Trends-in-Medicine

March 2008

by Lynne Peterson

SUMMARY

K-ras may prove to be a marker for response to EGFR inhibitors, but doctors aren't ready to start K-ras testing, in part because there is no commercially available test. ♦ Use of Imclone's Erbitux is growing slowly but steadily, but there is game-changing data coming at ASCO 2008. ♦ Oncologists were taking a more subdued or reasoned approach to Genentech's Avastin in various cancers. ♦ The news was positive but not dramatic about Bayer/Onyx's Nexavar. U.S. doctors are divided on how long liver cancer patients should stay on it; some treat through progression, and others stop on progression. The outlook in Asia will depend on reimbursement. ♦ The data in GIST for Novartis's Gleevec were described as "remarkable." ♦ Worldwide safety and efficacy data on Pfizer's Sutent showed no new toxicity and expected efficacy, but Pfizer's tremelimumab failed in gastric and esophageal cancer. ♦ Taiho/Sanofi-Aventis's S-1, an oral 5-FU, looks promising, but there is concern that the Japanese data are not sufficiently rigorous, and American doctors want to see the results of the ongoing U.S. trial in gastric cancer. ♦ Genomic Health has a genomic assay in development for CRC similar to its breast cancer test, Onco*type* DX.

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AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) 2008 GASTROINTESTINAL CANCERS SYMPOSIUM

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There were no hot topics at this year's ASCO-GI meeting. Dr. Jordan Berlin of Vanderbilt, the ASCO-GI program chair, said, "This year, I would say we don't have any hot topics where something dramatically new came up. Now, I think we are in a period where we are adjusting what we know with some of the side effects and learning more about the biology of the disease. It is a sense of refining treatment, with better dosing and different combinations – small steps to increase overall results."

There will be a consensus conference, with a statement, paper, and editorials in the ***Annals of Surgical Oncology***, out by summer on localized and resectable pancreatic adenocarcinoma. Dr. Berlin said, "This will be more on what we shouldn't do than what we should do, such as starting radiation immediately post-surgery."

K-RAS AS A BIOMARKER FOR EGFR RESPONSE

There were several data presentations on using a biomarker – K-ras mutations – to determine which patients respond to Amgen's Vectibix (panitumumab) and which don't. Dr. Heinz-Josef Lenz of the University of Southern California's Norris Comprehensive Cancer Center said, "K-ras has the potential to change how EGFRs are used." He pointed out that:

- "In all the studies where patients have mutant K-ras there is basically no response (to the EGFR inhibitor). In the presence of wild-type (WT) K-ras, you have responses from 10% up to 50%.
- "It will not predict 100% response, but it increases the likelihood of response.
- "K-ras mutation may be associated with tumor stages.
- "You could make the argument that mutant K-ras patients are sicker, have more metastases, or behave worse…but in (our) study there were no differences in the patient population of WT vs. mutant K-ras.
- "K-ras mutation status trends with PFS.
- "Data at AACR (American Association for Cancer Research) last year…showed clearly that patients with mutant K-ras did not have any benefit of EGFR inhibition, and patients with WT did have increased PFS, indicating WT allows more effective EGFR inhibition with downstream effects on tumor growth and angiogenesis.

- "K-ras may also affect the success of chemotherapy and chemotherapy in combination with targeted agents…In our 36 mCRC patients treated with FOLFOX + Avastin (Genentech, bevacizumab), we looked at K-ras, and there was a doubling of PFS in WT patients vs. mutant K-ras patients.
- "Is K-ras a marker of resistance and also a prognostic marker? We'll know at ASCO (2008)."

If K-ras has utility as a biomarker for EGFR response, it appears the utility is more with Vectibix than Imclone's Erbitux (cetuximab). K-ras appears to be a less significant test for determining response to Erbitux, and one expert speculated that this is because the Vectibix dose is the maximum tolerated dose (MTD), and the Erbitux dose is not the MTD. So, maybe, he speculated, if a higher Erbitux dose were given, you would see a differentiation between WT and mutant K-ras.

However, there were some experts arguing that K-ras is an appropriate way to select patients now for either EGFR inhibitor – Erbitux or Vectibix. Dr. Eric Van Cutsem of Leuven, Belgium, said, "At least in chemo-refractive patients, it is mature enough to be used."

K-ras in First-Line Treatment with Erbitux

Endpoint	Monotherapy		Overall assessment	
	Wild-type	Mutation	Wild-type	Mutation
Overall response	27.6%	0	55.2%	31.6%
Median PFS	N/A	N/A	9.4 months	5.6 months

Dr. Rafael Amado of Amgen reported on Vectibix efficacy and patient reported outcomes (PROs) in mCRC patients with WT K-ras tumor status from an analysis of an open-label, crossover Phase III trial of Vectibix in chemotherapy-refractory patients. He found, "In patients with chemotherapy, the clinical efficacy of panitumumab appears to be restricted to patients with WT K-ras…Patients considered for panitumumab therapy should be genotyped for K-ras status if a test is available."

K-ras Status in mCRC Patients Treated with Vectibix

Endpoint	Vectibix-treated patients		Best supportive care patients	
	Mutant	WT	Mutant	WT
PFS	7.4 weeks	12.3 weeks	7.3 weeks	7.3 weeks
Overall survival	4.9 months	10.1 months	4.4 months	7.6 months

Oncologists questioned about the use of K-ras stratification for panitumumab – or Erbitux – use generally agreed the data are interesting, but that it is too premature to deny an EGFR inhibitor to patients who have K-ras mutations. Few doctors plan to use K-ras tests to select patients for either Vectibix or Erbitux because:

1. There is no reimbursement yet for K-ras testing, and until there is, oncologists said they wouldn't do it.
2. There is no commercially available K-ras test. MD Anderson has its own K-ras test available to its doctors (and perhaps outside doctors), but not even all the oncologists there who treat CRC agree on the utility of K-ras testing or utilize it.
3. There is nothing else to offer K-ras mutant patients other than Erbitux or Vectibix, so doctors don't want to remove even a small chance of response.
4. There are still not quite enough data to convince oncologists that this test is ready for prime time. They will be looking for more data at ASCO 2008. Dr. Berlin said, "We are close to using K-ras, but how to use it is still not completely clear. In the next year or two, we will understand it…We keep looking for markers of effectiveness but find markers of ineffectiveness… (Eventually), K-ras will be like HER2. Breast cancer patients who are HER2 negative don't get Herceptin (Genentech, trastuzumab), and if patients are not WT K-ras, then most likely they won't get an EGFR-targeted agent…But we need to be sure K-ras testers know what they are doing. I recently saw a report that HER2 was being misinterpreted, and we want to make sure whoever interprets the K-ras test is doing it right."

Other comments on K-ras included:

- "K-ras can be different in different cancers. In esophageal cancer, K-ras is not so frequent (9%-10% of patients), so it probably would not have the same importance as in CRC."
- PharmaCell reportedly is working on an anti-K-ras test that measures circulating antibodies in the blood as a way to test for mutations.
- *Minnesota:* "K-ras testing will not increase use of panitumumab in my practice."

EGFR INHIBITORS

Dr. Van Cutsem discussed the integration of EGFR inhibitors into first-line therapy of colorectal cancer (CRC). He posed several questions and offered answers for some:

- *What is the optimal cytotoxic partner for EGFR inhibitors – irinotecan, oxaliplatin, or something else?* "Clearly, we need more data to answer this."
- *What is the optimal setting?* "EGFR inhibitors are accepted in third-line and chemo-refractive patients. What about first-line?"
- *What is the role of predictive markers?* "Predictive markers for response and activity are an important challenge. The K-ras data are focused mainly, for now, on chemotherapy-refractory patients. There are very little data on the role of K-ras in the first-line setting."
- *What is the importance of skin toxicity, and what is the relationship between skin toxicity and activity?*

- *What is the clinical significance of the increased resection rate of metastases with Erbitux in first-line therapy?* "This was seen in the CRYSTAL trial. This is probably important for some patients…We need more data and data in comparison to other combinations and to anti-angiogenesis inhibitors."
- *Can EGFR antibodies be combined with other biologics, like Avastin? How can we explain the negative findings of chemotherapy + Avastin + Vectibix in first-line metastatic colorectal cancer (mCRC)?*
- *What about the economic burden?*
- *Do EGFR inhibitors increase the activity of chemotherapy in the first-line setting?* "Yes, especially for Erbitux…But which subgroup of patients? It is clear we need to focus on subgroups, and there are no comparative data with Erbitux vs. chemotherapy + Avastin."
- *Do anti-EGFR antibodies increase the toxicity?* Yes.
- *Is toxicity in first-line acceptable?* Probably yes.
- *Is there an interaction between Vectibix and Avastin?* "We don't know."
- *Is K-ras a predictive marker for activity in first-line in combination with chemotherapy?* New data at ASCO 2008 may answer this.
- *Does Erbitux increase the resection rate in first-line mCRC?* Yes, according to the CRYSTAL trial data.
- *Are EGFR inhibitors an option in first-line treatment of mCRC?* "Probably yes, but the challenge is to determine for whom…We need more data on how to clinically select patients."
- *Are EGFR inhibitors today a standard treatment in first-line mCRC?* No.

PANCREATIC NEUROENDOCRINE TUMORS (PNET)

Dr. Mathew Kulke of Dana-Farber Cancer Institute reviewed current approaches to the management of PNET and GI carcinoids.

One of the biggest questions is what to do when patients progress on octreotide (Novartis's Sandostatin). Dr. Kulke offered his perspective on the treatment options:

PNET vs. GI Carcinoids

PNET	GI carcinoids
Well-differentiated with rare mitoses	Thought to be caused by secretion of serotonin and other neuropeptides into the systemic circulation
Ability to secrete neuropeptides, resulting in a variety of hormonal syndromes	Manifested by episodic flushing, diarrhea, and eventually right-sided valvular heart disease
Often resistant to standard cytotoxic agents	Treatment well-established with octreotide
Grows fairly slowly; often a fairly indolent course	

- **Interferon (IFN) –** "The data on this are somewhat mixed. It may have some benefit in stabilizing disease progression."
- **Treatment of liver metastases** – "Liver mets are one of the most common mets in patients with neuroendocrine cancer. Hepatic resection may be a good option, with 4-year survival ~70% and ~90% having improvement in symptoms…The difficulty is that there are often diffuse liver mets. Another option is hepatic artery embolization. Overall response rate (ORR) for this is 65%, with the duration of response 6.6 months. For hepatic artery embolization plus chemotherapy, the ORR is 81%, and the duration of response is 19.8 months."
- **Chemotherapy –** "The general sense is cytotoxic chemotherapy is less effective in patients with carcinoid tumors than with PNET." He said about a third of patients respond to streptozotocin (STZ) + doxorubicin, to dacarbazine (DTIC), and to temozolomide-based therapy (Schering-Plough's Temodar), but all of these work better in PNET than in carcinoid tumors. He added, "That doesn't leave many options in carcinoid tumors."
- **Somatostatin analogs,** such as 177 Lu-octreotate – "I look forward to looking at some of these to see how effective they might be and what the associated toxicity is."
- **Targeted therapies** – He called this an "exciting approach." But the response rates so far have been only about 7%-17% with Avastin, Bayer/Onyx's Nexavar (sorafenib), or Pfizer's Sutent (sunitinib). He added, "As single agents…one could say what's the big deal? But there are very high rates of stable disease (SD) – 75% with sunitinib in one study. It is difficult to determine what SD means…but the suggestion is that a number of patients had a minor response while not necessarily meeting RECIST criteria for response."
- **mTOR inhibitors,** such as Novartis's everolimus (RAD-001). Data at ASCO 2007 showed 17% PR and 75% SD, which Dr. Kulke called "encouraging activity." Two large randomized trials are ongoing.
- **Platinum therapy** – "There are some studies of platinum therapy in patients with poorly differentiated carcinoids… and those regimens do appear to be active."
- **Ki67** – "The Europeans may be somewhat ahead of us on this. It is commonly used in Europe. It does appear to have value, and it may become more useful, particularly as a stratification approach in the U.S."

Asked what he does today when he sees a neuroendocrine tumor patient not in a clinical trial, Dr. Kulke said, "That is one of the most challenging areas. It is very difficult to come up with a single algorithm that is good for all patients. Right now, we really are individualizing this. For example, a patient with primarily

hepatic mets that are relatively well-defined may benefit from surgical resection…Others with more diffuse disease may benefit from IFN, though that is associated with fatigue, and people don't like to use it much. The VEGF inhibitors and mTORs are exciting."

Asked whether he uses combination or single agent therapy if he is going to do systemic therapy, Dr. Kulke said, "Mostly, we start with single agents…I would caveat that in PNET, either STZ or a temozolomide-based therapy is a good option because we really are seeing a response rate there."

Asked if patients in large trials should be stratified by type – carcinoid or PNET – Dr. Kulke said "Absolutely. We used to lump them all together because the cells look similar under the microscope, but there are large differences…Mostly PNET do respond to chemotherapy and carcinoids don't, so I think the trials need to look at these separately."

Asked about the role of liver transplantation in neuroendocrine tumors, he said, "The data show that liver transplantation can result in very prolonged survival…Many patients will survive >5 years. The downside is many of those patients (>50%) will develop recurrences…So, it is a little difficult to determine if liver transplantation really is prolonging survival…And it is often very difficult to procure a liver for these patients."

Asked about the role of surgery in the management of these patients, Dr. Kulke said, "Surgery clearly has a role. These patients often have fairly indolent disease…We generally recommend surgery where there are 2-4 mets. It is less clear whether debulking surgery (is beneficial) where you know you will leave residual disease. In those cases, we lean more to chemotherapy."

Pancreatic Adenocarcinoma

Dr. Berlin said, "Ras could be the holy grail for pancreatic cancer, but it has a shape and behavior that makes it particularly difficult to block." Dr. Craig Logsdon of MD Anderson Cancer Center suggested that S100P may be a better target than EGFR in pancreatic cancer. S100P is a member of a large family of calcium-binding proteins. It is produced by pancreatic cancer cells, interacts with RAGE, and is elevated at the mRNA level in pancreatic cancer. It is really specific for pancreatic cancer; no expression is found in chronic pancreatitis.

The Ideal Pancreatic Cancer Therapy

Criteria	EGFR	S100P
Specificity for cancer	No	Yes
In a high proportion of tumors	Unclear	>94%
A critical function	EGFR is involved in several processes	S100P is involved in several processes
Preclinical data in a mouse model	Pretty good effect of EGFR inhibitor	Combination of cromalyn sulfate and Gemzar was better than an EGFR inhibitor
Preclinical efficacy	Limited to sensitive cells	Appears to increase the killing of resistant cells

And there is a drug that blocks S100P – cromalyn sulfate. The problem is cromalyn sulfate has no intellectual property, so no company wants to develop it for pancreatic cancer. However, several companies reportedly have cromalyn sulfate analogs in development for pancreatic cancer as well as other cancers.

Other Specific Drugs

Amgen's motesanib diphosphate (AMG-706) – effective in Japanese GIST patients

A Phase II study showed activity in Japanese GIST patients who were refractory to Novartis's Gleevec (imatinib): 3% PR, 20% SD ≥24 weeks, and median PFS of 113 days. The drug was "reasonably well tolerated," with manageable hypertensions, diarrhea, and fatigue the most frequent adverse events.

Amgen's Vectibix (panitumumab) – K-ras won't rescue this EGFR inhibitor

Vectibix was approved by the FDA in September 2007 for the treatment of mCRC, but use has been low, and there were no new data at ASCO-GI which is likely to change that. Vectibix *does* appear to have more utility in wild type K-ras patients than in mutant K-ras patients, but few doctors plan to use K-ras tests to select patients for either Vectibix or Erbitux.

An updated analysis was presented of the safety and efficacy of oxaliplatin/Avastin ± Vectibix for the first-line treatment of mCRC from the PACCE trial, which was stopped early because the Vectibix arm had more deaths (35% vs. 27%) and no improvement in response (45% vs. 46%). One of the investigators, Dr. Edith Mitchell of Thomas Jefferson University's Kimmel Cancer Center, commented, "While we expected skin toxicity to be higher with panitumumab, patients also had higher diarrhea, infections, hypomagnesia, and pulmonary embolisms…PFS was inferior with panitumumab in this study, and overall survival was also inferior with panitumumab. While dose intensity was similar in both arms, the number of patients with dose delays/reductions was *lower* with panitumumab…Based on the data of this interim analysis…(the addition of panitumumab) was associated with shorter PFS time and increased toxicity, indicating that this combination has an unfavorable risk:benefit profile in unselected patients with mCRC."

Dr. J. R. (Randy) Hecht reviewed the interim findings of the Phase IIIb PACCE trial, a U.S.-only community-based study of Vectibix, which was discontinued in March 2007. He concluded:

- Response rates appear to be higher in the panitumumab + Avastin/irinotecan arm but there were no significant differences in PFS and OS.

- Most patients withdrew due to non-progression events, limiting the utility of PFS as a valid endpoint in this study.
- The increased response rate with panitumumab in patients who had WT K-ras is a finding consistent with previously reported data in the monotherapy setting.

Dr. Charles Blanke of Oregon Health & Science University (OHSU), a consultant to Amgen, discussed the PACCE results. He commented, "Though I don't completely agree with all the conclusions, it was a well-conducted trial. The poor results were not entirely unexpected, given the previous report of (results with) panitumumab + oxaliplatin/Avastin. The major question from PACCE is, 'Should we close the C-80405 trial?' I believe the answer is no. the two antibodies are different agents, with different binding affinities and possibly different cellular effects...What about K-ras? I don't know. We can't definitively say yet…What is the future of panitumumab in CRC and other cancers?...It is not dead."

BAYER/ONYX's Nexavar (sorafenib) – use continuing to expand and news generally very positive but not dramatic

➢ **Asia:** The Nexavar liver trials in Asia are still ongoing, but the outlook is promising, and Asian doctors are excited about it (well, in their low key way). Several doctors – Japanese and Korean mostly – said that if it is approved, they would use it in "most" patients if it is covered by insurance/government, but they pointed out that there is no proof yet that it works. The speed of adoption and uptake will depend on, first, the data, and then on reimbursement.

Phase II Trial of Nexavar in GIST

Measurement	Gleevec-resistant GIST n=6	Gleevec- and Sutent-resistant GIST n=20
Median cycles given	4 (range 1-14)	
Dose reduction for toxicity	67%	
Efficacy		
CR	0	0
PR (confirmed)	17%	11%
Stable *	50%	61%
Progression-free survival	5.3 months, with no significant difference between the 2 cohorts	
Median overall survival	13.0 months	
Estimated 1-year survival	62%	
Grade 3 Toxicity (n=25)		
Hand-foot syndrome	28%	
Hypertension	24%	
Rash	20%	
Diarrhea	12%	
Fatigue	8%	
Thrombosis	4%	
Perforated bowel	4%	

* Several stable patients "showed substantial improvement in symptoms, despite a lack of objective response."

➢ **GIST:** The results here looked very promising in both Gleevec-resistant and Sutent-resistant patients, but dose reductions were required in two-thirds of patients. Based on data from 26 patients in an ongoing multicenter study (with planned enrollment of 32 patients) sponsored by the National Cancer Institute (NCI), researchers concluded that 400 mg Nexavar BID is active in GIST resistant to Gleevec and/or Sutent. However, dose reductions were required in 67% of patients.

Initially, the trial was only in Gleevec-resistant patients, but after the FDA approved Sutent to treat GIST, a second cohort was started for patients resistant to both drugs. Disease progression was documented by RECIST criteria. A mutational analysis is ongoing.

Asked if Nexavar should only be used in third-line GIST, Dr. Halla Nimeiri of the University of Chicago said, "At this point these data are preliminary for use of TKIs (tyrosine kinase inhibitors) as third-line, but with more data I think we will say this can be third- or even second-line in metastatic GIST… With a lot of TKIs in the pipeline, the mutational status may help us know which (agent) to use…At this point, we have a lot of options."

➢ **Liver cancer:** A subgroup analysis found that Nexavar is effective whether the patient has Hepatitis C or not. The efficacy in liver was described as "modest."

Should liver patients be treated through progression? The field appears to be divided and confused on this question. About half the doctors questioned said yes, and the other half said no. The main reason cited for continuing Nexavar was that there is nothing else to offer those patients. Other doctors simply saw no point in continuing it on progression and did not believe that patients worsened upon cessation. Comments included:

- *MD Anderson oncologist:* "We are trying to teach doctors to keep patients on it through progression, and we are trying to study and learn how to stop it."
- *Dr. Berlin:* "Some oncologists treat through progression, but I'm on the 'don't' side…There is a detriment in terms of cost and side effects. My experience is sorafenib really causes fatigue in a significant number of patients."
- *Memorial Sloan Kettering oncologist:*"Defining progression in hepatocellular carcinoma is difficult because of cirrhosis and the number of lesions. It's not like CRC."

The final Phase II interim data were presented from the randomized, double-blind trial of doxorubicin ± Nexavar in Child-Pugh A patients with advanced hepatocellular carcinoma (AHCC). After an unplanned analysis in January 2007, the DSMB recommended discontinuation of the trial because the results were so encouraging on TTP and OS.

Final Phase II Data of Nexavar in AHCC

Measurement	Doxorubicin + Nexavar n=47	Doxorubicin + placebo n=49	p-value
Primary endpoint: TTP	8.6 months	4.8 months	Nss, 0.076
CR+PR	4%	2%	---
SD	77%	55%	---
Secondary endpoints			
OS	13.8 months	6.5 months	0.0129
PFS	6.9 months	2.8 months	0.012
Adverse events			
Drug-related	92%	88%	---
Serious adverse events	38%	42%	---
Death within 30 days	11%	20%	---
Grade 3-4 neuropathy	55%	46%	---
Grade 3-4 hand-foot syndrome	9%	0	---
LV dysfunction	2%	0	---
Febrile neutropenia	4%	15%	---
Bilirubin elevation	11%	6%	---

Dr. Alan Paul Venook from the University of California, San Francisco, discussed the findings, commenting, "These are pretty profound results…But the LV changes, despite a low total doxorubicin dose, raise the issue of synergistic toxicity."

Nexavar is the only systemic therapy approved by the FDA and the European Medicines Agency (EMEA) for treatment of hepatocellular carcinoma (HCC). Dr. Fabio Piscaglia of Italy presented a subgroup analysis of Nexavar patients from the SHARP trial, looking at efficacy based on baseline liver function. The results were "consistent with those of the overall SHARP population…Nexavar was effective for patients with HCC regardless of HCV status – so it was effective in the patients we see in everyday life in our unit."

Dr. Venook, the discussant, said both studies (AHCC and SHARP) are "difficult to interpret," adding, "These advances, while landmark, are modest, and we have a whole lot more work to do." He said, "SHARP was a landmark study…(but) these were selected patients…(In this analysis) the benefits appear to accrue to HCV patients just as they did to the entire cohort. (But) I would emphasize these are still high performance HCV patients…and may not be representative of patients at large."

BRISTOL-MYERS SQUIBB's Sprycel (dasatinib) – possible activity in mCRC and in mutant K-ras

A poster presented data suggesting that Sprycel has activity in mCRC patients refractory to Erbitux, and there was preclinical data suggesting that it works in mutant K-ras. However, this agent would have to be combined with something; it is not monotherapy for mCRC. An EGFR + Sprycel may be a useful combination.

GENENTECH's Avastin (bevacizumab) – return to reasoned use

Avastin has shown activity in pancreatic cancer, but there is increased caution about patient selection and about its use in the neoadjuvant setting of all cancers. The hype around Avastin has died down somewhat. This wasn't exactly a negative meeting on Avastin, but it might be characterized as a "cooling down" period. An ASCO official described the Avastin mood as "increased caution in the neoadjuvant setting and in patient selection." There was nothing at this meeting to suggest Avastin use will increase over the next 6-12 months.

It has become clear that: (1) Avastin does not work in everything or even almost everything, and (2) the toxicity is not minimal. Avastin did show some activity in pancreatic adenocarcinomas, but it has to be used very cautiously before surgery in these patients (stopping at least 8 weeks before surgery). And more attention is being given to Avastin toxicity.

U.K. researchers reported on the combination of Avastin + Tarceva (Genentech, erlotinib) + capecitabine + Gemzar (Lilly, gemcitabine) in pancreatic cancer, and they reported it doubled the time to progression – from the 6 months expected with Gemzar alone to 14 months – but the capecitabine dose had to be cut by 15%. One researcher commented, "There is a scientific rationale for synergy." However, other researchers questioned those findings.

Dr. G. R. Varadhachary of MD Anderson Cancer Center said that a study of the combination of Gemzar + Avastin-based chemoradiation for resectable pancreatic adenocarcinoma was "unable to be completed due to the unexpectedly high rate of adverse events related to impaired wound healing…The post-op complication rate was unacceptably high…We believe the combination of Avastin with either radiation or gemcitabine or both may have contributed to the poor wound healing…The median time from Avastin use to surgery was 7.9 weeks, and this may have been insufficient…We recommend the delivery of pre-operative chemoradiation with Avastin should only be done within a clinical trial."

On the other hand, Dr. William Small of Northwestern discussed a Phase II trial of weekly Gemzar + Avastin + abdominal radiation therapy (XRT) in patients with localized pancreatic cancer, which found the combination was "generally well tolerated, with no obvious increase in operative morbidity."

Dr. Douglas Tyler of Duke University Medical Center reviewed these two presentations, concluding, "The exact clinical or pathological benefits of adding Avastin to the protocol is currently unclear. Avastin probably increases perioperative complications, especially within 8 weeks of the last dose, and the risk may be increased by concurrent radiation."

IMCLONE's Erbitux (cetuximab) – use is growing but still slowly, but watch for game-changing data at ASCO

Use in first-line CRC is starting to look appealing, and there were data that first-line use actually improves the surgical resection rate. However, oncologists want to wait for the data at ASCO 2008. There's a real buzz about this, and there will be a lot of attention on that data. If it is positive, use of Erbitux will go up.

There was no information and no buzz on any next generation antibodies from Imclone or from other companies at the meeting.

NOVARTIS's Gleevec (imatinib) – "remarkable" 3-year data in GIST

The results of the first trial of the use of Gleevec as adjuvant therapy in GIST were presented at ASCO-GI. In the Z9000 Phase II trial, Gleevec was started ~84 days after surgery and continued for one year, then the patients were followed for another two years. Patients could not have taken Gleevec prior to surgery to be eligible for the study.

Safety data from the Z9000 trial was presented at ASCO in 2006, and researchers reported at that time that 83% of patients had completed one year of prescribed Gleevec (400 mg/day), with ~18% of patients experiencing Grade 3 toxicity but no Grade 4-5 toxicity. Dr. Ronald DeMatteo of Memorial Sloan Kettering Cancer Center said that toxicity profile is very similar to what is seen with Gleevec in metastatic GIST.

In the data presented at ASCO-GI, overall survival at three years was a remarkable 97%. Dr. DeMatteo commented, "This shows how well the drug rescues people…There were very few recurrences in the first year (on Gleevec), and then after 1.5 years the slope of the line changes drastically…So, roughly speaking, one year of imatinib protects you for about 1-1.5 years, and then patients are at much higher risk of recurrence."

New data presented from the Z9000 trial showed a difference in response to Gleevec with several mutations. Dr. DeMatteo said, "Patients with an Exon 9 mutation have the poorest outcomes and the highest chance of recurrence, especially after stopping the drug…Patients with an Exon 11 mutation did better but not as well as patients with wild-type or PDGFRA mutations."

Results of Z9000 Phase II Trial of Adjuvant Gleevec in GIST

Measurement	Gleevec (n=107 evaluable)
Overall survival	
1 year	99%
2 years	97%
3 years	97%
Recurrence-free survival (RFS)	
1 year	94%
2 years	73%
3 years	61%

A second trial conducted at the same time (Z9001) looked at RFS in patients with tumors ≥10 cm. With Gleevec, RFS was 82% vs. 76% with placebo. Overall survival also significantly favored Gleevec ($p<0.001$), causing the trial to be stopped early. In this trial, RFS also fell off when the Gleevec was stopped after one year, and by Year 2, patients had a nearly 75% chance of developing recurrence. Dr. DeMatteo said the results of the two trials (Z9000 and Z9001) were "basically superimposable."

Asked how long Gleevec should be given after resection, Dr. DeMatteo said, "That's the million dollar question…If the goal is to prolong RFS and not just overall survival – because we don't have that (survival) data yet, most likely more than a year of therapy is indicated, and we are trying to design a trial to answer the duration question, which I think is the most important question at this time."

Dr. Paolo Casali of Italy discussed the findings in this trial. He pointed out that, even though the trial was long, it was small. He said that European researchers don't believe the findings are sufficient to declare that Gleevec should become the standard of care, "On the other side of the Atlantic, there has been some skepticism of the meaning of these results…At ESMO (European Society for Medical Oncology), we decided to keep adjuvant Gleevec as investigational, not standard… Basically, it was said (by the Europeans) that RFS at one year is too early to say a lot. The decision was to keep open the European randomized trial, despite the fact that we have a control arm without adjuvant therapy. We said RFS is not enough; we must look at overall survival, which is the endpoint of our trial. Our American colleagues recently said we are waiting too much – that there are a lot of GIST patients with a high risk of relapse, and they can't wait that long."

One of Dr. Casali's concerns is that RFS at one year could be only a delay, not an absolute decrease. He said that secondary resistance to Gleevec needs to be known, "There is the possibility that the time to secondary resistance may be shorter for patients already exposed to Gleevec as adjuvant therapy."

Dr. Casali also had a slightly different take on the mutational findings: "Exon 9 mutations didn't fare well. This might depend on the dose. We know from advanced (GIST) studies that 800 mg may do better in this selected subgroup of patients." The PDGFRA patients fared better, though there was a small number (n=10). One very important mutation in this group doesn't respond at all…The most responsive mutations have the worst prognosis, and the least responsive mutations have the best prognosis."

NOVARTIS's vatalanib (PTK-787) – may work in neuroendocrine cancer but Novartis not pursuing that

Novartis appeared to give up on vatalanib when it failed to delay progression in CRC, but a 17-patient Phase II study

done by researchers at Louisiana State University – without the support of Novartis – showed good response in progressive neuroendocrine cancer with vatalanib 1250 mg BID (29% PR in patients in accelerated phase and a 15% partial radiographic response).

PDL BioPharma's volociximab – probably no role in metastatic pancreatic cancer

Interim results from a Phase II study of volociximab in combination with Lilly's Gemzar (gemcitabine) in metastatic pancreatic patients were disappointing, and the drug may not go forward in pancreatic cancer. An investigator said, "I'm not convinced this study justifies going to Phase III…I think the company should try it in other disease (other cancers) – not more in pancreatic cancer – unless we get a biomarker to tell who will respond."

Volociximab is an angiogenesis-inhibiting monoclonal antibody. Its mechanism of action is thought to be different from other angiogenesis inhibitors. The study presented was a open-label, multicenter, Phase II study in chemotherapy-naïve patients, testing two doses – 10 mg every 2 weeks and 15 mg weekly. Here is an update of the 10 mg data and preliminary data on 15 mg. There was no unexpected toxicity and no response.

Interim Phase II Results of Volociximab in Metastatic Pancreatic Cancer

Measurement	10 mg Q2W n=18	15 mg QW n=16
Overall survival	6.6 months	4.8 months
Overall survival at Day 344	34% at 1 year	21% at Day 344
Overall survival at Day 628	7%	---
CR	0	0
PR	5%	10%
SD	50%	40%
Median PFS	3.8 months	3.4 months
Grade 3-4 adverse events		
Neutropenia	15%	20%
Lethargy	10%	0
Fatigue	10%	20%
Pleural effusion	10%	---
Ascites	10%	10%
Nausea	5%	10%
Vomiting	0	10%
Pulmonary embolism	---	20%
Stent occlusions	---	10%

Pfizer's Sutent (sunitinib) – no new toxicity, efficacy as expected

Pfizer researchers reported on the ongoing, open-label, multicenter, worldwide safety and efficacy trial of Sutent in GIST, which showed no new toxicity, and efficacy was as expected. Median follow-up for this analysis was 261 days.

Worldwide Treatment-Use Trial of Sutent in GIST Patients

Measurement	Sutent
Dose interruptions	57% (79% of these due to an adverse event)
Dose reduction	39%
Discontinuation for any reason	66%
Median TTP	37 weeks
Median OS	73 weeks
Most common treatment-related non-hematologic adverse events >30%	Fatigue, diarrhea, nausea, abdominal pain, vomiting
Most common treatment-related hematologic adverse events	Anemia, thrombocytopenia, neutropenia
Hypertensions	23% (Grade 3/4 6%)
Heart failure	0.5%

Pfizer's tremelimumab (CP-675,206) – failed in gastric and esophageal cancer

U.K. researchers presented Phase II data on use of this anti-CTLA-4 that showed no clinical responses by RECIST in patients with advanced gastric and esophageal adenocarcinoma, though two patients showed tumor shrinkage (≤18%). Grade 3 adverse events occurred in two patients, and one – who developed pan-colitis, a recognized toxicity of CTLA-4 blockade – died. The researchers concluded: "Given the lack of objective responses, it may be appropriate to consider combining tremelimumab with vaccines or other immunotherapies to augment its anti-tumor activity."

Regeneron's VEGF-Trap in CRC

There were no data – and no buzz – at the meeting about VEGF-Trap in CRC.

Taiho Pharmaceutical/Sanofi-Aventis's S-1, an oral 5-FU – good data in Asian patients, but most American oncologists skeptical

S-1, a combination of three agents – tegafur (a prodrug of 5-FU), 5-chloro-2,4-dihydroxypyridine, and potassium oxonate – is approved in Japan to treat gastric cancer and reportedly is the biggest selling drug in Japan for oncology. It is better tolerated than 5-FU. There was a lot of Japanese and some Korean data at the meeting on S-1 in gastric and other GI cancers, and the data looked very good plus it is an oral with better tolerability than 5-FU.

However, American experts were still skeptical. One U.S. doctor warned, "We don't trust the Japanese data." On the other hand, an American 5-FU researcher is "optimistic" about its chances for approval by the FDA for gastric cancer, an initial niche that could expand.

The Japanese had a lot of data on S-1 at the meeting, so this bears watching, and the outlook appears much better than for Bristol-Myers Squibb's oral UFT (that Taiho also developed), which the FDA turned down a few years ago. Reportedly, Taiho has done studies showing an additive benefit to each of the agents in S-1, so it may not have the same regulatory problems. Among the studies presented at ASCO-GI were:

- The SPIRITS trial in Japanese patients with advanced gastric cancer found that S-1 + CDDP was previously shown to be superior in overall survival to S-1 alone in overall survival, PFS, TTF, and response rate, making it a better combination than CPT-11 + CDDP. A new analysis at ASCO-GI found that the Kohne Index was a useful baseline risk factor predictor for overall survival in patients receiving S-1.
- The randomized Phase III GC-0301/TOP-002 trial in Japan found that S-1 + irinotecan produced significantly higher response rates than S-1 alone (p=0.035) as first-line treatment for advanced gastric cancer. Median survival was longer with S-1 but not statistically significant.
- A multicenter Phase II study of S-1 + Gemzar in 38 unresectable pancreatic patients in Korea. The response rate was 23.5% (all PR), with 41.2% SD. PFS was 5.4 months and OS 9.3 months, indicating the combination is effective. (The S-1 for this study was provided by Jeil Pharm.)

Interestingly, the dose used in Japan is ***higher*** than that which is tolerable in Americans. The Japanese dose in pancreatic and gastric cancer is 40 mg BID, but the U.S. Phase III trial in gastric cancer is using 5 mg BID. An American expert said, "With this, there is clearly a difference in tolerability, with Asian tolerance much better than U.S. tolerance. We think the differences are due to differences in diet. We have done U.S. studies in gastric cancer – and one trial is ongoing in pancreatic cancer – and we feel firmly that we need to confirm the Japanese data, which had small numbers, limited institutions, and highly selected (healthier) patients. I'm very cautious on the data, but there is a lot of encouraging data…There is also a disadvantage to an oral 5-FU. In GI disease, patients often have digestion problems. But the advantages outweigh the disadvantages."

OTHER AGENTS AND TESTS

Erythropoiesis stimulating agents (ESAs) – use continuing to fall

In mid-January, Amgen reported that sales of EPO fell 12% in 2007, and oncologists suggested that 2008 may show even further drops. Academic oncologists questioned at ASCO-GI insisted their use of ESAs has gone down substantially, but community use may still not have reached bottom. An expert pointed out that community oncologists may be lagging behind in changing their ESA use, "It tends to take 6-12 months to see a significant change in patterns of behavior (among community oncologists)." He said the first six months of 2008 are more critical to watch to determine changes in ESA use by oncologists.

Pegylated irinotecan – promising and with real utility

Several companies are working on pegylated irinotecan, and oncologists insisted that there is a need, just as there was for Abraxis Oncology's Abraxane (albumin-bound paclitaxel nanoparticles) in breast cancer. A Swedish researcher explained, GI toxicity is a limiting factor with irinotecan use. It is not a huge issue, and it is manageable, but there are certain patients, especially if they had a prior bowel problem, where is it an issue. A pegylated irinotecan might minimize the GI toxicity and increase the response." Dr. Berlin said, "The hope is that it will decrease toxicity (diarrhea), that this would cause a significant increase in quality of life and, hopefully, decrease neurotoxicity. There is also hope of better delivery into the tumor, but I'm cynical. If there is less toxicity, it would be used, but by the time it is available, there will be generic irinotecan…Pegylated irinotecan would be widely used because diarrhea with a low white blood count is a deadly complication, even though it is rare for someone to die from irinotecan. But the cost issue will limit how fast the change occurs."

Yakult, a Japanese pharmaceutical company, is one of the pharmas working on a pegylated irinotecan. A Yakult researcher said, the advantages include:

- Less toxicity (hopefully).
- Longer release profile.
- Low concentration but longer effect.

Tyrosine kinase inhibitors (TKIs) – no one knows how to tell them apart yet

A researcher working on Amgen's AMG-706 said, "It is very difficult. The safety profiles are a little different. We think AMG-706 is better than for Sutent, and there is less myelosuppression. Efficacy is comparable – depending on the patient's status and how heavily the patient is treated." Dr. Berlin agreed, "It is very difficult. It is a broad class that hits a variety of targets. It is hard for oncologists to follow the science…and the naming has gone wild, with names like Hedgehog, Sonic Hedgehog, etc. Non-uniform naming is confusing the heck out of people. It is like finding your way around the New York subway system without a map."

GENOMIC HEALTH – working on a test for CRC similar to Onco*type* DX (maybe Onco*type* CRC?)

Genomic Health is working on a reverse transcription-polymerase chain reaction (RT-PCR) assay for CRC that would quantify both the likelihood of recurrence and the amount of absolute benefit from chemotherapy in patients with Stage II-III CRC initially treated with surgery, much as their Onco*type* DX test does in breast cancer.

An official explained that Genomic Health is a CLIA reference lab, so it is governed by CMS and not the FDA. The FDA has been proposing to regulate multi-analyte tests, but it hasn't done that yet. The Agency has discussed it but has not issued a regulation. He refused to say whether the company will be doing any clinical studies for a possible PMA filing.

Technical feasibility and gene identification studies have been successfully completed, and the company is now conducting gene refinement studies. A validation study is planned to start this year, but details about the size or design have not been made public.

Two posters were presented at ASCO-GI on the relationship between tumor gene expression and recurrence in patients with Stage II/III CRC treated with:

- **Surgery + 5-FU/leucovorin in the NSABP C-06 trial.** The company reported that the prognostic genes were found confirming the results of studies carried out in patients treated with surgery alone in another NSABP trial (C-01/C-02) and at the Cleveland Clinic. A subset of these genes is being used to develop a treatment score.
  - 169 genes had a significant linear relationship with RFI ($p<0.05$).
  - 137 genes had a significant linear relationship with RFI ($p<0.05$) after controlling for important covariates.
  - 56 genes had a significant relationship with RFI ($p<0.05$) in C-06 and 2 independent, surgery-only studies (prognostic).
  - 69 genes had significant interaction between gene expression and treatment; most of the predictive genes were not associated with RFI in surgery-only studies (predictive).
- **Surgery only.** The company reported that 65 genes exhibited a significant relationship with RFI ($p<0.05$), and these will be validated in an independent study.

This test is likely to be priced similarly to the breast cancer test. A company official said, "We price based on the 'value' of the test."

JOHNSON & JOHNSON/VERIDEX's CellSearch

Dr. Neal Meropol of Fox Chase Cancer Center said tests like this, measuring circulating tumor cells (CTCs) are promising as predictive markers, but they still need to be further validated in prospective, randomized clinical trials, and he reviewed several ways such trials could be designed. He said, "Are they predictive markers? Maybe. There really are not data yet on phenotyping/genotyping CTCs and response to therapy, but this is an active area of investigation." He said many questions remain, including:

- What are "circulating tumor cells?"
- Are CTCs the same as *in situ* cancer? How are they different or similar?
- How does the cell separation process affect gene expression?
- How can CTCs be used in the drug development process?
- How can CTCs be integrated into routine patient care?

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