Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Amgen's panitumumab appears effective in metastatic colorectal cancer (mCRC), but questions were raised about whether the effect wanes with time. ♦ Analogs of the mTOR inhibitor rapamycin look efficacious in early studies, and sources were cautiously optimistic but generally not very excited about them. If they do pan out, they are likely to be used only in combination with other agents. ♦ Bristol-Myers Squibb's dasatinib looks promising as a follow-on to Novartis's Gleevec in CML, and in time may prove useful in combination with Gleevec or in lieu of Gleevec, but it still doesn't address T315I mutations. However, TargeGen has an agent in early development which appears effective against T315I mutations. ♦ It is early, but Millennium's MLN-8054, an oral selective Aurora-A inhibitor, looks promising as does MGI Pharma's Paclimer, a microsphere formulation of paclitaxel.

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AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR)

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Each year there has been a drug "theme" to the AACR meeting – genomic signatures, vaccines, VEGF inhibitors, epothilones, etc. – but this year the theme was more general: Connecting the dots between basic, translational, and clinical research. There was also a focus on clinical applications of agents. Dr. Daniel von Hoff of the University of Arizona also suggested an interesting new concept: "The tumor as an organ."

AACR officials are very concerned about cuts in cancer research funding. The federal government cut cancer research by $31 million for FY2006, the first hard cut since the passage of the National Cancer Act in 1971, and President Bush has proposed an additional $39.7 million cut for FY2007.

AACR officials said the cancer research community is bracing for a drop in the number of scientists in the field, predicting that these federal funding cuts will:

- Deter young investigators.
- Encourage some U.S. researchers to go overseas to work.
- Put a brake on future progress in cancer survival rates.

EGFR INHIBITORS

ASTRAZENECA'S Iressa (gefitinib) and GENENTECH'S Tarceva (erlotinib)

AstraZeneca researchers presented a pharmacokinetic (PK) comparison of these two drugs which found the two drugs:

- Possess "almost identical" activities across a range of preclinical assay/ models, suggesting they have an extremely similar pharmacological profile.
- Similar potencies.
- Did not have any significant difference in antitumor activity in either of the *in vitro* or *in vivo* models studied.

PK Comparison of Iressa and Tarceva

Measurement	Iressa 150 mg/kg/day	Tarceva 100 mg/kg/day
Inhibition of tumor volume	56%	54%
Change in body weight	-2.1 kg	-1.5 kg

AMGEN/ABGENIX'S panitumumab (ABX-EGF)

Panitumumab appears effective in metastatic colorectal cancer (mCRC), but questions were raised about whether the effect wanes with time. Many doctors said they would use it in lieu of ImClone's Erbitux (cetuximab) even if it is priced

comparably to Erbitux because it has less hypersensitivity reaction and doesn't require either premedication or a loading dose, but others said they will reserve it for patients who have reactions to Erbitux because Erbitux has more extensive data.

Comparison of Panitumumab and Erbitux

Measurement	Panitumumab	Erbitux
Antibody	Human	Chimeric
Half-life	Similar	
Data	Beginning	Extensive
Administration	Q2W	QW
Infusion reactions	1%	2%
PFS in mCRC	Similar	
Premedication	No	Yes
Loading dose	No	Yes
Hypersensitivity reactions	~5%	20% - 25%

Dr. Marc Peeters of Belgium presented details of the multi-center, pivotal Phase III trial of Amgen's panitumumab in mCRC patients who had failed standard chemotherapy. The company had previously announced that this 463-patient, randomized trial of best supportive care (BSC) ± panitumumab met both the primary endpoint of progression-free survival (PFS) and a secondary endpoint of objective response rate (ORR). PFS was reduced by 46% ($p<0.000000001$) compared to a pre-specified expectation of a 33% reduction. Amgen did not have a Special Protocol Assessment (SPA) with the FDA for development of panitumumab, but an official said the company has had "multiple" discussions with the FDA.

The treatment effect of panitumumab was consistent in all pre-defined subpopulations – sex, age, primary tumor type, ECOG status, number of prior regimens, number of metastatic sites, and EGFR status. Dr. Peeters said the findings suggest that EGFR status by immunohistochemistry (IHC) does ***not*** predict outcome.

Panitumumab is a fully human monoclonal antibody targeting IgG-2 directed against EGFR. In comparison, Erbitux is a chimeric antibody (34% mouse protein) and Merck KgA's matuzumab (EMD-7200) is a humanized antibody (10% mouse protein). In this Phase III trial panitumumab was dosed every two weeks, and median follow-up was 19 weeks. The

Oncology Drugs in Development by Big Pharma and Biotech

Phase I	Phase II	Phase III
Amgen's AMG-102	Amgen's AMG-706	J&J's trabectedin (cytotoxic that binds minor groove of DNA)
Amgen's AMG-623 (cell growth inhibitor)	J&J's CNTO-328 (anti-IL-6)	J&J's tipifarnib (FTI)
Amgen's AMG-386 (angiogenesis)	Schering's ZK-EPO (epothilone B)	Novartis's patupilone (EPO-906) (microtubule targeting cytotoxic)
Amgen's AMG-479 (IGF-1R)	Schering's MS-275 (HDAC)	Pfizer's ticilimumab (CTLA-4 inhibitor)
Amgen's AMG-655 (TRAIL)	Schering's ZK-304709 (multitarget) *	Pfizer's PF-3512676 (TLR agonist)
Amgen's AMG-951		
J&J's CNTO-95 (anti-α V integrin antibody)	Bristol-Myers Squibb's ipilimumab (MDX-010)	
J&J's S-CKD-602 (STEALTH) (liposomal topoisomerase inhibitor)	Bristol-Myers Squibb's vinflunine (BMS-710485, bifluorinated microtubule inhibitor)	
J&J's SCIO-469 (p38 MAPK inhibitor)	Bristol-Myers Squibb's BMS-275183 (oral taxane)	
Merck's MK-0752 (gamma secretase inhibitor)	Bristol-Myers Squibb's ixabepilone (epothilone B)	
Merck's MK-0457 (aurora kinase inhibitor)	Bristol-Myers Squibb's dasatinib (multi-targeted TKI)	
Merck's MK-0646 (IGFR inhibitor)	Novartis's gimatecan (oral topoisomerase inhibitor)	Schering's PTK-787 (multi-VEGF TKI)
Merck's MK-0731 (kinesin spindle protein inhibitor)	Novartis's RAD-001 (oral mTOR)	Schering's tocosol paclitaxel
Merck's V-390 (cancer vaccine)	Novartis's SOM-230 (somatastatin analog)	
Merck's MK-4711 (prostate stem cell antigen inhibitor)	Novartis's AMN-107 (TKI)	
Merck's MK-0683 (HDAC)		
Novartis's AEE-788 (TKI)		
Novartis's LBH-589 (oral and IV HDAC)		
Pfizer's PD-325901 (MEK inhibitor)		
Pfizer's CP-751,871 (Mab against IGF-1R)		
Roche's R-1550, R-547, R-1454, R-1530, and R-1645	Novartis's PKC-412 (oral FLT-3 inhibitor)	
Schering's L19-IL2	Pfizer's AG-013736 (oral RTK inhibitor)	
Schering's L19-TNF-α	Pfizer's AG-14699 (PARP inhibitor)	
Schering's ZK-261991 (VEGFR TK/Raf inhibitor)	Roche's R-1273, R-1492, R-744, and R-1273	
Schering's 4'– Thio-FAC (nucleoside analog)		

*** Ready to start Phase II**

two arms were well matched, and all patients were EGFR+. In an interim analysis of 250 patients, there was no statistically significant difference in overall survival. The patients who progressed on best supportive care alone were allowed to cross over to panitumumab therapy (creating a separate study group), and the 174 patients who crossed over may have confounded the survival data. Grade 3-4 adverse events were higher in patients on panitumumab, but most of these were reported to be associated with disease progression. In cross-over patients, the average time to crossover was 7.4 weeks.

However, Dr. James Abbruzzese of M.D. Anderson Cancer Center, the discussant at the presentation, noted that his analysis of the data provided suggested that panitumumab alters the early death/progression rate, but the impact on PFS after 20 weeks is more uncertain and suggests an emergence of resistance to panitumumab occurs. He pointed out that:

- In the first weeks of therapy, the hazard ratio (HR) is much lower for panitumumab than for BSC.
- After 5 weeks the HR stabilizes to an overall rate of 0.5.
- After 20 weeks the HR for panitumumab increases.
- The extrapolated median survival at 6.5 months was 6.4 months for panitumumab, with an HR of 0.93 and a p-value 0.6065.
- No difference in overall survival, but panitumumab was active in BSC patients crossing over to active therapy, and the impact on survival was confounded by the high percentage of BSC patients crossing over to panitumumab.
- Panitumumab efficacy is comparable to Erbitux but the side effects are fewer, especially the hypersensitivity reactions.

PFS Hazard Ratio Analysis

Patient population	Central radiology			Local radiology
	All events	Event in main study	Interval censored	
All randomized patients	0.54	0.41	0.60	0.39
Adjudicated prior failures (n=352)	0.59	0.45	---	0.42
Per protocol (n=337)	0.63	---	---	0.41

Panitumumab Crossover Patients

Objective response	Panitumumab in patients who progressed on BSC n=174
CR	1% (1 patient)
PR	9%
SD	32%
Disease control	42%

Study 408 Phase III Efficacy Results of Panitumumab in mCRC

Measurement	BSC + panitumumab 6 mg/kg Q2W n=231	BSC n=232
Demographics		
Colon cancer	67%	
Renal cancer	33%	
***Primary endpoint:* PFS**		
Week 8	49%	30%
Week 12	35%	14%
Week 16	26%	9%
Week 24	18% (p<.0001, HR 0.54)	5%
Week 32	10%	4%
Week 40	4%	1%
Week 48	1%	1%
***Secondary endpoint:* Best objective response (by RECIST)**		
PR	8% p<.001	0
SD	28%	10%
Disease control (RR + SD)	36%	10%
Other *secondary endpoints*		
Median time to response	7.9 weeks	N/A
Median duration of response in responders	17.0 weeks	N/A
Overall survival (interim analysis on 250 patients)	Nss	
Other results		
ORR at Week 8	8%	---

Phase III Safety Results of Panitumumab in mCRC

Adverse events	Panitumumab + BSC	BSC alone
Discontinuations due to adverse events	6%	3%
Skin toxicity (any)	90%	9%
Skin toxicity (Grade 3-4)	14%	0
Discontinuations for skin toxicity	<1%	0
Fatigue	24%	15%
Diarrhea	21%	11%
Hypomagnesemia	38%	2%
Hypomagnesemia (Grade 3-4)	3%	0
Hypersensitivity	5%	0
Grade 2 hypersensitivity reaction	1 patient (discontinued)	0
Abdominal pain	23%	17%
Abdominal pain (Grade 3-4)	7%	4%
Nausea	22%	15%
Grade 3-4 infusion-related reactions	0	0
Antibody formation	0	0
Secondary hypocalcemia	2%	0
Pulmonary embolism	1%	N/A
DVT	1%	N/A

Experts appeared impressed with the data. An AACR official said, "Panitumumab looks favorable compared to what's already out there." An Amgen researcher said no safety signal has been seen in mice.

Amgen officials made several comments about panitumumab:

- >1,300 patients have gotten panitumumab, mostly in mCRC, renal cancer, and solid tumors. It is also being studied more extensively in combination therapy in mCRC and NSCLC.
- A Phase II monotherapy trial of 50 patients in Japan, looking at complete response rate, is expected to be completed in 2Q06.
- Panitumumab can be given weekly, once every other week, or once every three weeks.
- They countered Dr. Abbruzzese's analysis of the Phase III data presented at AACR, saying it was based on a Kaplan-Meier curve provided by Amgen, not on the raw data. An official said, "It is important not to focus on means or medians, but to look at the whole curve and not at one point…You have a highly significant trial based on HR, which is the best way to evaluate the treatment…It is almost unfeasible to compare median PFS or mean PFS with values which are given with Erbitux…This is not based on scientific things. This is an indirect comparison." Another official said, "The two (Kaplan-Meier) curves separate from the beginning and never converge until the end, so median survival is not the best. Risk reduction rate would be a better rate to illustrate treatment effect."

mTOR Inhibitors: Rapamycin Analogs

Several analogs of rapamycin are in development, including Wyeth's temsirolimus (CCI-779), Novartis's everolimus (RAD-001), and Ariad's AP-23573. Sources were cautiously optimistic but generally not excited about the analogs. An expert commented, "I think there is reason to be optimistic that they will find a place…but it is very early in their development." Another source said, "The rapamycin analogs are looking quite interesting. I'm really excited. They are absolutely promising, but we don't know enough…They open the door for non-rapamycin inhibitors of TOR."

Another expert noted that rapamycin is already being used off-label in some cancers. One source commented, "I think people are already using rapamycin off-label for sarcoma and a lot of other cancers." He suggested that if an analog is approved, doctors may use generic rapamycin off-label instead since it will be less expensive. Another expert said, "SWOG is planning a Phase II trial in sarcoma of rapamycin in combination with chemotherapy."

A researcher reported that work in his lab suggests that ezrin is intimately linked to mTOR activation; blocking ezrin affects the downstream regulators of mTOR. He said, "We don't know how to inhibit ezrin, but we can inhibit mTOR through rapamycin or any of the analogs."

- In a mouse osteosarcoma experiment, Wyeth's temsirolimus (CCI-779) (at 5 mg/kg and 20 mg/kg, though 20 mg/kg was better) and rapamycin (5 mg/kg) were "equally and markedly effective" in inhibiting pulmonary metastases and prolonging survival.
- According to recent reports, patients treated with rapamycin clinically have had a compensatory hyperphosphorylation of Akt. He said, "We found that the dose of rapamycin markedly inhibited the target in the tumor for at least 72 hours…but Akt is activated, and it increases over 96 hours, with a marked increase by 24 hours. This is something we don't want to do if we are going to use this drug clinically (for cancer)."
- Adding a humanized antibody (Merck H7C10) to the IGF receptor completely abrogated the Akt phosphorylation. *In vivo* studies of this approach are ongoing. He said he believes the antibody and rapamycin work in "a relatively additive fashion."

In another talk, a researcher described how, based on work in lung cancer cell lines, he found the Akt and Raf kinase pathways are redundant, and both need to be inhibited to kill cells.

A third study found that rapamycin may sensitize patients to chemotherapy. A researcher said a marker may have been found to predict survivors and non-survivors in rhabdomyosarcoma (RMS). Historically, Stage 4 patients (metastatic) do poorly, and Stage 3 patients are "almost a coin flip" on who does well and who does poorly (~60% survival with no ability to identify who will and won't survive), while patients with Stage 1-2 do well and many are cured. A researcher reported that Stage 3 patients with high 4EBP-1 (an indicator of mTOR activation) had high overall survival vs. those with low 4EBP-1 (p=.0177). The data were replicated in a laser capture and protein array study. He said similar findings were made in breast cancer, "Our data suggest that rhabdomyosarcoma patients would be resistant to standard therapy, and rapamycin may sensitize patients to chemotherapy. Patients with low levels of 4EBP-1 have resistance to rapamycin…It is possible treatment of poor prognosis patients with rapamycin or an analog (of rapamycin) may convert them to improved response to therapy."

Rapamycin analogs and other direct mTOR inhibitors face at least one major pitfall in cancer: They also inhibit a negative feedback loop downstream of mTOR. As a result these drugs, in theory, could actually boost signaling along the PI3 kinase-Akt pathway instead of blocking it. That's because S6 kinase, a downstream effector of mTOR, inhibits IRS-1, which is required for extracellular growth factors to activate PI3 kinase, upstream of Akt and mTOR. So, mTOR inhibitors, by blocking this negative feedback loop, could increase signaling in this pathway even while blocking mTOR. To the extent

that mTOR inhibitors have not worked as well as expected in the clinic against cancer, some investigators blame these drugs' inhibitory effect on this negative feedback pathway.

Some of the other questions and issues that have surfaced about treating cancer with rapamycin and its analogs include:

➢ ***Since these drugs are immunosuppressants, can cancer patients take them long term?*** An expert said, "We are struggling with that question." Another expert said, "To me the biggest issue is the immunosuppression…It is a schedule-dependency issue…Could you give it on an intermittent schedule where it is effective but not profoundly immuno-suppressive? That is my hope. Maybe you could give it three days a week one week out of four forever. It is a scheduling issue on how to give it, but if it is given intermittently, then don't suppress the pathway completely…So, there is reason to think that, ultimately, we may want to go after the pathway with other inhibitors that don't have the immunosuppression that rapamycin has."

➢ ***Do the analogs all cross the blood brain barrier?*** Experts said they do. Dr. Peter Houghton of St. Jude Children's Hospital said, "It concentrates in the brain, perhaps regionally." An NCI researcher said, "There are two cases where rapamycin treated a benign brain tumor, tuberous sclerosis, so it must cross the blood brain barrier."

➢ ***Can PTEN mutations be used to identify responders?*** Probably not, experts agreed. Several researchers reported that they have seen responses in patients without PTEN mutations as well as in patients with PTEN mutations. PTEN mutations occur in a lot of cancers, perhaps 50% of cancers, including prostate and breast. An expert said, "This is a controversy in the field. Initially, people thought that PTEN mutations would tell us who would respond to mTOR inhibitors and allow us to select patients, but that is not true. Clearly, there are cell lines with PTEN mutations that are insensitive or very sensitive. There are examples where the theory holds, and others were it doesn't hold, so there is no magic bullet of prediction…Novartis did a lot of work in clinical trials trying to validate that…but it is not that easy." Another researcher said, "The results with PTEN mutations are not consistent." A third source said, "PTEN mutation may be indicative of responders, particularly at the exon 5 site." A sarcoma expert said, "There have been some suggestions that when PTEN mutates, the cells are more sensitive to rapamycin analogs – develop an 'addiction' – but a lot of the data are conflicting. There are examples of hypersensitivity to PTEN lines on both sides. A clinical trial is ongoing driven by the frustration with rapamycin in PTEN (-) glioblastoma, and the response rate is not higher."

➢ ***Is there a clinically significant difference in the analogs or between rapamycin and any of the analogs?*** Experts don't think so. There are differences in route of administration, solubility, and stability, but experts insisted there were no clinically significant differences. An expert said, "It's mostly just marketing." Another expert said, "The analogs metabolize back to rapamycin in humans, so you are giving the same drug." A third source said, "Rapamycin is not as stable (as the analogs)."

➢ ***Are the analogs efficacious?*** Sources generally agreed that all of them are equally efficacious, though they had questions about the degree of efficacy. A researcher said, "They are all similar in mTOR targeting…The only difference is administration and marketing." Another expert said, "They are all the same. There are slight advantages to different formulations. For example, CCI-779 is parenteral, so if you needed higher concentrations, you can get more than you can with RAD-001."

➢ ***Will they be most useful in monotherapy or combination therapy?*** Sources all agreed that these agents will be used in combination therapy, not as monotherapy, and especially in combination with an antibody to the IGF-1 receptor.

- *Sarcoma expert:* "Definitely combination because if you treat cells with rapamycin alone, in many instances you get a cytostatic growth delay, but if you combine rapamycin with another agent (like a DNA-damaging agent), you get a synergistic effect. But in other combinations, the effect could be additive or more than additive. Rapamycin converts from a cytostatic into a cytotoxic when you combine it with another cytotoxic…This suggests TOR protects some cells from DNA damage. The question is what will happen in animals. You may need a functional checkpoint to see this effect."
- "We need to learn how to use them, how to select the patients, and my guess is they will work most effectively in combination."
- "Some labs are trying combinations, especially with conventional DNA-damaging agents, and (the analogs) work better in combination."
- *Dr. William Tap of UCLA, who is doing a small study looking at AP-23573 in combination with adriamycin:* "It will be more interesting to see it in combination. Monotherapy is not a silver bullet."
- *Dr. Meeiva Jhanwar of New York Medical Center, who did a study in a glioblastoma multiforme cell line:* "We found with a cell line study that there is a mechanistic basis for enhancing mTOR-targeted glioblastoma therapy by possibly combining mTOR and Ras/MAPK inhibitors." However, a source suggested there is a problem with mTOR inhibitors in glioblastoma, "There appears to be activity in glioblastoma multiforme cell lines, but there is a syndrome where PTEN is deleted in the cerebellum, and that makes the cerebellum bigger and pushes against the skull."

➢ ***How will oncologists handle mucositis with these agents?*** The same way they handle it with other agents – by backing off the dose, holding treatment, using topical medications or pain medications. A sarcoma expert said, "The

same way you deal with overlapping toxicity with existing drugs…Patients will accept a lot if the result is a cure." Another source said, "You have no choice. The question is how high a concentration is needed to get mucositis. Could you lower the dose to avoid the toxicity?" A third source said, "A lot of patients can tolerate the mucositis. If they see a result, they will stay on (the treatment)."

The temsirolimus failure in breast cancer wasn't interpreted by experts as indicating that it doesn't work in breast cancer, just that it is not yet possible to identify which patients are responders. A source said, "The failure in breast sends no message."

A National Cancer Institute (NCI) researcher said temsirolimus also failed in brain cancer, blaming that on activation of Akt. He said, "Temsirolimus has an anti-tumor effect. The stumbling block for temsirolimus is in anti-metastasis. For patients at high risk of recurrence at a distant site, the drug may also have an impact, but that means giving it for a long time." Another expert said, "We need to select patients with activation of the pathway, and we don't have activation of the pathway distal to where rapamycin (or its analogs) could inhibit it…and no one is doing that because you need tissue samples to do that."

Wyeth and Novartis started their programs in breast, lung, and renal cancer. Sources said Ariad chose to develop AP-23573 in sarcoma because of a signal in sarcoma in broad Phase I studies in a variety of cancers. A sarcoma expert said, "AP-23573 looks very promising. They've seen responses in Ewing's sarcoma in Phase I."

Sarcoma is a very rare tumor. Sources estimated there are only about 6,000-8,000 newly-diagnosed cases a year, compared to 180,000 newly-diagnosed breast cancers annually. There are 13 varieties of sarcoma. Ariad has the lead in sarcoma with AP-23573. Among the comments on analogs in sarcoma were:

- "The sarcoma market is too small for large pharmaceutical companies. They want more pay-off, so they went after more common cancers…It may be smart for Ariad to get its drug approved in the smaller sarcoma market, and then it will be used off-label in other cancers."
- "That (the small size of the sarcoma market) also makes it harder to do the studies…Most patients don't go on studies (<10% go on studies). Most children go on studies but not most adults."
- "There are so few (pediatric sarcoma) patients that we can't waste them, so we more critically evaluate a drug before testing it in children…Most pediatric sarcoma is responsive – 60%-80% of kids respond – but non-responders are the issue."
- "Companies want multiple tumors for marketing. Ariad is last to develop an analog, and they knew RAD-001 and CCI-779 already had data in some tumors, so they chose another tumor type."
- "Ariad saw a signal in pediatric sarcoma. Wyeth tried sarcoma (with CCI-779) and failed, but Wyeth had two responses in renal cancer…(The difference in response) could be a scheduling issue, a patient population (subtype) issue."

Phase II on AP-23573 in sarcoma will be presented at ASCO 2006. Sources expect this data to be positive, but perhaps not sufficient to proceed to a Phase III trial without a Phase IIb trial. An expert said one of the questions to ask about the data is whether or not it confirmed the preclinical studies: Were the preclinical studies predictive?" Another source said, "In pediatrics, the only way to go is functional imaging. You can't get a biopsy."

Ariad reportedly has a second compound in development, and a source thought that might be more interesting than AP-23573 "because it concentrates in the bone."

The FDA has not issued any guidance specifically for the design of sarcoma trials. However, an FDA official noted:

1. Two trials may not be necessary in a disease that has as low an incidence as this.
2. A Phase III trial likely would be add-on therapy, though in Europe there could be a best supportive care arm.
3. European trial data might be acceptable for FDA approval. A researcher said, "The guidance is no different than for any cancer…There are some groups agitating to get sarcoma specifically classified as an orphan disease to maybe get things approved faster – some political effort by advocacy groups – but nothing has been done yet."

Sources suggested that a Phase III trial in sarcoma could be done a couple of ways:

1. Standard of care ± the experimental drug, with PFS or overall survival the primary endpoint in high risk patients (patients with large disease, large tumors, or particular sites with a high risk of recurrence and death). A five-year study would be required for overall survival, but for approval, most patients recur within a year, so a signal could be seen pretty quickly, an expert explained.
2. Treat all patients first with standard of care, and at the end of that therapy, randomize patients to analog vs. no therapy, with PFS as the primary endpoint.

There also are other competitors to the mTOR analogs in development, including:

- An antimalarial drug that affects the same pathway as mTOR inhibitors.
- **GENENTECH** reportedly has a compound in development that affects the pathway upstream from mTOR (an Akt inhibitor).

- **BIOTICA'S BC-210**, a bio-engineered analog of rapamycin in preclinical development, which a source called "really cool." And it is not the only rapamycin analog in Biotica's cupboard. A poster on BC-210 in glioblastoma multiforme reported that it is brain selective. A researcher said, "I think we can get over the oral (hurdle). I think the problem is the C_{max}, so with larger amounts or longer dosing, we could get to a critical brain level…In mice, there is a significant increase in survival time…I think this has a real differentiation from the other analogs, which are very similar…Ours is an incredibly specific compound." He said the advantages are: im-proved metabolic stability and potentially better absorption.

BC-210 vs. Rapamycin

Drug and formulations	Brain/blood ratio	Half-life
IV BC-210	1.5	59 minutes
Oral BC-210	0.1	N/A
IV rapamycin	0.6	40 minutes
Oral rapamycin	0.06	N/A

TYROSINE KINASE INHIBITORS

Several follow-on compounds are being developed to treat chronic myeloid leukemia (CML) patients who fail Novartis's Gleevec (imatinib). The significant relapse rate with Gleevec is 16% at 4 years in newly diagnosed chronic phase patients and 95% of those in blast crisis.

Some experts believe the follow-on agents will eventually replace Gleevec front line since the follow-ons are effective in more mutations than Gleevec, while others suggest they may be combined with Gleevec. The follow-on agents are: Bristol-Myers Squibb's dasatinib (BMS-354825), Novartis's AMN-107, and Pfizer's Sutent (SU-11248), but attention should be paid as well to TargeGen's TG-100598 because it appears to work in a mutation in which none of these other agents are effective – T315I.

BRISTOL-MYERS SQUIBB'S dasatinib (BMS-354825)

Dasatinib is an oral kinase inhibitor in Phase II/III trials. It has already been submitted to the FDA for approval in CML, based on Phase II data, and it is being tested in other cancers.

A poster at AACR on a cell line study by Dr. Ralf Buettner of City of Hope in Duarte CA called dasatinib a promising treatment for metastatic melanoma. Reportedly, three melanoma patients have been treated, with two very good responses. The conclusions of the cell line study were that dasatinib:

- Completely abolished SFK activity in melanoma cells.
- Directly and rapidly inhibited EphA2, which is an upstream activator of FAK and is also implicated in melanoma progression.
- Had little effect on proliferation and survival of the 8 human melanoma cells tested.
- Is a potential treatment and preventive of metastatic disease in patients with advanced melanoma.
- Inhibits the invasion of melanoma cells.
- Down regulates the expression of genes involved in aggressive melanoma cell phenotypes.
- Doesn't kill the melanoma cells and doesn't stop them from proliferating, but it blocks invasion and migration.

Currently, dasatinib is dosed BID, but Phase I dosing studies are underway. A Bristol-Myers official said the dosing schedule will depend on the tumor type. A researcher said, "At least in CML, we might be able to get away with intermittent, pulse therapy."

The side effects being watched with dasatinib are:

- **QT prolongation.** In Phase I, some QT prolongation was found, so the company had to do EKG testing in the Phase II CML studies. Asked about the findings from those EKG studies, an investigator, Dr. Charles Sawyers of UCLA, replied that no clinical sequelae have been observed. He said he did not believe QT prolongation is a concern, but he said he had not seen the QT data himself, though he had not specifically asked the company for it yet. A Bristol-Myers researcher also said he had not seen the QT data but didn't believe it was a clinical issue.
- **Pleural effusion.** A company official said this is the side effect the company is watching. Pleural effusion was reported as 13% in CML chronic phase patients and 23% in CML advanced phase patients.
- **Myelosuppression.** This is the major toxicity in CML, but an investigator said it has not been seen in solid tumor studies. He said, "Our interpretation is that it is efficacy data that show up as myelosuppression."

An update on 84 patients from a Phase I study initiated in 2003 was presented at AACR, looking at the effect of dasatinib in chronic phase response CML patients who were Gleevec-resistant. The take-away messages were:

- Dasatinib has a consistent half-life of ~5 hours, and there doesn't appear to be any retention effect of the drug on kinase inhibition in the cells. This is why the protocol was amended from QD to BID dosing.
- Dasatinib provides significant response rates in Gleevec failures, and the responses are durable, with some chronic phase patients continuing to respond at 19 months and some advanced phase patients continuing to respond at 13 months. The trial completed enrollment very rapidly. But there is still a need for another drug that works in T315I mutations. The T315I mutation remains a challenge. A speaker said, "It has been called the mutation from hell."

- Preclinical data suggest that combining dasatinib with Gleevec upfront might reduce resistance.

Another study looked at dasatinib plus Sanofi-Aventis's Eloxatin (oxaliplatin) in a mouse model of metastatic colorectal cancer. Researchers reported that:

- Both drugs alone inhibited tumor growth, but the combination inhibited tumor growth more than either alone, suggesting there may be a synergistic relationship.
- Only combination (not single agent) therapy resulted in a significant increase in tumor cell apoptosis.

Phase I Data on Dasatinib in CML

Measurement	QD	BID	Total
Chronic phase patients (n=40)			
Median duration of treatment	13 months		
Complete hematologic response	95%	89%	93%
Major cytogenic response	48%	42%	45%
Complete cytogenic response	48%	21%	35%
Partial cytogenic response	0	21%	10%
Advanced phase patients (n=44)			
Median duration of treatment	37 months		
Hematologic response in AP	---	---	81%
Hematologic response in MBC	---	---	61%
Hematologic response in LBC/P+ ALLAP	---	---	80%
Major cytogenic response	---	---	43%
Complete cytogenic response	---	---	25%

Comparison of Dasatinib and Novartis's AMN-107

Measurement	Dasatinib	AMN-107
Selectivity	Dual Src-ABL kinase inhibitor	ABL kinase inhibitor
Binds to	Active and inactive conformation	Inactive conformation
Potency vs. Gleevec	~325-fold more potent	20-fold more potent
Pattern of mutant sensitivity	Potently inhibits mutants	Similar to Gleevec
Inhibits T315I mutation	No	No
Sensitivity to ABL mutations	Yes	Yes

TargeGen's TG-100598

This benzotriazine compound inhibits wild type and T315I mutant ABL tyrosine kinase. There was no PK data, but the agent just started in-house animal studies.

TargeGen has two other programs underway:

1. TG-100801, a topical small molecule jac2+kdr inhibitor (or VEGFR2 inhibitor) in preclinical development for AMD. TargeGen hopes to file an IND in 2Q06. Reportedly, it passes through the retina quickly and accumulates in the back of the eye. A researcher said there is "tons of *in vivo* data saying this agent is safe and effective."
2. TG-100115, a PI3K gamma inhibitor in cardiovascular trials to prevent leakage after an AMI.

TG-100598

Compound	XIT proliferation		Enzyme assay	
	Wild type	T315I	Wild type	T315I
TG-100598	211	1600	0.43	3.5
Gleevec	3100	10,000	1.48	97,800
Dasatinib	3.2	10,000	2.5	2,490
SKI606	260	10,000	2.85	247

Other Agents

Dipeptidyl Peptidase (DPP) Inhibitors

Point Therapeutics' talabostat (PT-100) and PT-630. These are the first two of a "family" of DPPs that Point Therapeutics is developing for use in cancer, type 2 diabetes, and as vaccine adjuvants. At AACR, researchers from Fox Chase Cancer Center reported that both drugs inhibited fibroblast activation protein (FAP) enzymatic activity and attenuated tumor growth in experimental kidney and CRC tumors in mice. Talabostat has previously been demonstrated to upregulate the production of cytokines and chemokines leading to stimulation of the innate and adaptive immune system. In contrast, PT-630 inhibits FAP activity but is not known to induce cytokine and chemokine upregulation. An investigator said, "The anti-tumor activity of both talabostat and PT-630 is intriguing because it suggests a mechanism of action involving tumor-targeted FAP inhibition that may be distinct from immune stimulation in tumor types where FAP is expressed clinically."

Epothilones

The epothilones were described as having a "promising" pre-clinical profile. Among the epothilones in development are:

- **Bristol-Myers Squibb:**
  - ixabepilone (BMS-247550). Data in metastatic breast cancer are expected at ASCO 2006, and sources believe it will be positive. Phase II trials already have shown an ORR of 14% in renal cancer, 25%-33% in non-Hodgkin's lymphoma, and 9%-22% in pancreatic cancer. The DLT is neutropenia and peripheral neuropathy.
  - BMS-310705, a backup compound with a tweak to a side chain. The DLTs are neutropenia, diarrhea, and sensory neuropathy.
- **Kos Pharmaceuticals'** KOS-862 (epothilone D). A Phase II trial is ongoing in metastatic breast cancer. The DLT is impaired gait and cognitive and perceptual abnormalities.
- **Novartis:**
  - ABJ-879, a backup compound with a tweak to a side chain.

- patupilone (epothilone B). Trials are completed or ongoing in metastatic breast, lung, prostate, and ovarian cancer. The DLT is diarrhea, ***not*** peripheral neuropathy.

➢ **Schering AG's** ZK-EPO. This is being tested in breast and ovarian cancer. The chemical structure has not been publicly released yet.

Taxanes

Dr. Eric Rowinsky, chief medical officer of ImClone, offered a critique of taxane – paclitaxel, docetaxel, etc. – development. Among the points he made were:

- Paclitaxel, docetaxel, and the other taxanes have identical anti-tumor spectra, regardless of claims to the contrary.
- No taxane analog has ever shown activity outside of the anti-tumor spectra of paclitaxel/docetaxel, especially in CRC.
- There are rare examples of taxane analogs demonstrating superior efficacy to paclitaxel given at 175 mm^2 over three hours, but the studies are highly controversial, and 175 mm^2 is not the dose most often used, even though it is the FDA-approved dose.
- There is no question the taxanes differ in potency in affecting microtubule (MT) dynamics, but it is not clear that this translates into a clinically significant difference.
- No data indicate that taxanes differ in their principal microtubule effects, and claims to the contrary have largely been debunked. There also is no clear and conclusive data that the taxanes differ in their effects on cell biology.
- Beware of the claims about new taxanes, such as increased potency. Increased potency rarely translates into an increased therapeutic index.
- American Bioscience's Abraxane (ABI-007) has shown higher response rates, a statistically significant increase in TTP, and a decrease in Grade 3/4 neutropenia, but no significant increase in survival.

IDN-5109, an oral agent developed at Roswell Park Cancer Institute, overcomes multidrug-resistance in Pgp-positive tumors. IDN-5109 may increase the spectrum of therapeutic benefit of taxoids in breast, ovarian, and lung cancers as well as CRC, against which paclitaxel and docetaxel have been relatively ineffective.

Specific drugs worth watching:

➢ An aerosol p53 intratracheal gene delivery system (ANDp53) has been developed at SUNY Stony Brook for local delivery in NSCLC or bronchioalveolar cancer. It causes "minimal and reversible" lung inflammation.

➢ **AMGEN/GENENTECH'S Apo2L/TRAIL (AMG-951).** Phase I data on this IV agent are expected at ASCO 2006, and the agent is entering Phase II. A Phase Ib also is about to initiate in pancreatic cancer, a Phase Ib2 is starting in CRC and non-Hodgkin's lymphoma, and the protocol for a Phase Ia monotherapy trial is just about finished in an unspecified cancer. However, the development program is for combination therapy. TRAIL is administered in a one-hour infusion daily for five days in 21 days. There is no alopecia with AMG-951, which is made in *E. coli*. A researcher said there were early reports of toxicity, but the clinical compound, which is cleared renally, doesn't have any exogenous tags, which avoids the toxicity problems. The half-life is ~30 minutes in mice and ~1 hour in humans. The effect is pretty rapid (4-6 hours in cell lines), with cells dead in 8-12 hours. It has been shown to be active in a variety of cells: CRC, NSCLC, lymphoma, glioma, pancreatic cancer, melanoma, and myeloma. TRAIL and Biogen Idec's Rituxan (rituximab) reportedly synergize "nicely."

A study by an M.D. Anderson Cancer Center researcher found that when Millennium's Velcade (bortezomib) was given simultaneously with TRAIL (a human version, not the Amgen/Genentech product), the mice all died from GI toxicity. However, she found the combination was very effective (and not lethal) when administered sequentially, with at least 16 hours between drugs. An NCI researcher did not see toxicity with Amgen/Genentech's TRAIL + Velcade but he used them sequentially, not simultaneously.

➢ **CHROMA THERAPEUTICS Chroma-2797.** This is a QD oral agent in Phase I, where it reportedly has had two sarcoma patients show a response.

➢ **MGI PHARMA'S Paclimer.** This is a microsphere formulation of paclitaxel for intrauterine administration. A rabbit study found:

- No drug-related deaths or morbidity.
- Paclitaxel was detected in plasma, but at concentrations below the limit of quantitation. The plasma levels were significantly lower than the plasma levels following 24-hour or 3-hour IV infusion of commercially available paclitaxel. This suggests Paclimer may have lower toxicity than IV paclitaxel, allowing for dose intensification.
- The C_{max} did not correlate with the dose.
- Samples of brain, liver, and lung did not indicate any paclitaxel.
- High uterine tissue concentrations were observed following intrauter-ine administration with minimal plasma concentrations.

➢ **MILLENNIUM'S MLN-8054.** This oral agent is the first selective Aurora-A inhibitor. It is in Phase I trials in solid tumors. A poster discussed what happens to cells when Aurora-A is inhibited, and it showed that inhibition of Aurora-A causes abnormal spindle pole formation and abnormal mitotic spindles but, nevertheless, the cells still divided at a high incidence, resulting in an aneuploid division. The potency of MLN-8054 (an oral small molecule) to Aurora-A is 34 nm vs. 5.7 nm for Aurora-B.

A poster reported on tumor growth inhibition in a cell line study. The researcher said a Phase I trial in solid tumors began in December 2005, the MTD with MLN-8054 is 30 mg/kg BID, the drug has a novel scaffold, good selectivity of Aurora-A over Aurora-B, and it demonstrated robust tumor inhibition in preclinical trials.

MLN-8054

Enzyme	IC_{50}	IC_{50} with MLN-8054
Aurora-A	4	34
Aurora-B	172	5,700
CDK-1	10,000	---
CHK-1	10,000	---
CHK-2	10,000	---
PKC	10,000	---

Another study in a lung xenograft concluded:

- There was an increase in the mitotic index after a single 30 mg/kg oral dose, peaking at 6-8 hours post-treatment.
- MLN-8054 induces apoptosis, starting on Day 3 and peaking at the end of treatment (Day 20).
- Continuous treatment was most effective in the three tumor models tested, but dose holidays were tolerated (though QD dosing was not studied).
- 30 mg/kg BID 5 days on and 5 days off and 30 mg/kg BID 10 days on and 10 days off had equal efficacy, but both were less effective than 30 mg/kg BID 20 days on.

➢ **REGENERON'S VEGF-TRAP.** A poster by researchers at Thomas Jefferson University reported that a mouse study found this agent works best with radiation at a lower dose and without radiation at higher doses. A Phase II monotherapy trial is underway, but a researcher said there is potential for combination therapy.

VEGF-TRAP and Radiation

Treatment	Tumor volume			Tumor size doubling time		
	Prior to radiation	With radiation	Post-radiation	Prior to radiation	With radiation	Post-radiation
Control	27%	27%	31%	3.0 days	2.9 days	2.5 days
Radiation	11%	16%	15%	6.5 days	4.7 days	5.1 days
VEGF-TRAP (2.5 mg/kg)	12%	17%	16%	5.9 days	4.5 days	4.7 days
VEGF-TRAP (10 mg/kg)	7%	8%	8%	11.0 days	8.5 days	9.2 days
VEGF-TRAP (2.5 mg/kg) + radiation	7%	12%	10%	10.6 days	6.3 days	7.4 days
VEGF-TRAP (10 mg/kg) + radiation	5%	7%	6%	15.3 days	10.3 days	12.8 days

➢ **TELIK'S Telcyta (TLK-286).** The only data at AACR was an ovarian cancer cell line study, and there will be no additional data at ASCO 2006. A company official said they are waiting for the event-driven Phase III trial, which is fully accrued. The cell line study found:

- Exposing ovarian cancer cells to TLK-286 for 7-8 months did not induce resistance. The cells displayed severe growth defects, gross morphological changes, and an increased frequency of senescence-associated (SA) β-galactosidase positive cells.
- In human lung cancer cells, TLK-286 also induced SA-β-galactosidase activity in an active and dose-dependent manner. The growth arrest induced by TLK-286 persisted after removal of the drug, which is not the case with cisplatin and melphalan.
- Senescence induction may contribute to the anti-tumor activity of TLK-286, and the inability to develop resistance *in vivo*.
- The take-away message was that TLK-286, on various cancer cell lines, causes cell growth arrest and is followed in some cases with senescence, which can last a very long time, which is different from the platinums, where it is reversible in some cases (it is irreversible with TLK-286) – and resistance didn't develop.

TLK-286 Ovarian Cancer Cell Line Study

Drug	Resistance	Exposure time	Other factors
Carboplatin	5x - 9x	>8 months	Growth rate and morphology nearly identical to parenteral cells
Melphalan	~5x	>6 months	Growth rate and morphology nearly identical to parenteral cells
Paclitaxel	~30x	>8 months	Identical
TLK-286	~1x	>18 months	Extremely slow growing and enlarged, flat morphology

REGULATORY ISSUES

The **FDA** presented a poster at AACR on a genetic test for the management of the toxicity with Pfizer's Camptosar (irinotecan) for CRC. The purpose of the study and its presentation at AACR were to demonstrate that the FDA does not stop looking at toxicity issues once a drug is approved and the positive results that happen when a company works with the FDA.

Post-approval, the FDA worked with Pfizer on genetic studies of Camptosar, and the result was a modified package insert for the drug. This is an approach that the FDA would like to see done with other sponsors and other drugs.

Progression-free survival (PFS) is gaining popularity as a primary endpoint in oncology trials in the U.S. On the negative side, it can introduce investigator bias, with investigators more likely to declare progression in patients on control vs. experimental treatment or investigators delaying a report to give a patient additional treatment. On the other hand, PFS has been used – and a speaker said fairly well – in glioblastoma, and studies indicate it does correlate with survival.

Benchmarks for interpreting PFS are being developed. A speaker said, "If the six-month PFS rate is <15%, it probably is not an active agent, and 21% PFS rate at six months is the benchmark in recurrent glioblastoma, set by temozolomide (Schering AG's Temodar)…Those (drugs) with promise are in the 30%+ range."

Most accelerated approvals are based on objective response rate (ORR) in single arm trials, but the FDA has approved 28 different drugs for 33 different indications under the accelerated approval process. The clinical benefit was confirmed in 11 of these, 4 require no further confirmatory trials, and 18 have confirmatory trials planned or ongoing.

The **European Medicines Agency (EMA)** is moving away from the concept of approval based on a belief of positive benefit:risk to wait for proof of benefit. An EMA official said, "Lack of an adequate randomized clinical trial is the most important reason for rejection of a drug."

The EMA also is moving toward selective (conditional) drug approvals, where a drug is approved early, based on safety but a low effect, and then post-approval studies look for special populations or patients likely to benefit. The EMA official said this is a possible model for targeted therapies. Single-arm studies will only be accepted if the effect is dramatic, and drugs using this approach have a high risk of rejection.

Japanese regulators, according to an industry source, plan to issue new oncology guidelines soon, and they will start requiring Phase III trials for approval. In the past, Japan had a system somewhat similar to the U.S., where approval could be based on a Phase II trial, with a confirmatory Phase III trial done later.

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