Trends-in-Medicine

December 2006

by Lynne Peterson

SUMMARY

There wasn't a lot of breaking news at the EORTC meeting, but there was an interesting finding in ALL that could have implications for development of new therapies in that cancer. ♦ Combinations of targeted therapies and angiogenesis inhibitors got a push, but not without some controversy. ♦ The aurora kinase inhibitors getting attention were Millennium's MLN-8054, Nerviano's PHA-739358, and SuperGen's MP-529. ♦ Despite the challenges, telomerase remains an attractive target for cancer therapy. ♦ mTOR inhibitors are looking promising in cancer as well as immunosuppression, but there were reports of pneumonitis with Novartis's everolimus. ♦ Praecis Pharmaceuticals' PPI-2458, a MetAP-2 inhibitor, and Hana Biosciences' Talvesta (talotrexin) were particularly interesting. ♦ A variety of other drugs and approaches were featured, including: MEK inhibitors, oral taxanes, TKIs, anti-ROS, a non-polyglutamable antifolate, AKT inhibitors, heat shock protein (HSP) inhibitors, and kinesin spindle protein (KSP) inhibitors.

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC)

Prague, Czech Republic
November 7-10, 2006

The hot topics at EORTC were angiogenesis inhibitors and combinations of targeted therapies, but immunotherapy for melanoma, aurora kinase inhibitors, and telomerase inhibitors also attracted attention. Dr. Roy Herbst of MD Anderson said, "Angiogenesis as a target is moving beyond VEGF, and that is exciting…We are moving to targeting angiogenesis and thinking of tumors in more complex ways."

ANTI-ANGIOGENESIS AND COMBINATIONS OF MONOCLONAL ANTIBODIES OR SMALL MOLECULES

A National Cancer Institute official called this a "very big field," noting that there are currently 138 Phase I, 258 Phase II-III, and 59 Phase III trials underway with anti-angiogenesis agents. More than 30 agents are in NCI trials. At EORTC, a large percentage of the abstracts were on angiogenesis.

GENENTECH/ROCHE'S Avastin (bevacizumab)

Experts were not at all concerned about a Roche trial that found Avastin works with XELOX – Xeloda (capecitabine) plus Sanofi-Aventis's Eloxatin (oxaliplatin) – but not with FOLFOX (oxaliplatin, 5-FU, and leucovorin), in metastatic colorectal cancer. They called it a "statistical anomaly" that would not affect use of either FOLFOX or Xeloda.

Avastin in renal cell carcinoma (RCC)

An MD Anderson researcher reported that in 33 of 50 patients in the first trial of Avastin given pre-surgically in RCC, it was both safe and efficacious. Avastin was administered at a dose of 10 mg/kg IV for 4 cycles, and then Genentech's Tarceva (erlotinib) was administered orally daily for 8 weeks. After the 33 patients, investigators decided to stop the Tarceva because of another study that showed it had no benefit and added some toxicity. Dr. Eric Jonasch of MD Anderson Cancer Center said, "The key question of treating before nephrectomy is that we know nephrectomy improves survival modestly…The concern is that by delaying life-prolonging nephrectomy, you might be jeopardizing a patient's well being, and our data so far do not bear that out. It looks like this is overall doing very well."

Of the 33 initial patients, 25 were assessable by EORTC: 12% partial response (PR), 72% stable disease (SD), and 16% progressive disease (PD). One patient

showed CR in the target lesion and SD in a non-target lesion (bone). Two patients did not undergo surgery due to PD. Actuarially, PFS was 16 months, which compares to 6 months for Bayer's Nexavar (sorafenib) and 11 months for Pfizer's Sutent (sunitinib). There were no perioperative complications directly attributable to Avastin, but one patient developed a pulmonary embolism (PE) in the post-operative period. Another patient developed a delayed post-op site infection and ultimately died of complications, and three patients had mild wound healing problems.

Asked if he is using Avastin routinely off-label in RCC, Dr. Jonasch said, "No, not routinely. Reimbursement is an issue. Individuals who progress on sorafenib and Sutent will sometimes be placed on Avastin, and sometimes we see responses in those patients." However, he said his colleagues around the country are using Avastin off-label in RCC wherever it is reimbursed by Medicare or other payors.

Combination therapy

Experts were urging combinations of monoclonal antibodies – without suggesting how healthcare systems will pay for it. European doctors generally shook their head at the idea, in large part because of the high cost of this approach, but American investigators were more enthusiastic. Dr. Herbst said, "Combination therapy is feasible if it is personalized combination therapy…If we can develop a sense for which tumors respond to which agents, we can develop a cocktail… like the HIV cocktail (HAART)…All that combinations do, in my opinion, is make drugs that probably have specificity in some patients more applicable to the unselected population… Most patients are unselected today…but ultimately if we can select, then we will find a specific cocktail for any patient."

Combinations that were discussed by speakers included:

- **GENENTECH/ROCHE'S Herceptin (trastuzumab)** and **Omnitarg (pertuzumab).** Dr. Jose Baselga of Spain, President-elect of the European Society for Medical Oncology (ESMO), noted that the combination of anti-HER2 antibodies and small molecule TKIs results in improved clinical activity in HER2+ breast cancer. Another speaker agreed, saying that this combination is at least additive and probably synergistic in cell lines and in animals, so the combination has moved into clinical trials, and there may be data on this "very shortly."

- **GLAXOSMITHKLINE'S Tykerb (lapatinib)** and **Herceptin.** This may be synergistic and should be tried in combination, a speaker suggested.

- **Avastin** and **Erbitux.**

- **Avastin** and **Herceptin.** Updated data on a Phase I study of this combination will be presented in December 2006 at the San Antonio Breast Cancer Symposium.

- **ASTRAZENECA'S Iressa (gefitinib)** and **IMCLONE'S Erbitux (cetuximab).** His center is doing this study in colorectal cancer (CRC), head & neck cancer, and non-small cell lung cancer (NSCLC) patients who did not respond to standard therapy, and so far they have successfully escalated to the optimal dose of each without any significant toxicity. Of the 43 patients enrolled so far, 40 were evaluable, and he said it was interesting that the skin toxicity was not greater with the combination that would have been expected with either agent alone. He said PK studies showed independence of clearance, and no significant PK mutual influences of both agents. His conclusion: The combination is feasible, and there is encouraging clinical activity in advanced CRC and head & neck cancer.

Dr. Stephen Kelsey, Senior Group Director of BioOncology at Genentech, predicted that monoclonal antibodies will be combined more frequently in the future. He argued that most of these are extremely target specific, generally have invariable exposure/PK, no CYP issues, no bioavailability issues, and no or few compliance issues. He said that intuitively you wouldn't think two monoclonal antibodies would have any PK interaction, and that is what you see. For example, there is no interaction at all between Avastin and Herceptin once you get above the 2 mg/kg dose. Asked about the cost, he said, "All I can say is that if we are going to start doing this, which we will, then inevitably we have to find a value in it. I leave you to find the value yourself…The cost implications may be no different than for other novel therapies."

Advantages and Disadvantages of Combining Monoclonal Antibodies

Measurement	Positive	Negative
Efficacy	• Cross-lining of single target • Evidence that both targets are implicated in the disease process • Increasing understanding of interaction between RTKs	• Big molecules • Potential for steric interference
Specificity	Avoid off-target toxicities	Need more than one for more than one target
Cost	---	A big issue

Asked if preclinical safety tests should be done before combining monoclonal antibodies, Dr. Kelsey said, "In general, we have not chosen to perform preclinical tests of toxicity using combinations of any targeted therapies on the general basis that the results of any preclinical toxicity are of some utility but limited interpretability…and often you get information you wished you hadn't gotten. There are some reasons to do preclinical testing, some unique toxicities, and so some programs are amenable to that, but in the main we do not do that and rely instead on formal early stage clinical testing."

Asked if most combination tests are of approved or investigational agents, Dr. Kelsey said, "Most regulators, and certainly those in the U.S., will require a fairly comprehensive clinical safety package on an investigational agent alone before allowing combination testing…You need to understand the safety of the investigational agent first…The way we do drug development is not optimal, and there are certainly combinations we can put together earlier, but I don't think it will avoid getting a pretty thorough safety analysis first."

Asked if the need for combination therapy says the single agent is not as active as it could be, Dr. Kelsey said, "When you need two drugs against the same target, it is quite clear neither alone is doing the job properly…There obviously is leakiness in the system, and the more we shut down the pathway the better."

A poster by Novartis researchers reviewed the potential for combining everolimus (RAD-001) with Herceptin in breast cancer. They found that the combination showed enhanced antitumor effect in a mouse model, and they concluded that the combination "may have application in the treatment of ErbB2-overexpressing breast cancer patients."

Dr. Jean-Charles Soria of France tried to inject a clinical viewpoint into the discussion of combining tyrosine kinase inhibitors (TKIs) such as Tarceva and everolimus vs. developing multi-targeted TKIs. He said the key issues are:

- **Structural and chemical issues.** He argued there is not a single target TKI.
- **Metabolic implications.** He suggested that several TKIs might result in interaction at the level of absorption or metabolism, with CYP3A4 interactions.
- **Toxicity.** He insisted that targeting multiple kinases comes at a cost in terms of side effects, and he urged preclinical evaluations of TKI combinations before human testing, saying this may help avoid unexpected toxicity.
- **Efficacy.** He suggested there are two totally different situations that need to be distinguished:
  1. Where the tumor has a specific kinase-driven oncogenesis. The best approach here, he said, is a monotarget TKI with the lowest IC_{50}.
  2. Where the tumor has an unknown kinase-driven oncogenesis. Here he argued that the best approach may depend on the situations.

Comparison of the Cocktail Approach vs. a Multi-Targeted TKI

Measurement	Cocktail	Multi-targeted TKI
Specificity	Better	---
Toxicity	Better	---
Efficacy	Advantage to each	
Resistance	Better	---
Regulatory factor	---	Easier
Mechanism	---	Better

- **Resistance mechanism.** Suboptimal exposure of a specific target (i.e., poor IC_{50}) can lead to resistance. He used the analogy of antibiotics to point out that it is difficult to create one drug with optimal potency against several targets, and he suggested one way to overcome this may be to use a front-line cocktail that might delay or avoid resistance instead of a sequential approach.
- **Pragmatic issues.** Convincing companies to do a combined trial is difficult, there are intellectual property issues in combining agents, regulatory issues are likely to be challenging, and cost is a factor.

Dr. Mark Ratain of the University of Chicago discussed some of the issues in combining a "blockbuster" drug and a "wonderdrug." He said there are usually two hypotheses for the combination:

- Both have clinical activity, and the combination is hypothesized to have at least additive efficacy.
- Wonderdrug is hypothesized to sensitize or overcome resistance.

He pointed out that preclinical studies are not useful for anti-angiogenic agents, but PK/PD studies are important. He said, "If there is no PK or PD interaction, Phase I would show the ability to deliver full doses of both drugs, and Phase II/III would show if there is increased efficacy…I don't think we always need to do Phase I of Blockbuster + Wonderdrug – if PK interaction is unlikely from *in vitro* studies or knowledge of the metabolism and transport of both drugs, ***or*** if the *in vitro* hematotoxicity studies show no effect of Wonderdrug, ***or*** full dosing of both agents appears tolerable based on preclinical *in vivo* studies."

If there is a possible PK interaction, then Dr. Ratain suggested designing a Phase I trial to test the hypothesis. If there is a possible PD interaction, he recommended a formal Phase I test for the relationship of the Wonderdrug dose to the magnitude of effect or the toxicity of the Blockbuster, "I suggest using a full dose of the Blockbuster and do not simply count DLTs (dose-limiting toxicities) as these will occur by chance in the absence of the Wonderdrug at a full dose of the Blockbuster …And you might inappropriately conclude the combination is not feasible…Consider randomized Phase I design."

If there is no PK or PD interaction suspected or found, he proposed that, rather than a formal Phase I, testing the safety of a full dose of the combination as the initial part of the Phase II study, "The Phase II dogma is that the goal is to make a preliminary assessment of activity, and the historical design is intended to screen out drugs that do not meet a threshold level of activity…That is ideal for single agent studies, but this design does not work well for combinations for endpoints other than response."

His advice for developing combination therapies: A comparative randomized Phase II trial, which can accept a higher rate of false positives. Ideally, this is blinded, possibly

dose ranging, and of short duration (~six weeks). At progression, he would unblind the patient, then allow combination therapy (crossover) if the patient is not already receiving it. This approach would make for shorter and smaller trials (perhaps 30-50 patients per arm). He recommended only going forward in Phase III if it is positive, as opposed to "not negative."

MEDAREX/BRISTOL-MYERS SQUIBB'S Ipilimumab (MDX-0101, an anti-CTLA-4)

Dr. Jason Chesney, Associate Director of Translational Research at the James Graham Brown Cancer Center at the University of Louisville, called the outlook for this in ovarian cancer "promising." Dr. Jeffrey Weber of the University of Southern California/Norris Cancer Center tested increasing doses of MDX-0101 plus a vaccine. He reported autoimmune breakthrough events in 25 patients – and 13 of these had Grade II/III colitis, rash, or hypophysitis (inflammation of the pituitary gland), while 8 had dose-limiting events. He concluded that autoimmune breakthrough events are the best correlate of response.

AURORA KINASE INHIBITORS

Is an aurora-A, an aurora-B, or a broad aurora kinase inhibitor targeting A, B, and C better? The answer, for now, depends on whom you ask. There is no consensus among experts. Aurora kinases are proteins involved in regulating cell division (mitosis), which is uncontrolled in cancer. High levels are found in breast, bladder, colon, ovarian, lung, prostate, gastric, and pancreatic cancers. Among the comments on aurora kinase inhibitors were:

- "The only thing that is certain is that C is not important… Whether A is more important than B is not certain, though A is more oncogenic than B in preclinical models."
- "We want one that makes a tumor shrink, but you can't look at the data (on aurora kinases to date) and not be underwhelmed, to be polite…We know we want to inhibit A, but it will be interesting to see if a broad aurora kinase is better…Aurora A is overexpressed in pancreatic, breast, and prostate cancer, but 90% of colorectal cancers have amplification of A or B or both."
- "Combining an aurora kinase with a taxane could be interesting."

There are a raft of aurora kinase inhibitors in development, but the ones that are generating the most attention appear to be:

➢ **MILLENNIUM PHARMACEUTICALS' MLN-8054.** This is a selective, oral aurora-A inhibitor currently in Phase I. A poster was presented on MLN-8054 given BID in advanced animal models of prostate bone metastasis and disseminated NHL. Researchers found a dose of 30 mg/kg BID protected against bone loss and a 10 mg/kg BID dose protected partially. A researcher said, "I can't say an aurora-A is better than an aurora-B, but our compound focuses on aurora-A. It has high specificity for aurora-A, but both aurora-A and aurora-B are important."

➢ **NERVIANO MEDICAL SCIENCES' PHA-739358.** This is a broad-spectrum small molecule aurora kinase inhibitor, with more aurora-B effect. In preclinical studies PHA-739358 showed tumor shrinkage in solid tumors.

At EORTC, researchers reported on the first 36 patients in a Phase I study in advanced solid tumors that were progressing with standard of care. The drug was infused over a six-hour period on Days 1, 8, and 15 every four weeks. No responses were seen, but stabilization of disease (SD) was observed in 7 patients (lasting >7 months for 4 patients, and >1 year for one of these). Adverse effects included: reduction of white blood cells and mild-to-moderate diarrhea, nausea, vomiting, loss of appetite, and blood pressure increase. The DLT is neutropenia. Seven doses have been tried, and 330 mg/m^2 appears to be the recommended dose.

The next step is to reduce the time of the infusions to make it more convenient for patients, so another Phase I is planned with a three-hour infusion on Days 1, 2, and 3 every two weeks in hematologic malignancies. After these, Phase II studies will be undertaken, probably at a dose of 500 mg/m^2 without use of G-CSF.

➢ **SUPERGEN'S MP-529.** This is a selective aurora-A inhibitor. SuperGen is focusing on pancreatic cancer, which over-expresses aurora-A. An expert said SuperGen has "sort of a goal in pancreatic cancer," and that's why it is focusing on that. The company presented preclinical data on MP-529 at EORTC.

LEUKEMIA

A post-doc molecular biologist from Australia reported on an interesting finding in **acute lymphoblastic leukemia (ALL)** that could have implications for development of new therapies in that cancer. Currently, combination therapy cures about 80% of patients. Virtually all patients respond initially to chemotherapy, but ALL recurs in up to 25% of patients, and it is a lot harder to treat the second time because it is more resistant to chemotherapy. Seoyeon Choi, the post-doc, found that in resistant patients, a second clone was present at initial diagnosis, but in much lower levels than the primary clone, and it is that second clone which is responsible for the drug resistance. Thus, new therapies, or a slightly altered version of current therapy, are needed to target the second clone.

A different speaker, Dr. Dominique Bonnet of the U.K., suggested that current therapies for acute myelogenous leukemia (AML) may spare the leukemia stem cells, which may account for recurrence. He said, "Leukemia stem cells may subvert normal stem cell functions to evade cancer therapies…The leukemic stem cell is the critical target in AML therapy…There is a growing body of evidence that

differences in biology between leukemic stem cells and hemopoetic stem cells may be exploited for therapeutic benefit."

MERCK/VERTEX'S MK-0457 (formerly VX-680). Yet another expert pointed to this agent as something to watch. He said, "It is a marvelous inhibitor of T315I – the key mutation in chronic myeloid leukemia (CML) that is resistant to Novartis's Gleevec (imatinib) – and there have been data in CML and AML."

TELOMERASE INHIBITORS AND TELOMERE TARGETING AGENTS

Telomerase is an attractive target for cancer therapy, but the time it takes to see an effect with them means they require prolonged exposure, and that has been seen as a somewhat "negative" feature of – and a challenge in developing – them. In contrast, the telomere targeting agents have indirect effects but act more quickly. An expert said all these agents probably have dual mechanism of action – a fast and a slow pathway, and he noted that it is critically important to have some readout of the initial telomere length at the outset of therapy. These agents possess stand-alone *in vitro* anti-tumor activity in mice, and they also may have synergy with cytotoxic agents such as cisplatin.

BOEHRINGER INGELHEIM'S BIBR-1532, a telomerase inhibitor. A speaker said, "It takes 50-100 days to see an elevation from control. One can see *in vivo* a small effect, but only when cells are penetrated *in vitro* for 10 days."

CHONG KEUN DANG'S CKD-601, a telomerase inhibitor from a Korean company.

GERON'S GRN-163L, a telomerase inhibitor. This is probably the most advanced compound. It is now in Phase I in chronic lymphocytic leukemia (CLL) and, more recently, in solid tumors.

PHARMINOX'S RHPS4, a telomere targeting agent. Unpublished data were discussed that RHPS4 inhibits cell growth in breast and ovarian cell lines. A speaker called that data "exciting," saying, "In particular in breast cancer it had a really pronounced effect in two of five animals." Currently, RHPS4 is in preclinical development, dosed IV daily.

BRACO19, a telomere targeting agent. This is being investigated as both a single agent and in combination with paclitaxel, and an effect is starting to be seen as early as 6-7 days. However, a May 2006 article in the journal ***Pharmaceutical Research*** concluded that BRACO19 has very poor permeability, suggesting that "further applications will require a suitable formulation to warrant adequate delivery across cellular barriers."

Telomestatin. This was described as "probably the most potent telomerase inhibitor."

MTOR INHIBITORS

mTOR inhibitors are being found to have expanded uses far beyond immunosuppression for transplant patients. For instance, an expert said, "There are intriguing hints of activity with Novartis's everolimus plus Gleevec in GIST…It is an oversimplification, though, to say it is an mTOR class effect."

ARIAD'S AP-23573

An expert who has worked with this mTOR inhibitor in sarcoma said he is "very excited" about it, "The company is still struggling with how best to develop it and prove its value. The strategy has been to find a sensitive subtype, but I'm not sure we can identify that. So, do we have to do a large study? Probably, that's what we have to do. And I think we can do it if all the (sarcoma) doctors (consortiums) get together on this – and they are doing that."

NOVARTIS'S everolimus (RAD-001)

A researcher said he would give everolimus upfront with Herceptin or Tykerb as well as add it in Herceptin and Tykerb failures – but he would not replace Herceptin or Tykerb with an mTOR.

Canadian researchers reported on a multicenter, randomized, Phase II study in advanced breast cancer which found that everolimus has activity as a single agent that is potentially schedule-dependent, but there was an excess of pneumonitis, and a researcher suggested the pneumonitis is an mTOR class effect. A central radiology review of the pneumonitis cases is being done. A researcher said, "We are working on what the mechanism is for pneumonitis. It probably is mechanistic, but it could vary by dosage and schedule."

Everolimus Phase II Results in Advanced Breast Cancer

Measurement	Arm A 10 mg/day n=18	Arm B 70 mg/week n=16
CR	0	0
PR	3 patients	0
SD	8 patients	4 patients
Discontinued for toxicity	3 pneumonitis 1 CHF	1 pneumonitis 1 fatigue
Conclusion	Met criteria for expansion	No further study
Pneumonitis	61%	19%
Grade 3 pneumonitis	11%	0
Grade 4 pneumonitis	0	0

In the meantime, the protocol was modified:

- Baseline high-resolution CT of the chest is being done in all patients with a repeat at ≤8 weeks.

- Asymptomatic or mild pneumonitis patients may continue treatment with observations and pulmonary function tests (PFTs).
- Grade 2 pneumonitis patients have treatment suspended until the pneumonitis becomes Grade 1 or lower, and a dose reduction to 5 mg/day ± a low dose oral steroid is considered.
- Grade 3 pneumonitis patients have treatment suspended until the pneumonitis becomes Grade 1. Patients who recover to that level within two weeks may resume treatment at 5 mg with PFTs and bronchoscopy.
- Grade 4 pneumonitis patients are removed from the trial and treated as if they had Grade 3 pneumonitis.

WYETH

➢ **Rapamune (rapamycin).** A poster suggested that rapamycin may reverse breast cancer-acquired auto-resistance to Tykerb – and perhaps Herceptin. It was not the purpose of the study to demonstrate this, but that was the conclusion several experts drew after reading the poster.

➢ **Temsirolimus.** This is an IV formulation, but a researcher defended that mode of administration, saying, "IV may have advantages over oral mTORs in terms of compliance, higher peak concentrations, and possible QW dosing may have safety benefits that you don't have with chronic daily dosing." He said they have seen only very sporadic pneumonitis, and do not expect that to be a problem. An investigator-initiated sarcoma trial is starting.

OTHER SPECIFIC DRUGS AND AGENTS TO WATCH

ASTRAZENECA

➢ **AZD-2171 – an oral tyrosine kinase inhibitor**

Studies of AZD-2171 in combination with carboplatin, with paclitaxel, and with Iressa have been completed. Development programs in NSCLC and CRC are planned, and the company is currently assessing it in combination with other chemotherapy regimens. A speaker said the PK profile supports once daily oral dosing, and the drug is well tolerated up to 45 mg/day. There is a dose-depending PD effect on tumor size.

➢ **ZD-6244 (ARRY-142886) – a MEK inhibitor**

The MEK pathway is involved in up to half of all human tumors. In human tumor cell lines, ZD-6244 is a highly potent and selective uncompetitive inhibitor of MEK1/2. Dr. Alex Adjei of Roswell Park Cancer Center reported on a 9-patient Phase Ib PK/PD study in melanoma. One patient who had three cycles of the drug had 100% inhibition of pERK and 70% reduction of target lesions – but not non-target lesion progression in the brain. He concluded, ZD-6244 is well tolerated, showed substantial target inhibition in tumor tissue, and the dose for Phase II should be 100 mg BID. Multiple Phase II studies already are underway, and in 6 of 20 Phase II patients, there has been sustained clinical benefit (SD≥5 months). The side effects of ZD-6244 are diarrhea, rash, and some fluid retention and nausea, but no vomiting. Dr. Adjei's conclusion: In Phase I it looks promising, but Phase II results are needed to see if any other toxicity develops and if there is clinically significant efficacy. The earliest there will be any Phase II results is probably in a year.

BOEHRINGER INGELHEIM

➢ **BIBF-1120 – an oral triple angiokinase inhibitor**

➢ **BIBF-2992 – an oral irreversible dual EGFR/HER2 inhibitor**

➢ **BI-2536 – an oral Plk1 inhibitor**

BRISTOL-MYERS SQUIBB

➢ **Sprycel (dasatinib) – an oral tyrosine kinase inhibitor.** This was recently approved by the FDA to treat CML, but it is being investigated in solid tumors, either as a single agent or in combination with chemotherapy. A Bristol-Myers Squibb official said, "It is not meant to decrease the tumor but to stop proliferation. Dasatinib has a lot of potential to prevent metastases."

What about combining Sprycel with a mTOR inhibitor? The Bristol-Myers official said they don't know yet if that makes sense.

➢ **BMS-275183 – an oral taxane.** In Phase I studies, it showed activity in prostate cancer and NSCLC with weekly administration, but twice-weekly (BIW) administration appears better tolerated, with less neuropathy. At EORTC, a poster reported on a 17-patient extension of the Phase I 100 mg/m^2 twice-weekly schedule – which is the dose that will be used in Phase II – in advanced solid tumors refractory to standard therapy. As expected, neutropenia and neuropathy were the DLTs, but it was less with twice-weekly administration (Any Grade 53% BIW vs. 65% QW; Grade ≤1 78% BIW vs. 15% QW).

COLBY PHARMACEUTICALS' MDL-72,527 – an anti-ROS for prostate cancer

Is there an agent that could replace anti-androgen therapy for men with prostate cancer? Maybe. Hirak Basu PhD, Chief Scientific Officer at Colby Pharmaceuticals, said Colby's MDL-72,527 blocks androgen-induced ROS (reactive-oxygen species) production in prostate cancer cells. It was the first report on specific enzyme inhibition of androgen-induced oxidative stress in the prostate preventing spontaneous tumor development. Dr. Basu said treatment with MDL-72,527 delays prostate tumor development in mice – and increases the survival of transgenic mice that develop spontaneous prostate

tumors, "No one has reported any compound which extends mouse life 10-12 weeks longer than the usual 22 weeks."

Phase I trials are expected to start in 12-18 months. The maximum tolerated dose (MTD) is 100 mg/day. The goal is to develop this as a therapy for naïve patients. Dr. Basu said, "We are promoting this as a tamoxifen for prostate cancer…Initially (prostate cancer) patients get radiation or surgery, and those who are high risk get anti-androgen therapy. We expect this will replace that (anti-androgen therapy). It would replace anti-androgen therapy after surgery."

EXELIXIS

This company appears to have a strong portfolio, and sources were especially impressed with the potential for the company's MEK inhibitor in lung, ovarian, and breast cancer. A source said, "They are listening to the clinical investigators…I would do lung next."

HANA BIOSCIENCES' Talvesta (talotrexin) – a non-polyglutamable antifolate

Two Phase I trials were undertaken with this injectable agent targeting DHFR to prevent DNA synthesis in tumor cells and to inhibit tumor growth: one in the U.S., which is not yet finished, and an international trial. The company presented additional data from a completed, international Phase I trial in NSCLC. In addition to NSCLC, Talvesta is being tested in ALL and solid tumors.

International Phase I Trial of Talotrexin in NSCLC

Measurement	13.5 mg/m^2	27 mg/m^2	54 mg/m^2	90 mg/m^2	135 mg/m^2
C_{max}	2.6	8.2	17.4	23.3	33.5
T_{max}	0.1	0.1	0.1	0.2	0.1
$T_{1/2}$	4.7 hours	7.0 hours	6.1 hours	6.7 hours	6.8 hours
AUC (ng.h/L)	7.0	26.8	48.6	82.9	92.7
CR	0				
PR	8% (2 of 26 patients)				
SD≥4 cycles	31% (8 of 26 patients)				
PD	38% (10 of 26 patients)				
Death	19% (5 of 26 patients)				
Not-evaluable	4% (1 patient)				
Adverse events					
	All grades		**Grade 3-4**		
Anemia	35%		3%		
Leukopenia	12%		3%		
Neutropenia	23%		19%		
Thrombocytopenia	31%		23%		
Anorexia	50%		3%		
Mucositis	50%		31%		
Weakness	35%		12%		
Fatigue	27%		19%		
Dyspnea	19%		8%		
Back pain	15%		8%		
Pneumonia	15%		8%		
Alopecia	12%		0		

The international Phase I study was a dose-escalation trial of a 5 minute IV infusion given on Days 1-8 on a 21 day cycle in Stage III and IV NSCLC patients. Most – but not all – patients got supplementation with folic acid and B-12. Researchers concluded that myelosuppression and mucositis are the DTCs. They also found a linear PK and PR + SD of 38%. They said future PK studies will determine whether diminished renal or hepatic function warrant dose modifications.

In the U.S. trial, the dose continues to be escalated, though the dose had to be reduced in the international trial. A U.S. researcher explained that the international dose reduction may have been site-specific (Russia) and due to a failure to give patients sufficient supportive therapy. He said, "In the U.S. we have taken the dose higher than in the international trial. We are now giving it three weeks out of four, and we have a lot of cohorts because we thought we would see toxicity and we haven't. It is surprising how much we can give. In the international trial when they audited the data from Russia, they had to reduce the dose quite a bit. We didn't have that problem, so we are actually increasing the dose. I think the international trial may have decreased the dose more than necessary. We are giving more drug than they gave in Russia, and we give patients adequate support – folate and B-12. We bolus patients with those, so we don't get off-drug toxicity… There are significant impediments in interpreting data from developing countries."

KERYX'S perifosine – an AKT inhibitor

There weren't any data on perifosine at EORTC, but an expert said, "It is not very potent. Quite a few companies are working on more potent AKT inhibitions…There are three different isoforms of AKT, and perifosine is conspicuously broad on all of them. AKT-1 overexpression in animals produces poor survival. AKT-2 overexpression increases survival, so you want to select for AKT-2, and perifosine is not that selective."

LILLY

Lilly presented preclinical data on an oral prodrug of Gemzar (gemcitabine). It doesn't have a number or name yet, but it is due to start Phase I trials in 2007 in solid tumors.

PRAECIS PHARMACEUTICALS' PPI-2458 – a methionine aminopeptidase-2 (MetAP-2) inhibitor

PPI-2458 is a semi-synthetic derivative of fumagillin. This first-in-class small molecule is orally administered every other day, and it has already shown real promise in animals as a therapy for rheumatoid arthritis (RA). The work

in oncology is very early, but it looks fairly interesting, particularly in non-Hodgkin's lymphoma (NHL) and melanoma, and the safety in oncology does not appear to indicate any problems for RA.

➢ **PPI-2458 in NHL.** In a multicenter, open-label, dose-escalation Phase I trial (Study 2458-04-01), PPI-2458 was given for two 28-day cycles. Patients were allowed to continue treatment, in the absence of unacceptable toxicity, until evidence of disease progression. Interim results were presented for 32 patients at doses from 2 mg to 8 mg, and the trial is continuing with some patients getting up to 12 mg. The MTD has not yet been reached. Seven of the 32 patients had stable disease at the end of the first two treatment cycles (56 days).

Dr. J. Paul Eder of Dana-Farber Cancer Institute is excited about PPI-2458 in cancer, predicting it could lead to a paradigm shift in cancer treatment. However, he said it may take longer to see responses with PPI-2458 because it is a cytostatic agent. In Phase I studies, PPI-2458 appears safe, but Dr. Eder believes higher doses need to be tested for activity. He said, "The soft measure of how long patients are on study for stable disease seems to be getting better as the dose goes up."

Interim Phase I Results with PPI-2458 in Various Cancers

Measurement	2 mg n=9	3 mg n=9	5 mg n=7	8 mg n=7
Completed 2 cycles of treatment	22%	33%	86%	N/A
NHL	44%	0	0	N/A
Head & neck cancer	11%	0	29%	N/A
Ovarian cancer	0	22%	0	N/A
CRC	11%	11%	22%	NA
Average treatment time	~30 days	~41 days	~69 days	~75 days
Response				
Stable disease at Day 56	11%	0	43%	43%
DLTs				
Elevated liver enzymes	11%	0	0	0
Change in nerve conduction	0	0	0	14%
Toxicity (Grade ≥2)				
Abdominal pain	0	11%	0	N/A
Constipation	11%	0	0	N/A
Diarrhea	0	0	14%	N/A
Nausea	0	11%	0	N/A
Vomiting	0	11%	14%	N/A
Fatigue	0	11%	29%	N/A
Asthenia	0	0	14%	N/A
Arthralgia	0	11%	0	N/A
Pain in extremity	0	11%	0	N/A
Dizziness	0	0	14%	N/A
Confusion	0	0	11%	N/A
PK				
C_{max}	2.3 ng/mL	6.5 ng/mL	5.2 ng/mL	N/A
AUC	1.1 hr.ng/mL	5.3 hr.ng/mL	3.9 hr.ng/mL	N/A
Half-life ($T_{1/2}$)	0.3 hours	1.6 hours	1.5 hours	N/A

In Phase III, PPI-2458 will be tested in large cell lymphomas, and Dr. Eder called that "challenging," adding, "Those patients do poorly, and that will be a good test of this drug. You won't wonder in those patients if the drug is working; it's not an indolent disease…In solid tumors, 56 days (the longest time reported at EORTC) doesn't tell you anything, but in large cell lymphoma, patients do poorly and quickly, so you will know early if it is working."

A higher dose will be used in Phase II. Dr. Eder said, "All patients in Phase I were under-dosed. We are up to 12 mg in Phase I. We think 18 mg is the MTD, but we will have to see; it could be higher…We will keep taking the dose up until we get some indication that this is not tolerated."

A Praecis official said that preclinical studies suggested there might be GI side effects and weight loss with PPI-2458, but "that really has not been an issue." The key side effects appear to be:

- **ALT increases.** Dr. Eder said, "I expect we will see some ALT, but it is probably idiosyncratic, and it is reversible, so that is not a show stopper."
- **A drop in blood count.**
- **Fatigue.** This may not be drug-induced.
- **Diarrhea.** In animals, the DLT was diarrhea, and Dr. Eder said this side effect is of the most clinical concern, but it may not be drug-induced.
- **Neuropathy.** This was described as "like cisplatin or paclitaxel." Dr. Eder said, "In animals neuropathy was not clinically observed, but there was evidence of neuropathy on autopsy…There might be a type of neuropathy (in humans)…So all patients will get neurometric testing for the appearance of subclinical toxicity (neuropathy)." The neurometric testing measures latency and conduction through nerves, looking for changes of >15%, which Dr. Eder called a high standard for safety. Only one patient has developed neuropathy, and he is diabetic and previously had oxaliplatin, both of which are associated with neuropathy. That patient did not have symptoms, but he was removed from the study. Dr. Eder added, "If we see that (neuropathy), and if it is significant, it could be the DLT."

An expert not involved in the development of PPI-2458 commented, "Fifty-six days follow-up is not enough to tell us whether this works."

➢ **PPI-2458 in melanoma.** Another study in melanoma cell lines suggested that PPI-2458 may have a novel mechanism of action in melanoma. Gerhard Hannig PhD, a Praecis researcher, presented a poster showing that PPI-2458 decreases the cellular level of microphthalmia-associated transcription factor (MITF) protein, a master regulator of the melanocyte lineage. MITF has been shown to be a melanoma survival

oncogene, and MITF may play a role in the development and progression of melanoma since studies have shown that patients with metastatic melanoma and high MITF levels in tumor tissue tend to have worse overall outcomes than patients with lower MITF levels.

Dr. Hannig said he now wants to try two subclinical doses in melanoma, and see if there is an additive or synergistic effect with Schering Plough's Temodar (temozolomide, TMZ). He said, "PPI-2458 can be monotherapy, but it also may be a chemosensitizer or have a synergistic effect with another drug. PPI-2458 30 mg/kg + TMZ 75 mg/kg should be a good combination to see if there is a benefit to combination therapy."

Dr. Eder called this another very promising area for PPI-2458. He said, "As our basic understanding of the disease (melanoma) increases, we may have a better understanding of what we need to do to make melanoma respond. MITF is important in melanoma, and what is unique is that MITF is a transcription factor, a prime mover…It is a domino that hits other dominos…No one has a drug that targets transcription factor yet in any solid tumor. So, we are proceeding in parallel with the necessary Phase I, getting safety and efficacy data, and the basic researchers are pursuing this. There are very encouraging data so far, but more studies are needed to be sure MITF is the direct target…It is particularly exciting. Antisense failed in melanoma…Here is a small molecule that could be taken as a pill. It is very, very exciting that we might have a truly unique target here…What also is exciting is the effect on melanoma cell differentiation…Here is a drug that seems to induce that activity…It may have a role in stabilizing tumors by changing their fundamental biology. It may not make them regress, but it may keep them from progressing." Dr. Eder said it might also be possible to combine MITF with an mTOR inhibitor or immunotherapy.

➢ **PPI-2458 in RA.** At the Inflammation Research Association meeting in October (See ***Trends-in-Medicine****: Inflammation Research Association*, October 2006), a Praecis official said every-other-day administration at 5 mg/kg and 10 mg/kg completely inhibited MetAP-2. The company hopes to use the safety database in oncology for an aggressive trial program in RA.

For RA, an official said the company will apply for an IND (investigational new drug) using 2 mg, 5 mg, 8 mg, and 12 mg, but the doses that are mostly likely to be the final dose(s) are 5 mg and 8 mg. Asked if the toxicity seen in the oncology data presented at EORTC is low enough to be tolerable by RA patients, Dr. Eder said he was confident it is. Praecis expects to seek an IND in RA in early 2007. The main downside to this drug appears to be a ~25% reduction in blood T-cells, but there is also some diarrhea at the lowest dose, and a decrease in body weight gain in animals.

Small, open-label Phase II trials will be done before a randomized Phase II trial vs. a control. Dr. Eder said, "If we see enough activity in the single-arm studies, then we will expand and randomize, but we need to understand the lower level toxicity for the FDA." A company official added, "The diarrhea and nausea we see are common with antibiotics – they happen to sick patients."

MISCELLANEOUS

Combination therapy. Dr. James Crowell of the National Cancer Institute (NCI) said combination agents may increase efficacy synergistically. For example in breast cancer, preclinical efficacy has been shown with these combinations:

- Tamoxifen + retinoids.
- Tamoxifen + antioxidants.
- Tamoxifen + indole-3-carbinol.
- Ligand Pharmaceuticals' Targretin (bexarotene) + statins.

A speaker from the U.K. suggested another combination for chemoprevention: low dose coxibs plus statins or EGFR inhibitors.

Elongation factor-2 (eEF-2) kinase

This is a new target for anti-cancer drugs. It is based on the idea that some cancer cells survive through autophagy (a "starvation" response). A speaker said that it appears glio-blastoma, for example, is capable of surviving harsh conditions and the onslaught of chemotherapy and radiation by utilizing autophagy to survive, and targeting eEF-2 kinase may make those cancer cells more susceptible.

Epothilones

Four years ago at the American Association for Cancer Research (AACR) meeting, experts were excited about epothilones, but they stalled over toxicity issues. At EORTC, experts generally agreed one or more will eventually make it to market, and they are watching the class, but there was little excitement about any of them. One expert said, "I can't get very interested in them. If we didn't have the taxanes, I might feel differently, but they are just one more tired drug that targets microtubules. They won't be a paradigm shift." Dr. Herbst said, "Epothilones may have a future in breast cancer, but there isn't a lot of room for them. They will come back when we do genomic profiling and can correlate response with specific agents."

Kosan is continuing to develop KOS-1584, and a poster was presented at EORTC on an ongoing dose-ranging trial in solid tumors in which the drug was administered over 1 hour vs. over 3 hours as has been done in previous trials.

Heat Shock protein 90 (HSP90) inhibitors

HSP90 is a protein chaperone that binds to several sets of signaling proteins, known as "client proteins," such as mutated

p53, Bcr-Abl, Raf-1, ErbB2, and other kinases as well as steroid hormone receptors. Disruption of HSP90 protein complexes leads to cancer cell death.

Doctors remain convinced that this class will prove useful. An expert said, "The outlook is very good. There are really exciting signals with these agents…There are small molecules and derivatives that are very interesting." Another expert said, "They (HSP90 inhibitors) have reasonable toxicity…and they don't have much single agent toxicity…We know HSP90 is an important co-factor in many oncogenes...So, they still look promising, but always in combination, not as single agent drugs." A third expert said, "These small molecules have advantages. They are less complicated to make and hard to derivatize…I think Conforma's HSP90 inhibitors are the best at this point." A fourth expert said, "The small molecules are untested in patients. The question is whether they have toxicity."

A German study presented at EORTC found HSP90 inhibitors may be effective in GIST.

There are several HSP90s in development, but the ones getting attention at EORTC were:

- **CONFORMA**
  - **CNF-2024.** This totally synthetic HSP90 is in Phase I.
  - **CNF-1010.** This is a nano-emulsion formulation of 17-AAG.
- **INFINITY PHARMACEUTICALS' IPI-504.** Researchers reported on 14 patients from an ongoing study of IPI-504, a water-soluble HSP90, in metastatic GIST following failure of TKI therapy (Gleevec, Sutent). IPI-504 was infused over 30 minutes IV on Days 1, 4, 8, and 11 of a 21-day cycle.
- **KOSAN**
  - **Tanespimycin (KOS-953).** This is Kosan's lead HSP inhibitor and has been granted orphan drug status in multiple myeloma in the U.S. and Europe. It has completed a Phase I/II trial. Kosan reportedly plans to submit it for use in combination with Millennium Pharmaceuticals' Velcade (bortezomib) in patients having a first relapse.
  - **Alvespimycin (DMAG, KOS-1022).** This second-generation HSP90 is in Phase II as both an oral and an IV agent. This is an oral, water soluble 17-AAG derivative. An expert said that this may not be as hard to synthesize as 17-AAG, but it is still difficult. He also noted that there is some hepatic toxicity. However, in Phase I (reported at ASCO 2006) there were 2 PRs in breast cancer, some minor responses, and "a lot" of SD.
- **ONCOGENICS' OGX-427.** This HSP is being tested in pancreatic cancer as an enhancer for Gemzar.
- **SERENEX'S SNX-5542.** This was described as "a completely different structure" from CNF-2024.

Immunotherapy

While immunotherapy is being tested in several cancers, speakers at EORTC emphasized efforts in melanoma, which is expected to kill 41,000 Americans this year, and a disproportionate share are young adult women (age 25-34). The average life expectancy for a person with Stage IV melanoma is 7 months. Melanoma is hard to treat because chemotherapy doesn't work.

One theory is: The immune system is deactivated by **regulatory T cells** which function normally to prevent auto-immune diseases. These regulatory T cells are increased in the lymph nodes of cancer patients, where they may prevent the activation of the immune system against tumors. The goal of immunotherapy is to inactivate regulatory T (Treg) cells.

Dr. Chesney reported on a Phase II trial which found that Ligand Pharmaceuticals' Ontak [denileukin difitox, DAB(389) IL2], which is already used to treat T-cell lymphoma, does just that – selectively depletes Treg cells, allowing the immune system to combat the melanoma. In that trial, so far 7 patients unresponsive to standard therapies have been given 9-12 µg of Ontak once a week for 3 weeks, in 4 cycles. Five of the 7 patients had a PR: 2 regression of multiple subcutaneous metastases, 1 resolution of hepatic mets, 1 stable/regressing subcutaneous mets, and 1 stable/regressing axillary lymph-adenopathy (LAN). He said the down side is some retinitis.

Dr. Chesney said, "We found a lot of their tumors disappearing. We found a decrease in Treg cells within three days of giving Ontak, about a 30% reduction. One patient with a life expectancy of 7 months is still alive at more than one year. Another patient still had disease after 4 cycles, but the tumors all shrank, and 5 sites went away. This just doesn't normally happen in melanoma…And Ontak is an outpatient therapy…In the future, immunotherapy that depends on Treg cell depletion ***may*** become standard of care for all cancer types (e.g., lung)…My guess is that in the future all cancers will be treated this way (with immunotherapy)." Dr. Chesney said that a Phase III trial – head-to-head against the best agent at that time – will be initiated after the Phase II trials are completed.

In a Phase I dose-escalation study another researcher, Dr. Tyler Curiel of the University of Texas Health Science Center in San Antonio TX, tested a single infusion of Ontak in heavily pre-treated patients with advanced-stage cancer – ovarian, lung, pancreatic, etc. He said, "The data in ovarian cancer are promising." They found a dramatic response in one ovarian cancer patient, and a Phase II trial has been initiated in Stage III-IV ovarian cancer patients of a single monthly dose of Ontak 12 µg/kg IV, and the plan is to enroll 60 patients.

So far, 8 patients have been enrolled in the Phase II trial, and they've seen 1 PR, 5 SD, and 2 PD. Toxicity reported is "minimal," 1 Grade II edema, swelling, and fatigue/fever.

An expert not involved in these studies offered a note of caution, commenting, "The problem is there is no Phase III trial evidence to sustain the hypotheses…All biochemotherapy trials (in melanoma) have failed to show a benefit…The combination of four to six therapies may show response but not necessarily an improvement in survival…In melanoma that is the case…In the last 15 years, >30 trials have failed… There is no formal evidence any intensive treatment is better than DTIC alone…That is how desperate the situation is in malignant melanoma. Though, we see encouraging signs with these approaches and with anti-CTLA-4, let's not forget that in melanoma everything still remains to be proven. That is how bad the situation is. We've lived through early reports of success many, many times."

Kinesin spindle protein (KSP) inhibitors

Merck and GlaxoSmithKline both have KSP inhibitors in development, and other pharmas appear to be looking at this class as well. An expert said, "These are targeted agents. The neurotoxicity is engineered out."

- **MERCK.** At ASCO 2006, Merck showed 24-hour infusion data on its KSP inhibitor.
- **GLAXOSMITHKLINE/CYTOKINETICS' ispinesib**, a selective KSP inhibitor. This is being tested in a Phase I trial with Xeloda. An EORTC poster reported on a Phase I study in 22 patients with advanced solid tumors. Ispinesib was administered in escalating doses (12-18 mg/m^2) in 1-hour infusions on Day 1 of a 21-day cycle along with escalating oral doses of Xeloda on Days 1-14. The most common toxicities were fatigue, hand foot syndrome, diarrhea, pain, leukopenia, and neutropenia. DLT of prolonged Grade 4 neutropenia was observed at doses of ispinesib 15 mg/m^2 and 18 mg/m^2. Researchers concluded there is no PK interaction between Xeloda and ispinesib.

Preventive agents

The NCI's Dr. Crowell pointed to several preventive agents in early development that bear watching, including:

- UAB30, a rexinoid.
- Tricin.
- SR-13688, which the NCI is considering for a Phase I trial in ovarian and breast cancer.
- Polyphenon E, which is in trials in Barrett's esophagus, breast, and other cancers.
- Wyeth's Rapamune (rapamycin).

Stem cell vaccine

Observations have indicated that pregnancy *per se*, especially having several children, protects against breast (and uterine, ovarian, and maybe even lung) cancer. The usual explanation is some kind of "hormonal effect," but researchers are now postulating a different explanation – that pregnancy might "vaccinate" a woman against cancer. John Eaton PhD, Deputy Director of the James Graham Brown Cancer Center at the University of Louisville, explained that tumors are like embryos, "Both grow as a ball of cells, both have a circulation and derive nutrients from the host, and both are 'foreign' and share similar antigens."

Dr. Eaton is helping to develop a vaccine with embryonic stem cells, and so far it has prevented lung cancer in mice. In his experiment, mice vaccinated subcutaneously with embryonic stem cells either had very small tumors or did not develop tumors at all. He concluded that mice vaccinated with embryonic stem cells are protected against an implantable form of lung cancer and against the development of lung cancer in a model which mimics cigarette smoking. At least in mice, the vaccine did not cause any side effects and appeared safe. He added, "This raises the exciting prospect of developing a vaccine to prevent the development of lung cancer."

The mechanism by which the stem cell vaccination works is not fully understood yet, but Dr. Eaton suggested, "We think when tumors first appear, they have an embryonic appearance to them…and it may be that type of cell we are attacking with the vaccine." He also is hopeful that the vaccine will be effective in other cancers, especially cancers of the gut.

Asked how the vaccine might be used, he said, "We would start with people at very high risk…And we would need a change of government and a change at the FDA. This (vaccine) requires live embryonic stem cells. We don't kill them. We don't know why they have to be live, but they do. Anything that knocks them off, they stop working…So, people at high risk would be the first to be tested…I think it is safe, so I would volunteer, but there may be side effects…I worry most about triggering an autoimmune reaction of some kind…And there may be crossover immunity to adult pluripotent stem cells, and depleting that would be bad." ♦