follow-on compound, BMS-310705.	Phase I just started.	Phase I started in early 2002 in Europe and US. Phase II to start summer 2002. There is a backup compound in pre-clinical stage.	Phase I ongoing. Another Phase I began in May 2002 in advanced solid tumors. Phase II to start in early 2003.	Phase I just starting.
IP status	Patented	N/A	No patient on compound, just method of use.	Patented	Method of use patent.
Manufacturing issues	Reported, Bristol is "beating the heck out of its process group to make this cheaper."	N/A	N/A	Easy and relatively cheap to produce by fermentation.	More complex to produce but the company claims to have perfected the necessary steps for scalability.
Issues	1. Neurotoxicity in animals and in the clinic. An official said, "We are learning to deal with it in the clinic, to manage it." However, this appears to be a cumulative problem. 2. Multidrug resistance. 3. Dosin. It is being tested in different regimens (q3w, qw) and doses.	N/A	No neurotoxicity seen in animals or humans.	No neurotoxicity seen in animals or humans. Dosing is still not resolved. In the first Phase I, KOS-862 is admin-istered q3w IV. In the second Phase I, administration is qdx3 every 3 weeks.	1. No neurotoxicity seen in animals (no human data yet). 2. Researchers claim it has little or no multi-drug resistance. 3. Reportedly, a larger therapeutic window than the Bristol drug, so you can give a lower dose ($1/10^{th}$).

mTOR Inhibitors

Ariad Pharmaceuticals' AP23573. This is another analog of rapamycin that is scheduled to enter the clinic later this year. Tumors that lack PTEN (e.g., glioblastoma, prostate, and pancreas) are most sensitive to this compound. A company official said, "In mice, we showed a reduced rate of tumor growth and in some cases regression of tumor. We are looking at both injected and oral administration. We dosed intermittently (once a week or 5 times every two weeks) and still got a tumor effect, but avoided the immunosuppression side effect that occurs with daily dosing and which is undesirable in a cancer setting." Asked how this agent differs from CI-779, he said, "CI-779 is a prodrug, and ours is not, and that may have certain benefits that will come out in clinical studies in terms of the kinetics of the effect."

Wyeth's CI-779, an analog of rapamycin administered IV. Reportedly it has shown an OR of 15%-20% in Phase II trials. Several sources pointed to this as a very promising agent.

Taxols

Among new formulations of Taxol (paclitaxel) in development are:

American Pharmaceutical Partners' ABI-007, a nano-particle paclitaxel encapsulated in human serum albumin. A competitor (NOTE: Sonus) said, "It looks as if there is a lot of neuro and ocular toxicity with this (30%-35% neuropathy in Phase I at 300 mg/m^2)." A researcher said, "There are two Phase II trials underway in about 100 patients. We are starting another Phase II in the next month looking at taxane failures. So far, at the 30 mg dose, there have been 40% responses (3 out of 7 evaluable patients, probably PR and not CR) in taxane failures."

Bristol-Myers Squibb's BMS-184476. There was no data on this Phase II agent at the meeting, but there will be data at ASCO 2002.

Cell Therapeutics' CT-2103, a polygulutnated-paclitaxel (PG-TXL). A researcher for a competitor warned that if any new toxicity (e.g., skin or ocular) showed up, it would set the efficacy hurdle very, very high. The FDA is telling us that any big study in breast, NSCLC or ovarian cancer will require a positive control with a survival endpoint." The company has indicated that clinical trials had to be redesigned, so FDA approval now is unlikely before 2005.

OSI

> **lurtotecan** (OSI-211, formerly a GlaxoSmithKline agent and then Gilead's NX211). This is the first liposomal camptothecin analog made totally by synthesis; the others are semi-synthetic. This is in Phase II trials in small cell lung cancer and ovarian cancer. Apparently, the company is changing to a more frequent dosing schedule.

> **OSI-7994L,** a liposomal formulation of a thymidylate synthase inhibitor, that is in Phase I trials.

Sonus Pharmaceuticals' S-8184, a vitamin E paclitaxel emulsion with a p.glycoprotein inhibitor with a longer half-life than Taxol (20.1 hour at 225 mg/m^2 v. 13.1 hours). There was a lot of traffic at a poster on this agent, and interest appeared high. Current administration is q3w by IV push. The MDT is 175 mg/m^2, and researchers insisted they have not seen any unusual toxicity, though one patient at 225 mg/m^2 had Grade 3 neuropathy on the fifth cycle. Antihistamines are being given for flushing. So far, seven Phase I patients have shown stable disease lasting out to three or more months.

Four single-arm Phase II trials (testing 175 and 200 mg/m2 with weekly dosing) have just started – in ovarian, NSCLC, bladder cancer and CRC – to look for tumor response against the published Taxol response. All of these are being conducted in Russia by a CRO, and an official explained, "The FDA said it wants tumor response in taxane-naïve patients for a clean comparison, and we think Russian is best for that. We expect to complete 150 patients by year-end. We will do two Phase II trials for our pivotal data, one in Russia and one in the US in carbo (etc.) failures vs. Taxol. " Another official said, "After 15 patients, we will decide whether to (1) continue enrollment, (2) add a control arm, (3) bring the trials back to the U.S., (4) start a combination trial, or (5) start a U.S. salvage study.

Sonus officials pointed to Cell Therapeutics as the primary competitor. One of the key differences between these drugs is that S-8184 is active, and CT-2103 needs to be enzymatically cleaved when it goes into the cell to become active. One said, "I watch CT-2103 more than the others because the company is six to 12 months ahead of us. The issues with CT-2103 are: neurotoxicity and enzymatic cleavage to release the drug. How will they dose it so patients get a consistent dose? We think we could have a manufacturing cost advantage down the road, and we have pre-filled syringes, while liposomes require reconstitutions, which might give us an advantage."

Tauchi's Protaxel, a paclitaxel prodrug. It currently is a cremophor formulation, but the company is working on a non-cremophor formulation.

Other Companies and Agents Worth Watching

Genentech's Herceptin (trastuxumab). Trials combining Herceptin with either Iressa or Tarceva are ongoing. Doctors were asked if it is likely that the dose of Herceptin will be able to be reduced with either of these combinations, and they all

said that this will not happen in the clinical trials and they doubted it would happen in clinical practice either.

Hoffman-La Roche's Ro31-7453, an oral cell cycle inhibitor is in Phase II trials in Europe and U.S. in solid tumors in combination with gemcitabine.

Immusol. Reportedly, Novartis has "heavily" partnered with this company and thinks it has very good technology.

Kosan has several agents in development, including:

> **KOS-862**, an epothilone. Kosan does not have the financial ability to take this agent past Phase IIa and is looking for a partner now. One possibility is Johnson & Johnson, with whom Kosan is working on antibiotics.
> A GI motility drug in preclinical development.
> An FK-506 analog. Kosan reportedly is in discussion with a stent company for use of this agent on a drug-eluting stent.
> A rapamycin analogy for drug-eluting stents.

Millennium Pharmaceuticals

> **PS-341:** An expert said, "I think it will be held to the same rigorous standard as thalidomide….There has been an enrollment problem in multiple myeloma, but people (oncologists) want this. The issue is neurotoxicity."
> **CT-53518**, a Flt3. IRB approvals are being obtained now for a Phase I trial in AML, so that should start soon.

Pfizer's PD-173955, a tyrosine kinase inhibitor that potentially would compete with Novartis' Gleevec (STI-571). Memorial Sloan Kettering researchers have been trying to convince Pfizer to develop this – or sell it so someone else can. No new information on this agent was found at the meeting.

Pfizer/Agouron's AG-2037, an antifolate in human clinical trials. The company is investigating two dosing regimens: (1) qw administration with high doses and no folate supplementation, and (2) q3w administration with lower doses. A researcher noted that an earlier antifolate (Lilly's lometrexole) given q3w killed patients. The side effects to watch with AG-2037 are thrombocytopenia and neutropenia.

Novartis has an aggressive oncology research program underway. Some of the key agents appear to be:

- EPO-906, an epothilone B
- Tyrosine protein kinase inhibitors:
  - PKI-166.
  - EGFR-kinase, which is in Phase II development.
  - PKI-166, a VEGFr kinase in Phase II trials.
- XAA296 DDM
- RAD001, an mTOR inhibitor (a rapamycin analog) in Phase I trials.
- LAF389, a synthetic analog of bengamide B, a marine sponge, a methionine aminopeptidase inhibitor for refractory malignancies. In early studies, there was no reported response and blurred vision side effect, but the company is continuing to pursue this agent.
- PTK787
- SMT487A, somatosatin analog in Phase II.
- PKC412A, a Flt3 inhibitor in Phase II.
- ICL670A, the first oral iron chelator.

Sankyo's TRA-8, a fully human monoclonal antibody that showed a striking anti-tumor effect in mice when administered with paclitaxel or adriamycin, and human breast cancer trials may start within the next 12 months. A researcher said, "There have been impressive, complete regressions, and it may have advantages over TRAIL."

TelikTLK-286. There was a lot of interest in this prodrug, and trials are underway as single agent monotherapy in very refractory patients with a variety of solid tumors, including ovarian, CRC, NSCLC and breast cancer. Administration has been q3w, but researchers are moving to qw. A researcher said, "There is a mild tox profile and documented antitumor activity. We are working with different schedules to get more drug in. This is a very interesting agent."

A company official said Telik expects to be talking with the FDA by summer 2003 about starting a randomized Phase III trial in the tumor type in which the best response has been seen by then. It has not yet been determined whether this agent is orally active. To determine how well this agent is performing, a researcher suggested watching for stable disease that lasts at least four months and warned that an OR <10% would be a concern.

Telik also has TLK-199, an agent to treat low white blood cell counts that occur as a toxic side effect of chemotherapy and certain other conditions, in Phase I trials. ♦