Trends-in-Medicine

May 2005
by Lynne Peterson

SUMMARY

Use of Genentech/Roche's Avastin is likely to expand with new data that it improves survival in lung cancer and breast cancer. ♦ Data on the benefits of Genentech/ Roche's Herceptin in adjuvant breast cancer are building, and some oncologists are even looking at combining Herceptin and Avastin. ♦ In advanced colorectal cancer, researchers insisted that there is still hope for Novartis/Schering AG's oral VEGFR inhibitor, vatalanib (PTK-787). ♦ In renal cell carcinoma, oncologists are not sure yet how they will choose between Pfizer's Sutent and Bayer/Onyx's sorafenib, both of which appear to be effective and safe, but they expect to split their use equally until they have more experience with them. ♦ In GIST, Pfizer's Sutent looks a little less promising than earlier data suggested.

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

AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)

Orlando, FL
May 13-17, 2005

ASCO President-Elect Dr. David Johnson said the focus at ASCO this year is the big cancers: "We're not minimizing CML (chronic myelogenous leukemia) or GIST (gastrointestinal stromal tumor), but this year we will hear major advances in the big cancers – lung, colon, and breast…And in each of these areas, there is at least one presentation that will change how we treat that disease."

The two key drugs most likely to change treatment are both by Genentech/Roche – Avastin (bevacizumab) and Herceptin (trastuzumab). However, there also was news about renal cell carcinoma (RCC), GIST, multiple myeloma, melanoma, and vaccines. ASCO CEO Dr. Charles Balch said, "These are the richest advances in any of the last six years. Practice changing things will come out of this meeting." Dr. Roy Herbst of M.D. Anderson Cancer Center said, "We've clearly seen that angiogenesis is certainly here to stay in some of the major tumor types."

LUNG CANCER

More than 172,000 new cases of lung cancer are diagnosed each year, according to the American Cancer Society, with more than 163,000 deaths per year. About 85% are NSCLC, and about 85% of NSCLC is non-squamous.

GENENTECH/ROCHE'S Avastin (bevacizumab)

A second planned interim analysis of a Phase III trial (ECOG E4599) of 878 patients found adding Avastin to standard combination chemotherapy (paclitaxel + carboplatin) improves survival in Stage IIIb/IV NSCLC. The trial was powered to show an improvement in median survival from 8.0 months with standard chemo-therapy to 10.4 months with the addition of Avastin.

This trial excluded patients with a history of hemoptysis (bleeding of the lung), brain metastases, or squamous cell lung cancer, since earlier Avastin studies had found a serious risk of life-threatening bleeding in patients with that form of lung cancer. An expert said, "The bleeding we saw may represent not just annoying side effects, but a potential efficacy effect…Future studies will be done to see if we can treat squamous cell patients who potentially may benefit more."

Doctors were asked whether they would now use Avastin off-label in lung cancer, on the basis of this data. Their responses included:

- "Based on the data I just saw, I would give Avastin, and it should be the new standard-of-care. It has some risk, but the risk is manageable, and it is being used in patients with an incurable disease."
- "I'm enthusiastic, but I need it to be approved or in the Compendia before we start using it (because that is what determines reimbursement)."

- "This is just the beginning for Avastin in lung. Now, we'll be looking at it in combination with chemotherapy and radiation, in locally-advanced disease, with chemotherapy in adjuvant disease, and in combination with other targeted agents… Instead of saying Avastin adds two months to survival in lung cancer, I would tell patients that they have a 25% better chance of living to one year and to two years with Avastin."
- "Doctors will definitely use Avastin off-label in NSCLC now if they can get reimbursed for it. This is the first positive survival study in lung cancer in a long time. It is big news…The hemoptysis is a predictable but manageable side effect."

Phase III Trial of Avastin in NSCLC

Measurement	Avastin 15 mg/kg + standard chemotherapy n=434	Standard chemotherapy alone n=444	p-value
Primary endpoint: Median survival	12.5 months (30% improvement)	10.2 months	.0075
Survival at 12 months	51.9%	43.7%	---
Survival at 24 months	22.1%	16.9%	---
Secondary endpoint #1: Response rate	27%	10%	<.0001
Secondary endpoint #2: Progression-free survival	6.4 months (61% improvement)	4.5 months	<.0001
PFS at 6 months	55.0%	32.6%	---
PFS at 12 months	14.6%	6.4%	---
Grade 4/5 neutropenia	24%	16.4%	---
Deaths due to hemoptysis	5 patients	0	---
Grade 3/4 thromboembolism	3.8%	3%	---
Hemorrhage	4.1%	1.0%	---
Treatment-related deaths	9 patients (5 due to hemoptysis)	2 patients	---

COLORECTAL CANCER (CRC)

NOVARTIS/SCHERING AG'S vatalanib (PTK-787) in advanced CRC

Researchers continue to insist that this oral VEGFR inhibitor is not yet dead. In initial findings from the randomized, double-blind, placebo-controlled, 168-patient Phase III CONFIRM-1 trial, vatalanib + FOLFOX missed its early primary endpoint of progression-free survival, but the trial is continuing as researchers wait for the late primary endpoint of overall survival. The final results are expected in 2006. Side effects included hypertensions and thromboembolic events, nausea, fatigue, vomiting, and dizziness, but there was no increase in bleeding or bowel perforation vs. placebo.

9.4-Month Interim Analysis of Phase III Trial of Vatalanib in CRC

Measurement	Vatalanib 1250 mg QD + FOLFOX	Placebo + FOLFOX	p-value
Analysis of central lab			
Primary endpoint #1: PFS	7.7 months	7.6 months	Nss (.118)
Primary endpoint #2: Overall survival	Not reached yet		---
PFS in patients with high blood level of LDH	7.7 months	5.8 months	.010
Investigator analysis			
PFS	7.7 months	7.5 months	.026
PFS in patients with high blood level of LDH	9.6 months	5.8 months	.002
Grade 1-4 adverse events			
Pulmonary embolism	6.0%	1.4%	---
Arterial thromboembolism	3.6%	1.7%	---
Grade 3 adverse events			
Hypertension	20.6%	5.9%	---
Diarrhea	14.5%	10.3%	---
Dizziness	6.6%	2.1%	---
DVT	4.7%	3.0%	---

An investigator analysis was more positive than the central lab's analysis, and investigators identified patients with high levels of LDH, an enzyme that breaks down glucose. A researcher said, "One of the problems with targeted therapies is finding which patients to give them to. In CRC, at least, that has been difficult. This is interesting data…very intriguing data. It opens up a whole field of research to find out why LDH is important. You can conjecture…but this may indicate a group of patients that are VEGF-driven, but that is very conjectural. This is a place to start for further research."

Asked how optimistic he is about this drug, the researcher said, "Progression-free survival was the first primary endpoint, and that was a fairly high bar because if this hit, it would be the first colorectal cancer trial to use progression-free survival for regulatory approval. I don't think all the data are in…I remain optimistic on the survival benefit (the other primary endpoint, which hasn't been reached yet). We deliberately made progression-free survival difficult. It would have been nice to hit it, but it didn't...I haven't given up optimism about the second primary endpoint (survival)."

BREAST CANCER

GENENTECH/ROCHE'S Avastin (bevacizumab) in metastatic breast cancer

Before ASCO, Genentech announced that an interim analysis of the randomized, Phase III, 715-patient, ECOG E2100 trial of Avastin + Taxol in first-line therapy of HER2+ locally recurrent or metastatic breast cancer was positive. The trial was powered to show a two-month improvement in progression-free survival (PFS), but the trial actually showed a 4.86 month improvement in PFS with Avastin (10 mg/kg EOW), a 50% improvement with Avastin. However, longer follow-up is required to assess overall survival.

Interim Analysis of Phase III ECOG E2100 Trial of Avastin in Metastatic Breast Cancer

Measurement	Avastin + paclitaxel n=365	Paclitaxel n=350	p-value
Primary endpoint #1: Progression-free survival	10.97 months	6.11 months	<.001
Overall response rate	28.2%	14.2%	<.0001
Overall survival	HR 33% improvement	---	.01
Grade 3/4 adverse events			
Hypertension	13.3%	0	---
Thromboembolic	1.2%	1.2%	Nss
Bleeding	0.9%	0	---
Proteinuria	2.4%	0	.004
Neuropathy	25.5%	14.2%	<.001
Fatigue	5.0%	2.7%	---
Neutropenia	5.3%	3%	---
Reduced LVEF	0.3%	0	---

GENENTECH/ROCHE'S Herceptin (trastuzumab) in adjuvant breast cancer

Herceptin is approved to treat metastatic breast cancer. Four trials have been undertaken in adjuvant breast cancer, and three – NSABP-B-31, NCCTG-N9831, and HERA – are being reported at ASCO. The company already released the top-line results from these trials. The two North American trials (NSABP-B-31 and NCCTG-N9831) showed a 52% improvement in the primary endpoint of progression-free survival and a statistically significant improvement in the secondary endpoint of overall survival. The BCIRG-0006 trial is still ongoing. An expert commented, "It is very unusual for a breast cancer trial to see a survival benefit starting in the second year."

Researchers reported that 3% of patients experienced transient of permanent heart damage as a result of Herceptin, with the risk higher in patients over age 60 and those with pre-existing cardiac risk factors. An expert explained, "In one trial, patients over age 60 had a ~6% congestive heart failure (CHF) rate, while younger patients had ~2% rate…So, there is an age factor."

However, they insisted some heart failure is reversible with standard therapy. Another expert said, "The cardio-toxicity (in the HERA trial) was much less than we thought it might be. In HERA, Herceptin was given sequentially, and that may be part of the key. Our stopping rule was 4.0%, and we had only 0.5% compared to 1.0% with paclitaxel. We monitor patients carefully, but we also know that cardiac failure tends to get better and responds well to diuretics and CCBs, etc. The big concern is when you are treating well women, but you have to balance that against the cancer risk, which is huge in this group of women who relapse early and die early.

Asked why Herceptin causes cardiac problems, an expert explained, "HER2 is thought to be a survival mechanism for a number of cells, including cardiac cells. It is also activated in the fetal myocardium…In the adult, we think it is related to the insult the cardiac cells receive from chemotherapy. HER2, by being interfered with by this antibody, cannot then be activated to serve as the survival mechanism…It just enhances the underlying cardiac toxicity. Our cardiologists called this not heart damage but 'heart stunning,' but we still have to demonstrate whether this is totally reversible or not. This is an important issue that clinicians will have to be careful about in the adjuvant setting because, while these patients have a high risk of recurrence, many of them will be cured by treatment."

Asked how the cardiotoxicity can be reversed, he explained, "All patients on these trials had both baseline evaluation by cardiac scan and were monitored with repeat cardiac scans and physical exams every 3-6 months. At the first sign of a cardiac event, that particular situation was flagged and reviewed by a group of cardiologists to determine whether it conformed to the definition of CHF, and simultaneously the patients were immediately evaluated by a local physician team…If there were cardiac symptoms, they were treated the same as we treat CHF from other causes. Virtually all the patients who developed symptoms or signs of CHF had their

Results of 3 Trials of Herceptin in Adjuvant Breast Cancer

Measurement	Herceptin + paclitaxel	Paclitaxel	p-value
Pooled results of NSABP-B-31 and NCCTG-N9831 trials			
3-year disease-free survival	87%	75%	---
4-year disease-free survival	85%	67%	$3x10^{-12}$
Deaths	62 patients	92 patients	---
NSABP-B-31 trial			
3-year disease-free survival	87%	74%	---
4-year disease-free survival	85%	66%	$1x10^{-9}$
Risk of reduction in events	55% relative 13% absolute at 3 years	---	$1x10^{-9}$
NCCTG-N9831 trial			
3-year disease-free survival	87%	78%	---
4-year disease-free survival	86%	68%	.0005
Risk of reduction in events with simultaneous administration	45% relative 9% absolute at 3 years	---	$5x10^{-4}$
Risk of reduction in events with sequential administration	13% relative	---	.29
HERA trial			
Risk of reduction in events	45% relative	---	$<1x10^{-4}$
Disease-free survival	46% reduction	---	<.0001
Cardiac toxicity			
NSABP-B-31	4.1%	0.7%	---
NCCTG-N9831	2.2%-3.3%	0	---
HERA	0.5%	0	---

symptoms controlled. There was only one cardiac death that I know of…About two-thirds had their cardiac medication eventually discontinued. At this point, they are performing normally…We need to follow them, so monitoring is an important part of these trials."

The unresolved question after these trials is which is better – sequential or simultaneous therapy. The NCCTG-N9831 trial has a sequential arm that has not yet reached significance.

There were no data at ASCO about the combination of Avastin and Herceptin, but experts admitted they are thinking about it. One commented, "We know there is interaction between HER2 and angiogenesis. It makes sense to block both, so it may be a potential treatment now that we are getting proof of concept."

PFIZER'S Sutent (sunitinib malate, SU-11248) in advanced breast cancer

A researcher from Indiana University Cancer Center reported the results of a 64-patient Phase II trial of Sutent in advanced, refractory breast cancer. Early results found that ~15% of women had no progression of the disease or ≤50% reduction in the size of their tumors. The researcher commented, "This is very encouraging."

NOVARTIS'S Femara (letrozole) in recurrent breast cancer

The initial findings of the BIG-1-98 trial were presented at the St. Gallen Conference in January 2005. Researchers reported that Femara, an aromatase inhibitor, is more effective than tamoxifen in preventing the recurrence of breast cancer. The Kaplan-Meier curves, shown at ASCO, demonstrate a substantial and increasing benefit in disease-free survival with time of Femara over tamoxifen.

The BIG-1-98 trial was a five-year, Phase III study of 8,028 postmenopausal women with ER+ breast cancer. It found Femara resulted in a 19% risk reduction of recurrence and a 27% risk reduction of cancer outside the area of surgery. What was new at ASCO was efficacy in key subgroups based on estrogen and progesterone receptor content of the primary tumor, prior chemotherapy, prior radiotherapy, and age.

Asked if this trial is enough to change practice, an investigator said, "This is in line with all other aromatase inhibitor trials

Adverse Events in BIG-1-98 Trial

Adverse events (any grade)	Femara	Tamoxifen
Thromboembolic events	1.5%	3.6%
Vaginal bleeding	3.3%	6.6%
Joint problems	20.3%	12.3%
Bone fracture	6.7%	4.0%
Hypercholesterolemia	43.6%	19.1%
Cardiac side effects	4.1%	3.8%

…We, as a group, endorse the ASCO assessment statement concluding that an AI should be strongly taken into consideration in every treatment plan in postmenopausal women with hormone-sensitive breast cancer…I would be comfortable using it in patients who meet the eligibility criteria for E4599 and have the means to pay for it."

GLAXOSMITHKLINE'S lapatinib

Glaxo announced it would delay by another year or two its plan to seek FDA approval for lapatinib for the treatment of breast cancer. The firm said the delay was based on ongoing Phase III trials that are expected to provide Glaxo with more support for its filing as a drug for treating patients in late stages with the disease.

RENAL CELL CARCINOMA (RCC)

About 36,160 Americans will be diagnosed with kidney cancer in 2005, according to the American Cancer Society. The disease will be responsible for about 12,660 deaths, almost two-thirds of them men. Standard treatment for metastatic kidney cancer is interleukin-2 and IFN-α, which have a response rate of 15% and are associated with significant side effects in almost all patients. After little to offer these patients, doctors may soon have two very exciting new drugs – Pfizer's Sutent (sunitinib) and Bayer/Onyx's sorafenib (BAY-43-9006).

If sorafenib and Sutent are both approved in RCC, as expected, oncologists pointed out that they will have two on-label drugs, and one off-label agent, Avastin, to treat these patients.

- Sorafenib has great TTP data, but hasn't shown much if any response.
- Sutent has impressive response rates but is more toxic and requires a two-week drug holiday in every six-week cycle.
- Avastin is the best known, but expensive.
- Both sorafenib and Sutent are oral, so they are easier to give than Avastin.

What will doctors choose? Most aren't sure yet, and they may split their use equally, tailor it to individual patients, or base the choice on cost/reimbursement. An oncologist who has worked with both these agents offered some interesting observations, including:

- "Avastin doesn't have an indication (in RCC), and the expense makes it difficult to use off-label…So, most doctors are shying away from that…And the Avastin studies are somewhat limited. They really aren't as rigorous and robust in terms of the number of patients treated…So, there is not the same sense of efficacy (as with sorafenib and Sutent)…With a drug that expensive, you want a little more data on the clinical benefit, which

is prolongation in time-to-progression in a randomized clinical trial or an increase in survival."

- "I don't expect an FDA advisory panel on either sorafenib or Sutent. There is no need to take them to ODAC (FDA's Oncology Drug Advisory Committee). It is a slam dunk for approval of Sutent in GIST, and the RCC data are an approvable indication for them with the Phase II data. The question is whether the label will be refractory disease or all renal cancer."
- "I don't know which I'm going to use…It may be an individual patient thing. One is more toxic, but they are both easy to give…The 'holiday' with Sutent is not an issue. Most people need the holiday."

Knowledgeable sources predicted Pfizer would submit Sutent to the FDA for both RCC (using this Phase II data) and GIST (using Phase III data) around mid-2005, and Bayer/Onyx will file sorafenib as early as June 2005. There are rumors that Pfizer is not finding the FDA receptive to this filing approach, but a regulatory source said he believes the FDA would accept the Phase II filing. The problem, he explained, would come up if Bayer gained accelerated approval for sorafenib before Pfizer filed. In that case, Sutent probably could not get accelerated approval. But if both Bayer and Pfizer file in RCC about the same time, the question of approval will come down to which one finishes the regulatory review first. And those reviews are done on parallel tracks inside the FDA, not together. If sorafenib is finished first and gets approved, then Pfizer might be issued an approvable letter, not granted full approval, for Sutent. If Sutent is finished first, it could be approved. The source emphasized, "Survival trumps response rate."

PFIZER'S Sutent (sunitinib malate, SU-11248) in metastatic renal cell carcinoma (mRCC)

Researchers reported at ASCO that two consecutive randomized, double-blind, placebo-controlled, 169-patient, Phase II trials of Sutent in second-line mRCC showed a substantial effect from the drug. In one trial, the partial response rate was 40%, and eight of the patients remain progression-free, including two whose tumors became operable as a result of the treatment. In the second trial, 39% of patients had tumor shrinkage >30%. Six patients remain on the therapy, which was generally well-tolerated, with patients experiencing mild-to-moderate side effects, including fatigue, nausea, diarrhea, and stomatitis (mouth inflammation).

Phase II Trial of Sutent in mRCC

Measurement	Sutent
Trial 1 (n=63)	
Partial response (PR)	40% (25 patients)
Continuous response >12 months	6 of 25 patients
Median duration of response in responders	10+ months
Median TTP	8.7 months
Median survival	16 months
Trial 2 (n=106)	
Confirmed PR (tumor shrinkage >30%)	39% (41 patients, including 1 CR)

An expert said, "SU-11248 is absolutely impressive in renal cell cancer. The tumor shrinkage is impressive. There is no question patients benefit." Another source suggested that the points Pfizer will make in marketing against Bayer's sorafenib include:

- "Sutent targets more receptors (VEGF-PDGF-Flt3-RET-cKIT), so resistant mutations are less likely."
- "The response rate is greater with Sutent."

PFIZER'S AG-013736 in refractory mRCC

This is an oral small molecule tyrosine kinase inhibitor (which targets VEGFR-1-2 and PDGFR-β) that is being developed for solid tumors. Like Bayer/Onyx's sorafenib and Pfizer's Sutent, it appears active in RCC. Sutent and AG-013736 target the same proteins, but the advantage of AG-013736 over Sutent may be its ability to be dosed continuously, while patients taking Sutent need to take a two-week holiday after every four weeks of treatment. However, a researcher emphasized that AG-013736 is much earlier in development and has been tested in fewer patients.

1-Year Results of Phase II Study of AG-013736 in RCC

Measurement	AG-013736 5 mg BID n=52
Best response by RECIST criteria	
PR	40%
PD	25%
Discontinuations for adverse events	6% (including one patient for drug-related hypertension)
SD	69%
Median TTP	Not reached
PR patients that relapsed	1 patient at 232 days
Drug-related hypertension	33%
Grade 1/2 adverse events	
Fatigue	29%
Nausea	29%
Diarrhea	27%
Hoarseness	19%
Anorexia	17%
Weight loss	15%
Neutropenia >Grade 1	0
Drug-related Grade 3/4 adverse events	
Hypertension	12%
Aggravated hypertension	6%
Diarrhea	6%
Fatigue	6%
Blister	4%
Limb pain	4%

In Phase I trials, AG-013736 made tumors less dense, even if they didn't shrink. In this Phase II study in 52 RCC patients it appeared to be effective in very refractory RCC patients, though there were no CRs, but the principal investigator said there were near CRs in 3-4 patients. The primary endpoint was overall response rate. The drug-related hypertension is a concern, but a researcher insisted it is manageable with medication, though some patients required dose interruption, and two patients permanently discontinued AG-013736.

The 5 mg BID dose is the dose going forward. AG-013736 also is being tested in melanoma, thyroid cancer, and NSCLC, and results so far were described as "encouraging."

BAYER/ONYX'S sorafenib (BAY-43-9006) in mRCC

Sorafenib doubles time-to-progression in mRCC, investigators reported. The companies, which are expecting FDA approval in early 2006, plan to make sorafenib available before FDA approval to ~6,000 patients not in clinical trials on a compassionate basis.

However, sorafenib has not shown much, if any, response. An expert said, "There are a lot of regressions with BAY-43-9006, but not at the level of a partial regression (response). They don't reach the 30% (tumor reduction) level, but they are in the range of 5%-25% reduction of tumor size. Response rate is very low compared to Sutent; response rate is non-existent with sorafenib, but response rate doesn't necessarily mean patients feel or do better…The clinical benefit is delay in progression or increase in survival."

Results of Phase III Trial of Sorafenib in RCC

Measurement	Sorafenib n=207	Placebo n=105
Primary endpoint: TTP	24 weeks	12 weeks

GASTROINTESTINAL STROMAL TUMOR (GIST)

Novartis's Gleevec (imatinib) is standard-of-care today in GIST, but median survival in metastatic disease is only 18-26 months. Resistance to Gleevec commonly results from secondary mutations in the original kinase (KIT or PDGFR-α). Thus, there is interest over newer agents.

PFIZER'S Sutent (sunitinib malate, SU-11248)

A bit of the excitement waned over Sutent with new data at ASCO. Sources believe the drug still is approvable in both RCC and GIST, but questions were raised about the survival data in GIST. The trial showed only a response benefit so far (8%). Did the placebo patients show less benefit (0%) because they worsened because of the withdrawal of Gleevec?

At ASCO last year, researchers presented the results of a Phase I/II trial of Sutent in GIST. That trial found Sutent has activity in patients with primary resistance to Gleevec. At this year's ASCO, Dr. George Demetri of Dana-Farber Cancer Institute discussed the previously-announced results of the 312-patient Phase III trial of Sutent in GIST. In February 2005, all patients in the trial were offered Sutent after a planned interim analysis found a significant (four-fold) benefit in time-to-progression with Sutent. The trial was conducted in the U.S., Australia, Europe, and Asia (Singapore).

Among the interesting points made about this trial were:

- Of the patients who crossed over to Sutent before the trial was unblinded, 10% of these had a partial response.
- There were similar benefits with Sutent regardless of the McGill pain score at baseline.
- Median survival has not been reached yet in either arm. An investigator said there was a survival benefit in favor of Sutent despite the ability of patients to cross over, but the survival benefit may be underestimated due to the crossover of patients from placebo to Sutent.

The principal investigator also made some interesting comments about Sutent:

- Asked if the shorter survival with the placebo patients could be due to a "flare" when Gleevec is discontinued, he responded, "The field has moved incredibly fast. The flares we've seen when Gleevec is removed probably explain why the control group did far worse than the study was originally powered to anticipate. In terms of patients for who, Gleevec was losing control, I do believe continuing some suppression of kinase is important. We may never know the answer to the question of what the results would have been if this study had been designed with Gleevec continually given in one arm and SU-11248 in the other. But I think continual kinase suppression seems to be the validated endpoint of this study, and is standard-of-care…"
- "I think we can say progression has now been highly validated as a surrogate for survival from this study."
- "To prove a drug is safe and effective as we did here is reasonable. Effective compared to what is the bigger question."

Dr. Richard Pazdur, Director of Oncology Drug Products for the FDA, offered his personal views on the trial. Among the comments he made about Sutent were:

- "This was an excellently done study."
- "The primary endpoint was achieved at the first interim analysis, and the time-to-progression had a p-value of <.00001. This gives credence that this is a real finding."
- "It is important this was a randomized trial. If we looked simply at RECIST in a single-arm study, we would have an 8% effect, and that would give little confidence and would not give patients adequate information."

- "The real impact of this therapy was probably observed in patients with stable disease >6 months."
- "This trial shows some difficulties in using response rate, and only response rate by RECIST…Obviously, this drug had an 8% response rate. If we had a single-arm trial, what would this mean? It would not provide adequate information for patients to determine if this is an adequate treatment, no confidence to regulators, and no advice to physicians."

Dr. Pazdur also took the opportunity to urge pharmaceutical companies to do more randomized clinical trials in oncology. His comments included:

- "We are seeing increasing numbers of registration trials and attempts to gain approval on the basis of response rate from a single-arm study in a refractory disease population. We have numerous sponsors. It is a short-cut for accelerated approval for marketing in the U.S…The results of this trial underscore the advantages of a randomized trial."
- "With a single-arm trial, you can look at response rate or response duration, but you cannot have a credible analysis of TTP or survival."
- "Randomized clinical trials also better characterize safety, especially events that occur in the disease process or in prior therapies. It corroborates a drug's effect through secondary endpoints, such as symptom improvement and health-related quality of life, especially if the trial is double-blind."

Sutent Phase III Trial in GIST

Measurement	Sutent n=207	Placebo n=105	p-value
Duration of treatment	2 cycles	1 cycle	---
Dose reductions	11%	0	---
Dose interruptions	29%	20%	---
Crossover before study unblinded	59 patients	0	---
Primary endpoint: Median TTP	6.3 months (66% reduction)	1.5 months	<.00001
Secondary endpoint: **Objective response rate**			
PR	7.7%	0	---
SD overall	58%	50%	---
SD <6 months	47%	49%	Nss
SD >6 months	19%	1%	---
PD	20%	39%	---
Not evaluable/missing	14 patients	11 patients	---
Treatment-related Grade 3 adverse events			
Fatigue	7%	3%	---
Diarrhea	4%	0	---
Nausea	1%	1%	---
Sore mouth	1%	0	---
Skin discoloration	0	0	---
Neutropenia	8%	N/A	---

- "If a sponsor wins in the face of crossovers, it strengthens the survival benefit…Crossovers may show actual use in clinical practice."
- "Symptomatic progression is an area we (FDA) are interested in investigating. We have proposed it to several sponsors with no takers."
- "Is a convincing and clinically meaningful effect on TTP an endpoint for approval? We've been doing workshops in different diseases looking at this question. There are a considerable number of people who would look at a TTP delay as demonstrating clinical benefit. We are interested in looking at, in this situation, large, convincing effects. We told sponsors to power for survival to allow for a survival analysis, but we would look at TTP as an eventual approval endpoint, especially in situations such as this where crossover can confound the analysis."

Multiple Myeloma

Celgene's Thalomid (thalidomide)

A Phase III trial of 668 patients found adding thalidomide to standard therapy for previously untreated multiple myeloma (Total Therapy 2) increases a patient's chance of achieving remission and reduces the risk of recurrence, but was not shown to improve overall survival. Median follow-up was 35 months. DVTs were a problem with thalidomide, but the addition of heparin reduced the incidence.

Phase III Trial of Thalidomide in Multiple Myeloma

Measurement	Thalidomide n=323	Total Therapy 2 n=345
CR	62%	43%
Primary endpoint: Event-free survival ≥50% at 5 years	55%	4%
OS to date	68%	63% (p=.90)
DVT	34%	16%
Neuropathy	12%	4%
Motor nerve problems	21%	13%

Melanoma

Pfizer's Sutent (sunitinib malate, SU-11248)

Last year a Phase II trial found little activity of Sutent as a single agent in melanoma, but an open-label Phase I dose escalation trial presented this year at ASCO suggested the combination of Sutent and DTIC may have activity in this disease. The combination was well tolerated, and the 400 mg BID dosing was determined to be the dose to go forward. Interestingly, there was no evidence that B-RAF status predicts good response. Further Phase II trials are recruiting patients.

Historically, DTIC has shown 10.2% PR, with mean survival 6.3 months. An expert who reviewed the DTIC + Sutent data commented, "I call this a Phase I/II trial, so we can ask more efficacy questions than we normally would ask in a Phase I trial. This was a largely previously untreated patient population, and LDH was elevated in half the patients, which is a known negative predictive factor. There was a suggestion of 22% response rate. I would editorialize to say patients followed for 6 weeks might become responders if they were followed longer, and that could raise the response rate…One wonders if the response rate might improve over time…I conclude the data are…quite strong, suggesting we can't use B-RAF mutational status to identify patients."

Phase I Trial of Sutent Plus DTIC in Melanoma

Measurement	200 mg Sutent BID + DTIC n=3	400 mg Sutent BID + DTIC n=6	Sutent MTD or 400 mg BID * + DTIC n=9
Dose interruption	67%	26%	---
Dose discontinuation	0	26%	---
Response in patients without mutations	2 PR, 1 SD, 1 PD		

* whichever lower

Vitaxin MI-CO095 Phase II Trial Results in Melanoma

Measurement	Vitaxin 8 mg/kg QW n=57	Vitaxin 8 mg/kg QW + DTIC 1000 mg/m^2 Q3W n=55	Historic DTIC control * n=385
Primary endpoint: Overall response	0	13%	7%
CR	0	0	<1%
PR	0	14%	6%
Secondary endpoint #1: SD	47%	44%	28%
PD	51%	42%	48%
Inevaluable	2%	0	20%
Missing patients	2	5	0
PFS	42 days	78 days	49 days
Median survival	12.7 months	9.4 months	7.9 months
Secondary endpoint #2: Survival at 12 months	53.4%	41.5%	---
Adverse events			
All	~46%	~50%	---
Drug-related Grade 3/4	~7%	~10%	---
Total serious adverse events	~17%	~14%	---
Acute MI	4%	0	---
PE	2%	2%	---
Platelet count increased	0	2%	---
Guillain-Barre syndrome	2%	0	---
Hypotension	0	2%	---

* From Genta's Genasense trial

MEDIMMUNE'S Vitaxin (MEDI-522)

The news wasn't very good for Vitaxin. Interim results from a 110-patient, Phase II trial (MI-CO095) in unresectable Stage 4 metastatic melanoma showed little benefit to this humanized monoclonal antibody. MedImmune tried to put a positive spin on the data, but sources were disappointed. An investigator said, "Vitaxin alone or in combination (with DTIC) is well-tolerated. Progression-free survival ***may*** be increased by the combination. Preliminary overall survival in both arms suggests potential clinical activity for the combination…If repeated in a larger study, this may be a valuable agent, but there isn't a lot of support for the combination."

VACCINES

DENDREON'S Provenge (APC-8015)

A researcher presented the final survival data from a randomized, 127-patient Phase III study of Provenge (Q2Wx3) in asymptomatic, androgen-independent prostate cancer, but the benefit of Provenge was still not clear. The trial was powered to show a median TTP of 16 weeks with placebo and 31 weeks with Provenge. There was no benefit in terms of TTP with Provenge, but survival was improved. Numerous alternative explanations for the survival advantage other than a drug effect were explored (including LDH, disease localization, PSA, number of bone metastases, weight, etc.) – and all except age were dismissed by the investigator. He said, "After allowing for all the prognostic factors in this model, Provenge remained a strong independent predictor of overall survival, with p=.002)…Provenge represents the first non-chemotherapeutic agent providing a survival advantage in androgen-independent prostate cancer patients." Asked if 4.5 months of additional survival is enough, he replied, "We'd like more, but that is pretty impressive…Our sense is that mechanistically it takes a therapy like this several months to have an immune effect."

Phase III Provenge Trial in Prostate Cancer

Measurement	Provenge n=82	Placebo n=45	p-value
Primary endpoint #1: Time to objective progression	HR 1.43	---	Nss (p=0.061)
Primary endpoint #2: Time to onset of disease-related pain	Trend favored Provenge	---	Nss (p=0.218)
Median survival	25.9 months (HR 1.7)	21.4 months	.01
Alive at 36 months	34%	11%	.0046
Deaths	54 patients	40 patients	---

NOTE: All analyses were ITT.

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