Trends-in-Medicine

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By Lynne Peterson

SUMMARY

The hot news was that genetic mutations correlate with response to EGFR inhibitors and may be predictive of which NSCLC patients respond, with never smoking the strongest correlate. A commercial mutation test is expected within a year. However, some mutation negative patients respond or have stable disease, so it is unclear whether use of AstraZeneca's Iressa and Genentech/OSI's Tarceva will be determined by mutation positivity. ♦ Tarceva showed a survival benefit in NSCLC, which may give it a marketing advantage over Iressa unless and until the Iressa survival trial is completed in 2005, and it showed benefit in combination with Avastin in renal cell cancer. ♦ Bayer/Onyx's sorafenib and Pfizer's SU-11248 both appear to work in renal cell cancer, but it appears that sorafenib could reach market first. ♦ ImClone/Bristol-Myers Squibb's Erbitux showed outstanding results for head & neck cancer, and efficacy was speculated in lung cancer patients without mutations.

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ABBOTT'S Atrasentan (ABT-627): A failed Phase III trial but not dead yet

In M00-211, an 810-patient Phase III trial, once-daily 10 mg atrasentan – a selective endothelin-A receptor antagonist (SERA) with a half-life of 25 hours – failed to meet its primary endpoint of reducing time-to-progression in advanced metastatic, hormone refractory prostate cancer. Statistically significant improvements were seen with atrasentan in quality of life (delayed bone pain) and a reduction in markers of disease progression – bone alkaline phosphatase, total alkaline phosphatase, and PSA.

A pooled meta-analysis was presented of 1,097 asymptomatic, metastatic, hormone-refractory prostate cancer patients from two large, randomized trials – 809 men from M00-211 and 288 from the Phase II M96-594 trial. In this meta-analysis, atrasentan showed a statistically significant effect on TTP. Dr. Michael Carducci of Johns Hopkins, who presented the data, said, "In both the Phase II and the Phase III trials, atrasentan showed a trend to delay in progression, but on an intent-to-treat analysis did not meet the primary endpoint (in each trial)…When we pooled the two trials, there was a statistically significant delay in TTP, with a hazard ratio of 1.19, so men on atrasentan had a 19% lower risk of progression…In the pooled analysis, the time to onset of bone pain as an adverse event was 100 days longer with atrasentan, and that is a significant delay. Patients maintained quality of life longer with atrasentan. So, the secondary endpoint suggests there is a clinically meaningful benefit to atrasentan…A lot of folks say this is a fairly modest benefit, but to patients without pain, who have metastatic disease and are looking at moving to chemotherapy, they may see this as an option to delay the need to go to more toxic therapies…There is no data on integrating this with other therapies, but I don't see why we can't do that…Men are looking for less toxic agents, and a drug like this is likely to fit in well…This pooled analysis could be used as a confirmatory study (if M00-244 is positive)…and all secondary endpoints clearly demonstrate biologic and clinical activity, and that's what is clinically meaningful, in my opinion."

Pooled Analysis of M00-211 and M96-594 Atrasentan Trials

Measurement	Atrasentan 2.5 mg and 10 mg n=1,097	Placebo	p-value
TTP by ITT	N/A	N/A	p=.013
Primary endpoint in M00-211: TTP by ITT	N/A	N/A	Nss
Primary endpoint in M96-594: TTP by ITT	N/A	N/A	Nss
Reduction in bone pain	N/A	N/A	p<.05
Median time to onset of bone pain	>7 months	100 days less than atrasentan	p<.05
Safety of 10 mg dose			
Headache	21%	13%	N/A
Peripheral edema	39%	13%	N/A
Rhinitis	34%	14%	N/A
Discontinuations due to adverse events	8.9%	5.5%	N/A

Since atrasentan did show improvement in M00-211 in secondary endpoints – the development of bone pain, PSA level, and biochemical markers of skeletal progression – other Phase III studies in prostate cancer and Phase II studies in other tumor types will continue, including:

➢ **M01-366**, a 200-patient Phase II study in men with rising PSA following prostate cancer surgery

➢ **M00-244**, a Phase III pivotal trial in men with non-metastatic prostate cancer. This randomized trial is fully enrolled with 941 patients and was described as "maturing." The primary endpoint is TTP for first metastasis. Data could be available as early as ASCO 2005 or at least by late 2005. Dr. Carducci offered these comments about this trial:

- "About 30% of patients have been on therapy two years, and 60% have been on therapy more than one year, with the number of events less than 350."
- "Dropouts haven't been like in the M00-211 Phase III where bone scans were mandated and 45% of patients had more disease on scan. In M00-244, patients got past that time, so there is a much fuller data set that we will be able to explore."
- "Our estimates were that 60% of patients would not progress in a year, and the data so far is that about 70% of the atrasentan patients did not progress, so we are in the ballpark of what we estimated…We expect that in the next year to year and a half, we should reach the event point."
- "I'm optimistic we will meet the primary endpoint…My gut feeling is that the event rate will pick up over the next six months."

Abbott is using a rolling NDA for atrasentan, and it is likely that Abbott will seek approval of atrasentan for prostate cancer if the M00-244 trial is positive, using the pooled analysis as the confirmatory study. Dr. Carducci said, "With a first-in-class like this, and an endpoint that is relatively novel for prostate cancer, I think the new Phase III (M00-244) would bring the data home. If patients were at ODAC (the FDA Oncologic Drugs Advisory Committee), I think they would say it makes sense to approve on an meta-analysis, but how big a benefit is needed to convince them is not clear to me."

When the atrasentan M00-211 data was presented, the discussant said rather strongly that more data was needed and questioned how meaningful the "modest" effect shown is, but she said she believed development should go forward. Dr. Carducci said the discussant did not have all the data when she prepared her talk, and, in particular, she did not have the pain data, "I clearly think she was impressed with that and had not had a chance to evaluate that…The data on quality of life, the longer time to onset of bone pain in a setting of 20% delay in progression suggest biological activity…It was the clinical significance that she was questioning."

Abbott officials had suggested that atrasentan could be a $1 billion drug, but it is not clear how they can accomplish this. The market for atrasentan in prostate cancer may actually be urologists more than oncologists. Dr. Carducci said, "These patients are at the cusp of where medical oncologists see them…These (M00-211) patients were 60% from urology practices…Urologists will be happy to give an oral drug that will delay progression and keep their patients from going to therapies which historically are more toxic."

AMERICAN PHARMACEUTICAL PARTNERS' ABI-007: Investigations continuing

In Phase II trials, ABI-007 has been administered weekly. A researcher said the company is going for approval of once-every-three weeks to once-weekly dosing schedules and will then do a head-to-head with Aventis's Taxotere (docetaxel). He cited lack of cremaphor and increased activity as the advantages, "The National Cancer Institute thinks increased activity is more important than lack of cremaphor."

The DLT with ABI-007 is neuropathy for lightly pre-treated patients, but there is no peripheral neuropathy in heavily pre-treated patients. The MTD is 150 mg/m^2.

ASTRAZENECA'S Iressa (gefitinib): Effective in bronchioalveolar carcinoma

Researchers reported on a 138-patient trial which found a benefit to 500 mg Iressa QD in advanced bronchioalveolar carcinoma (BAC). The best responses were in female non-smokers who got a rash from the drug. There was no data on mutation status of the patients, but an investigator said that would be done in the future, "We will be testing that…We collected tissue on all of these patients…so we can go back and look."

Measurement	No prior treatment n=69	Prior treatment n=22
Response rate (CR+PR)	19%	9%
CR	6%	0
Stable disease	30%	36%
Progressive disease	33%	36%
Inadequate/unknown	17%	18%
Median survival	12 months	13 months
One-year survival	~50%	~50%

Variable	Median Survival	Response rate
Gender (female vs. male)	19 vs. 8 mo	20% vs. 3%
Rash (Yes vs. no)	13 vs. 5 mo	21% vs. 0%
Smoking Status * (Never vs. Former/Current)	NR vs. 10 mo	13% vs. 18%

* Never smoked is defined as <150 cigarettes in a lifetime.

One-year survival in AstraZeneca's 35,000-patient expanded access program for Iressa is 30%, which an expert said is "more than we would expect…If I were AstraZeneca, I would look at a boosted dose in mutation negative patients."

BAYER/ONYX'S Sorafenib (BAY-43-9006) and PFIZER'S SU-11248: Both appear to work in renal cell cancer – but who will be first?

Both of these oral agents showed very good data at this meeting – SU-11248 in GIST and renal cell carcinoma and sorafenib (BAY-43-9006) in renal cell carcinoma. Investigators described the two drugs as very comparable, despite differences in side effect profile. One source said, "They are both highly active, and both probably help patients, though they have different toxicities…Both will go far, and they will be competitors, but you can't compare them on the data presented." Another researcher said, "I can't say one works better than the other or that one is safer than the other."

Comparison of SU-11248 and BAY-43-9006

Measurement	SU-11248	BAY-43-9006
Side effects	Fatigue, Hypertension, Skin rash	Hypertension, Dermatitis (hand/foot syndrome)

Bayer and Pfizer chose different measurement scales, which also makes comparisons difficult. Bayer used the WHO scale, and Pfizer used the RECIST scale. Dr. Robert Motzer of Memorial Sloan-Kettering Cancer Center, an SU-11248 researcher, said both are accepted and reliable, "The WHO approach, which has been used since the 1980s, measures the greatest diameter of the lesion by CT scan, and multiples by the total lesions to get a product value, with PR a >50% reduction. In the 1990s, NIH did an assessment and felt RECIST would be more 'user friendly' and applicable…But both approaches basically represent that the volume of cancer decreased by >50%." Dr. Mark Ratain of the University of Chicago, a BAY-43-9006 researcher, said, "We used WHO because investigators had the most experience with that."

Renal cell cancer is diagnosed in about 30,000 Americans annually and has a five-year survival rate of ~55%. The current standard therapy for metastatic renal cell cancer is interleukin-2 and interferon-alpha, but only 15% of patients respond.

BAYER/ONYX'S Sorafenib (BAY-43-9006): Dr. Ratain reported on the results of the first 106 of 203 patients in a Phase II trial of BAY-43-9006, a RAF kinase and VEGFR inhibitor, in advanced, metastatic renal cell carcinoma. The trial, which used a dose of 400 mg BID orally, was a randomized discontinuation study in which 484 patients with various tumor types received an initial course of treatment for 12 weeks, and then were sorted according to their initial response. Patients with SD (tumor shrinkage or growth <25%) were randomized to BAY-43-9006 or placebo. The randomized portion of the trial has not yet been unblinded, though that is expected to happen in the next three or four

Sorafenib Phase II Results

Measurement	BAY-43-9006 n=106
Tumor status at Week 12	
Shrinkage ≥25%	37%
Shrinkage ≥50%	45%
Growth ≥25%	7%
Efficacy at Week 24	
PFS in randomized patients (n=38)	41%
PFS in open-label patients (n=37)	88%
Median TTP for patients progression-free after 24 weeks	48 weeks
SD	42%
Safety	
Patients requiring dose reduction for adverse events	5%
Discontinuation for adverse events	18%

months. The last patient was enrolled at the end of January 2004, and the trial will be unblinded when the last patient has 24 weeks of treatment. Outside of renal cell cancer, the most exciting area for BAY-43-9006 may be sarcoma, a researcher said.

Bayer may get to market ahead of Pfizer; the interim data on BAY-43-9006 was so good that if it holds up when the other half of the patients complete, Bayer likely will file – and Bayer, not Onyx, is handling the filing and regulatory issues – and will probably get approved. Bayer officials said they are in "regular contact" with the FDA on the progress of this drug. Dr. Ratain said, "When this trial is finished, the data could be sufficient for filing. We will have 70-80 patients at the end of randomization. If the p-value is low enough, Bayer could file early, and there is a real possibility there will be dramatic results, and the company will file on this…(But) European regulators demanded Phase III data. The Phase III trial is a placebo crossover study with no unblinding."

PFIZER'S SU-11248. Two studies were reported that showed a benefit to once daily SU-11248 in patients with gastrointestinal stromal tumors (GIST) who had developed resistance to Novartis's Gleevec (imatinib), and other GIST trials are ongoing.

Phase I/II Trial of SU-11248 in GIST

Measurement	SU-11248 Benefit (response+SD >6 months) n=92
PR or SD for ≥6 months	54%
PR	13%
Response in patients with mutations in KIT Exon 9 (where Gleevec works worst)	79%
Response in patients with mutations in KIT Exon 11	33%
Response in patients with secondary mutations in KIT Exon 13 or 14	56%
Response in patients with no mutations	50%

- A Phase II trial found SU-11248 was active in 60 of 92 patients. Tumors shrank more than 20% in 8% of patients and stabilized the disease for ≥6 months in 58%.
- A Phase I/II trial in 48 Gleevec-resistant GIST patients also had positive results.
- A randomized Phase III clinical trial in GIST is one-third enrolled and was described as "proceeding rapidly."

Dr. George Demetri of the Dana-Farber Cancer Institute, an SU-11248 investigator, said, "If we can figure out the significance of this (mutation) pattern, we've got the match between the mechanism and the activity." Asked why SU-11248 shouldn't be used ahead of Gleevec in GIST, Dr. Demetri said, "That may be the approach in the future…Most of us still feel Gleevec is the standard of care, but once Gleevec resistance develops, then give this."

SU-11248 also is being explored to treat renal cell carcinoma.

- A pivotal, non-randomized, ~700-patient, Phase III trial of SU-11248 vs. IFN-α as second-line therapy in renal cell cancer is ongoing. Pfizer is expected to wait for that trial to be completed in 2005 before filing SU-11248, which would put it on the market in late 2006 or early 2007. Dr. Motzer said there have been no changes in the design of this trial. Pfizer probably could file sooner for a niche indication in GIST, but sources indicated that Pfizer does not intend to do that. And Pfizer sources did not appear concerned about being second to market.

- In a single-arm, multicenter, Phase II trial of 63-patients with metastatic renal carcinoma who had failed to respond to standard therapy, 50 mg QD oral SU-11248, given in repeated six-week cycles, showed promising results. There were more partial responses and longer TTP than with standard therapy or with Genentech's Avastin (bevacizumab). At six months, the SU-11248 response persisted in some patients, with 22% continuing on treatment with an ongoing partial response. Dr. Motzer, the principle investigator, said, "Avastin binds to VEGF around the cancer cells…SU-11248 and BAY-43-9006 bind at the receptor and block at that level…SU-11248 binds to VEGF, PDGF, C-KIT (which is important for GIST tumors), and multiple other receptors in cancer cells…I'm convinced that SU-11248 shows activity in refractory advanced (renal cell) disease."

SU-11248 in Metastatic Renal Cell Carcinoma

Measurement	SU-11248
Partial response	33%
Stable disease >3 months	37%
Progression	30%
Average months to progression	8.3

The problem with SU-11248 has been excessive fatigue, but researchers believe a new regimen with four weeks on, two weeks off has resolved this.

Comparison of Therapies for Metastatic Renal Cell Carcinoma

Measurement	Number of patients	PR	Average TTP
SU-11248	63	33%	8.3 months
IL-2	65	5%	N/A
IFN-α	48	2%	N/A
Avastin (high dose)	39	10%	4.8 months
Mutation agents in Phase II trials	37	3%	2.9 months
Placebo	40	0	2.5 months

BIOGEN IDEC/GENENTECH'S Rituxan - ROCHE'S MabThera (rituximab): Benefits in all CD-20+ lymphomas

The 824-patient, randomized, Phase III MInT trial of rituximab in diffuse large B-cell lymphoma (DLBCL) was stopped early in December 2003 for a positive effect. Researchers reported that the addition of rituximab to CHOP-like chemotherapy increased complete remission, decreased progression, increased TTF, and significantly increased overall survival. An investigator said, "Most importantly, all gains were achieved without additional toxicity. The adverse events were the same in both arms…What was surprising was the benefit in low-risk, younger patients…It confirms the French (GELA) finding that this antibody works most efficiently in the low risk patients… It also works in high-risk patients, but very fast growing tumors are not as affected by the antibody."

2-Year Results of Phase III MInT Trial

Measurement	R-CHOP	CHOP	p-value
Overall Survival	95%	85%	<.05
Free of treatment failure	81%	58%	<.05
Complete remission	84.7%	66.0%	N/A

Another Phase III study reported on the advantages of rituximab in previously untreated mantle cell lymphoma patients. Mantle cell lymphoma is a relatively rare disease (2-3 cases/100,000/year), with a dismal prognosis (median survival 3-4 years) and moderate to poor sensitivity to chemotherapy (a response rate of 70%-80% and a response duration of 12-14 months). The study found no difference in survival yet, but a researcher said the observation time is still too short (22 months). An expert said, "This is not a breakthrough, but it is a major step forward…R-CHOP should be standard of care for mantle cell lymphoma. Today, all my mantle cell lymphoma patients without a contraindication get R-CHOP."

22-Month Rituxan Results in Mantle Cell Lymphoma

Measurement	R-CHOP	CHOP
CR	34%	7%
CR/PR	94%	74%
Time to treatment failure	22 months	14 months
Granulocytopenia	63%	53%
Serious infections	1%	1%

A third study – E-1496, an ECOG and CALGB study – found a benefit to maintenance Rituxan therapy (375 mg/m^2 every six months for two years). In this Phase III, randomized trial of advanced, indolent NHL patients, maintenance rituximab prolonged progression-free survival by 2.7 months after completion of CVP, with no increase in Grade 3-4 toxicity. The trial was stopped early (in November 2003) after reaching its pre-specified efficacy endpoint. At that time, 322 (305 evaluable) patients were included in the interim analysis. A researcher said, "The greatest rituximab benefit in PFS is seen in patients with high tumor burden at entry, follicular histology, and minimal residual disease following induction chemotherapy…Every patient who finishes (chemotherapy) treatment goes into a high anxiety state about when the lymphoma will come back…This (maintenance therapy of a course every six months) breaks the chronic pattern of relapse."

Rituxan NHL Study E-1496

Measurement	Rituxan n=154	No Rituxan n=149	p-value
Median PFS	4.2 years	1.5 years	=.00003 Hazard ratio .5
Patients free of disease progression at 2 years	73%	43%	N/A
Patients free of disease progression at 4 years	58%	34%	N/A
Survival	96%	89%	Nss (p=.06) with 27 deaths in 305 evaluable patients

Asked what these findings mean for clinical practice, the researcher said, "Giving this kind of maintenance therapy every six months…seems effective…This study moves it earlier – giving it immediately after chemotherapy…This is clearly a – if not the – standard of practice…There are reimbursement indications, but using maintenance rituximab is the best strategy…Maybe we are really at the edge of curative therapies for some lymphomas." Another researcher said, "In lymphomas we tend to be 'splitters' (dividing patients into various types of lymphoma)…But this treatment looks beneficial in all CD-20+ lymphomas (which are 90% of all NHL)…Given the lack of toxicity, combining rituximab with chemotherapy is emerging as a way to improve remission duration and perhaps, with more follow-up, an increase in survival."

GENENTECH/OSI PHARMACEUTICAL'S Tarceva (erlotinib): A big win in NSCLC

The results of BR-21, a 731-patient Phase III trial of Tarceva in refractory NSCLC outside the U.S., were as exciting as expected. Experts called this a "landmark trial," and a researcher said that the drug showed a positive effect in all subgroups. She said, "There was no subgroup where the hazard ratio was not <1.0…We saw it (an effect) in every subgroup…So, although there were significant differences in response, this did not entirely translate to (lack of) survival benefit…We looked at EGFR positivity, and there was a trend but no statistically significant difference in relative risk or survival for EGFR+ patients."

However, there was one unusual finding in this trial: 17% of placebo patients got a rash – and those patients lived longer. The investigator had no explanation for this.

A Tarceva investigator suggested that the level of survival benefit in this trial means that mutation positivity may play less of a role with Tarceva response than Iressa response. A Tarceva investigator said, "We don't believe this response level would be attributed to the small subset of patients with the mutation." She plans to go back and test all of the patients in this trial for mutation positivity and hopes to have the results for ASCO 2005. That study is funded with grants. Another expert said, "It is hard to imagine that the Tarceva benefit could be due only to mutation positivity. I think the drug helps mutation negative patients as well." A mutation expert said, "Most of the response in the Tarceva trial is accounted for by mutation positivity. Survival is probably different by subgroup:

a. No response – mutation negative.

b. Responder – mutation positive.

c. Stable disease – possibly a mutation negative patient who benefits. The question is how to identify those patients."

Key findings:

- **Objective response 8.9%**. This compares to a 10.6% objective response in the pivotal Phase II trial of Iressa.
- **Overall survival 2.0 months**, a 42.5% improvement over best supportive care, and a 29% reduction in relative risk
- **Discontinuations for toxicity <5%**.
- **Response duration: 7.9 months** vs. 3.7 months with best supportive care.

BR-21: Phase III Trial of Tarceva Monotherapy in Refractory NSCLC

Measurement	Tarceva 150 mg/day n=488	Best supportive care (BSC) n=243	Values
Demographics			
One prior regimen	~50%		
Two prior regiments	~50%		
Primary endpoint: Overall survival	6.7 months	4.7 months	p<.001 Hazard ratio 0.71 42.5% improvement
SD/PD/NE	5.7 months	4.75 months	.073
SD/PD	7.4 months	6.7 months	.037
Patients alive at 1 year	31%	22%	41% improvement
Deaths related to drug	<2%	<1%	41% improvement
Secondary endpoint #1: **Time to Symptomatic Deterioration**			
Cough	4.9 months	3.68 months	p=.04
Pain	2.79 months	1.91 months	p=.01
Dyspnea	4.73 months	2.89 months	p=.01
Secondary endpoint #2			
Progression-free survival	2.23 months	1.84 months	p<.001
Secondary endpoint #3			
Objective response	8.9%	<1%	p<.05
Other Results			
Median duration of response	7.9 months	3.7 months	p<.05
Safety			
Fatigue	79%	74%	N/A
Rash	76%	17%	N/A
Diarrhea	55%	19%	N/A
Nausea	40%	34%	N/A
Ocular	28%	9%	N/A
Vomiting	25%	23%	N/A
Dose modifications for adverse events	19%	2%	N/A
Dose reductions due to rash	12%	0	N/A
Dose reductions due to diarrhea	5%	0	N/A

Subgroup Analysis of BR-21 Trial

Measurement	Group 1 response	Group 2 response	p-value	Comments
Gender	Females = 14%	Males 6%	.0065	Good predictor of response but not survival
Type of cancer	Adenocarcinoma = 14%	Other 4%	<.001	Squamous cell cancer is predictor of poor survival
ECOG	PS 0-1 = 8%	PS 2-3 = 11%	N/A	Good predictor of survival
Smoking	Ever smoked = 4%	Never smoked = 25%	<.001	Never smoked is good predictor of survival
EGFR status	Positive = 12%	Negative = 3% Unknown = 10%	.18	Not predictive of survival
Prior platinum therapy	Yes = 9%	No = 7%	1.0	Poor predictor of survival

Asked if Tarceva is doing something good for patients with SD, an investigator said, "This is the ongoing debate – how much SD contributes to the overall survival (benefit with Tarceva)…The curves are superimposable for the first two to three months and then diverge…So there is a cohort that derives no benefit...and I suspect those fall into the progressive disease while on therapy category…The significant survival benefit, I think personally, is made up in part from responders and in part from stable disease...Stable disease is an extremely arbitrary endpoint…If you have a 50% reduction in tumor mass, you are a responder…If there is a 45% reduction, you are stable disease, but you can have survival and symptom benefits from <50% reduction in tumor mass."

Tarceva patients lived longer if they were female, had tumors with adenocarcinoma histology, or were never smokers than if they were male, had tumors with squamous cell carcinoma histology, or were smokers. However, Tarceva improved survival in all subsets of patients in the study including males, patients with squamous cell carcinoma, and smokers.

Measurement	Tarceva	Placebo	Hazard ratio
Median Survival in Months			
Never smoked	12.2	5.6	0.42
Current or former smokers	5.5	4.6	.87
Adenocarcinoma	7.8	5.4	.71
Squamous cell carcinoma	5.6	3.6	.67
Female	8.4	6.2	.80
Male	5.7	4.5	.76

Based on these findings, OSI expects to submit an NDA during the summer of 2004, and Roche plans to file in Europe in 3Q04, with a possible approval there in 3Q05 or 4Q05.

Another Tarceva trial – TRIBUTE – found that Tarceva+ carboplatin/paclitaxel as first-line treatment for advanced NSCLC did not increase survival compared to chemotherapy alone. However, Tarceva did improve survival and TTP in never-smokers.

TRIBUTE Trial Results

Measurement	Placebo	Tarceva
Median survival based on rash level		
None	9.8 months	8.4 months
Grade 1	12.7 months	10.8 months
Grade 2	12.2 months	13.5 months
Grade 3-4	N/A	13.2 months
Patients who never smoked		
Overall survival	41 patients	64 patients
Median survival	10.1%	22.5% (p=.01)
TTP	4.3 months	6.0 months (p=.002)

Asked how they would choose between Iressa and Tarceva if Tarceva were approved today, most doctors questioned indicated that Tarceva will have the advantage because it has survival data and Iressa doesn't. Sources said it is likely to be at least a year or even two years before there is survival data on Iressa.

However, marketing will play a big role in the choice of agent, several sources predicted. An expert said it is unlikely that either Genentech or AstraZeneca will sponsor a head-to-head comparison study of Tarceva and Iressa, and academicians probably won't do it either because they have "more pressing things to look at." An investigator said, "We believe this will move Tarceva further up front in the treatment of patients… Having a study showing prolongation in survival gives us confidence to move the drug earlier in treatment." Another expert said, "There is a definite possibility of treatment now for a group of patients with no option for treatment…Patients who failed other therapy now have an option with minimal toxicity…And Iressa (sic) is licensed in some but not all countries…Some countries were waiting for a documented survival advantage before approving any drugs in this class…So, I think you may see Iressa (sic) approved in other counties."

Other doctor comments included:

- "Tarceva was tested at a higher dose, and it is more toxic. There is more skin rash, mucositis, nail toxicity, and diarrhea with Tarceva – and these side effects can be quite substantial. In six months, I might have two-thirds of my second-line patients on Iressa and a third on Tarceva. In third-line, it is likely that 80% of my patients will be on Iressa and 20% on Tarceva."
- "Tarceva is the only one with a survival advantage…It is a good question whether Iressa will be able to keep accruing in its survival trial."
- "I would use the drug with the proven survival benefit – so Tarceva until Iressa is shown to have a survival benefit…There are a bit more side effects with 150 mg Tarceva than 250 mg Iressa, but the side effects of 150 mg Tarceva is comparable to 500 mg Iressa."
- "Some doctors will choose Iressa, and others will choose Tarceva. It will be a marketing issue. These are very similar drugs – as similar as statins or aromatase inhibitors. No company will do a head-to-head study, and academicians are not very interested in doing them either. For mutation positive patients, I would give Tarceva first-line. For mutation negative patients:
  - First-line: Chemotherapy
  - Second-line: Alimta (Lilly, pemitreximed) or Taxotere
  - Third-line: Tarceva instead of Taxotere every three weeks (Taxotere has more side effects than Tarceva)."
- "I would look at a boosted dose in mutation negative patients."

- "It is too early to conclude that mutation positivity does not apply to Erbitux."

Genentech officials attempted to downplay the importance of the mutation discovery. One commented, "Mutation data will certainly prove to be interesting if not important for Tarceva." Another official said, "It is a misconception that all EGFRs are created equal." Officials also hinted that Tarceva would be priced at a premium to Iressa.

Other comments by Genentech officials included:

- "10% of patients got a large benefit, and 33% of patients got a moderate benefit…Our take is that Tarceva is a drug that broadly benefits patients with second- and third-line lung cancer."
- "We dosed very close to the MTD."
- "We believe that some of the cell line data presented… showed there are cell lines with relative sensitivity to Tarceva. That is really important and may explain why Tarceva gives a survival benefit."
- On reimbursement: "We expect this to be like other oral (cancer) medications."
- "I don't know if EGFRs will be used first-line...I think it will be hard to do the trials, and without that, patients are unlikely to use them first-line."
- "(Dr. Richard Pazdur, Director of Oncology Drug Products for the FDA) has made it clear that the issue is patient benefit, and there are differences in the two drugs (Tarceva and Iressa)…They are, at least theoretically, quite different, and Pazdur generally will value what is proven vs. what he might imagine to be similar or dissimilar."

Iressa vs. Tarceva

Iressa (gefitinib) may do better than expected. With such good survival data on Tarceva in NSCLC, some people may conclude that Tarceva will destroy Iressa. However, most clinicians believe that this is a class effect. While they agreed that Tarceva will have a marketing advantage with its survival data, they pointed out that Iressa is tried and true, and most expect to have a substantial (50%+) share of their EGFR patients on Iressa six months after Tarceva approval.

Mutations and Tarceva

Dr. Mark Kris of Memorial Sloan-Kettering Cancer Center presented a poster which looked at mutations in Exon 18-24 in bronchioalveolar carcinoma (BAC) patients given Tarceva. He said, "The mutation is driving EGFR, which drives the cancer…A mutation test is expected in a few months; the technology is not complex. But we don't need to test for mutations; just find out if the patient never smoked." He found:

- 6 of 6 never-smokers had mutations in Exon 19, 23
- 1 of 3 former smokers had mutations of Exon 21
- 0 of 6 patients without a PR had a mutation

Dr. Kris said going forward he plans to:

- Test 17 more patients to complete this study.
- Construct a tissue microarray to compare sensitive with resistant patients.
- Compare the frequency of tobacco-related mutations, such as p53 and K-ras.
- Screen for other targets and other activating EGFR mutations.
- Look at stable disease patients.

Measurement	Number of patients	PR rate
Smoking history		
Never smoked	20	45%
Former smokers	56	18%
Current smokers	2	0
Years smoked		
0	22	9 patients
1-5	6	3 patients
6-9	2	1 patient
10-19	4	1 patient
20-29	7	2 patients
30-39	9	1 patient
40-49	9	0
50-59	6	1 patient
≥60	10	0
Other characteristics		
Women		27%
Skin toxicity Grade 0		0
Skin toxicity Grade 1-2-3		38%
No prior chemo		21%
1 prior chemo regimen		35%

Ongoing Tarceva trials

A Genentech official said there are "not a huge number" of ongoing trials.

- A randomized trial in pancreatic cancer, which was described as enrolling slowly. Results are expected in 3Q04.
- A randomized trial in glioma. Results are expected in 4Q04. A go/no-go decision will be made in 3Q04 or 4Q04.
- A Phase II trial in lung cancer.
- No new combination trials of Avastin+Tarceva are ongoing, but more Phase II trials may be initiated now, probably in lung and renal cancer.

GENENTECH/OSI's Tarceva plus Avastin (bevacizumab): Full-speed ahead on combination therapy for renal cell cancer

The combination of Tarceva and Avastin appears to be synergistic, not just additive. Cost does not appear to be

dampening enthusiasm for combination therapy with these two agents. An expert said, "Seven of the top oncology drugs are supportive therapy drugs. If we can switch patients to drugs with increased survival, we may be able to use fewer supportive care drugs."

A Phase II trial found the combination Avastin+Tarceva was "one of the most active and best tolerated regimens in the treatment of advanced renal cell carcinoma." The Tarceva dose used (150 mg QD orally) was the standard MTD dose, and the Avastin dose (10 mg/kg IV infusion every two weeks) was the same as in previous kidney cancer trials, which is higher than is used in colorectal cancer. Median follow-up was 11 months. Principal investigator Dr. John Hainsworth, Director of the Sarah Cannon Cancer Center in Nashville TN, said, "The activity of the combination appears greater than the activity of either agent used alone…Even most of the patients classified as stable disease had some tumor shrinkage, indicating the drug was active to some extent."

Phase II Trial of Avastin+Tarceva

Measurement	Tarceva+Avastin n=58 evaluable	
CR	0	
PR	21%	
SD/minor response *	66%	
Progression	13%	
Median PFS	12 months (vs. 4.8 months with Avastin)	
Progression-free survival at 6 months	67%	
Progression-free survival at 12 months	50%	
Overall survival at 6 months	92%	
Overall survival at 1 year	81%	
Discontinuations for toxicity	2 patients (thought due to the Tarceva)	
Safety	**Grade 1-2**	**Grade 3-4**
Rash	89%	13%
Diarrhea	71%	10%
Nausea/vomiting	32%	10%
Hypertension	27%	8%
Bleeding	39%	5%
Proteinurea	40%	3%
Pruritis	37%	3%
Neuropathy	8%	3%
Edema	8%	2%

*** 12 patients (21%) had minor responses**

GLAXOSMITHKLINE'S Lapatinib (GW-572016): Early results promising in metastatic breast cancer

Interim results from an open-label, multicenter, Phase II trial indicated that oral lapatinib (which targets Her-2 and EGFR) has anti-tumor activity in advanced metastatic breast cancer patients resistant to Genentech's Herceptin (trastuzumab). Patients received lapatinib until their disease progressed and were evaluated every eight weeks. The trial is continuing to enroll patients, with a goal of 80 patients.

Measurement	Lapatinib 1500 mg n=41 evaluable
PR/SD lasting 8-16 weeks	46.3%
PFS at 16 weeks	24.4%
Adverse events	
Grade 2 decrease in LVEF	1 patient
Grade 3 rash	5%
Grade 3 fatigue	5%
Grade 3 diarrhea	10%
Grade 4 respiratory failure (not considered due to lapatinib)	1 patient

IMCLONE/BRISTOL-MYERS SQUIBB'S Erbitux (cetuximab): Outstanding results in head & neck cancer; efficacy speculated in non-mutation lung cancer

Worldwide 500,000 head and neck cancer patients are diagnosed annually, with 40,000 of these in the U.S. The majority of these patients have locoregional advanced cancer.

A Phase III, 424-patient trial found Erbitux far superior to radiation alone in locoregionally advanced SCCHN. An investigator said, "As a clinician, I would very much like to use this agent in my clinic." Asked about the comparison to radiotherapy (RT) alone rather than RT+chemotherapy, he said, "There are many tumors that qualify for radiotherapy alone, where radiation is the standard of treatment…A MD Anderson group recently published on T1 and T2 patients with various stages of neck disease, and their conclusion was that chemotherapy would not have helped…So, there are groups where RT alone is standard of care."

Results of Phase III Trial of Erbitux in Head & Neck Cancer

Measurement	Radiation only (70 Gy) n=213	Radiation+Erbitux (400 mg/m^2 IV) n=211
Primary endpoint #1: Median survival	28 months	54 months p=.02 (log rank)
Two-year survival	55%	62%
Three-year survival	44%	57%
Primary endpoint #2: Locoregional control at 1 year	59%	69% p=.02 (log rank)
Locoregional control at 2 years	48%	56%
Safety		
Grade 3-4 mucositis	52%	55%
Grade 3-4 infusion reaction	0	3%
Grade 3-4 skin reaction	18%	34%

Researchers also presented the results of a Phase II study of Erbitux in combination with cisplatin and vinorelbine vs. cisplatin+vinorelbine alone in EGFR+ advanced NSCLC. They concluded the addition of Erbitux improved the efficacy

of carboplatin/vinorelbine and did not aggravate the typical toxicities of cisplatin/vinorelbine, inducing only "a few" additional side effects. Skin reaction did appear to be predictive of efficacy. A mutation analysis is ongoing.

Results of Phase II Trial of Erbitux in NSCLC

Measurement	Erbitux + cisplatin+vinorelbine n=43	Cisplatin+ vinorelbine n=43
Primary endpoint #1: ORR (CR/PR confirmed)	3%	28%
CR/PR ***not*** confirmed	53%	33%
Stable disease confirmed	49%	40%
Stable disease ***not*** confirmed	30%	35%
Secondary endpoint: Median survival	8.3 months	7.0 months
PFS	4.8 months	4.2 months
Survival at one year	32%	26%
Survival at 18 months	14%	0
Survival at 24 months	14%	0
Grade 3-4 Toxicity		
Nausea/vomiting	17%	14%
Asthenia/fatigue	19%	2%
Skin reaction	12%	0
Fever/chills/sweating	10%	5%
Infection	5%	2%

KOSAN/ROCHE'S KS-862: Excessive toxicity in colorectal cancer

Shortly after ASCO, Kosan and Roche announced that they were halting trials of its epothilone, KS-862, in combination with oxaliplatin in colorectal cancer due to unexpected toxicity. The companies are continuing development in prostate, breast, and lung cancer. Prostate cancer appears the most promising area.

At ASCO a researcher testing 90-minute infusions of KS-862 commented, "All epothilones have neurotoxicity. We are seeing Grade 3-4 neurotoxicity (with KS-862), mostly peripheral neuropathy, plus some hallucinations and confusion with some administration schedules, but not with continuous infusion…I hope the company will start a new Phase II trial with continuous infusion."

LILLY'S Evista (raloxifene): Less risk of breast cancer but no reduction in non-vertebral fractures

The original 7,705-patient MORE trial, which lead to the FDA approval of Evista, was extended for another four years as the 5,203-patient CORE trial. The primary endpoint of MORE was bone fractures, and Evista improved bone density and reduced the number of fractures in MORE. CORE found that Evista lowered the risk of breast cancer, but there was no difference in non-vertebral fractures, and the two-fold increase in VTEs persisted. Hot flashes and leg cramps, which were more frequent with Evista during MORE were comparable to placebo in CORE. Bone mineral density was measured in a subset of 1,000 U.S. CORE patients; that data is being analyzed and will probably be presented at ASBMR 2004.

There were no new safety issues in CORE, though VTEs remain an issue. An investigator said, "What we find is no loss of effectiveness as we plot through the eight years. The difference remains constant…My personal clinical practice is if a woman is going on a long flight – to Europe or around the world – then perhaps for a day or so she might want to avoid taking the drug."

The U.K.'s NICE has recommended against using Evista for osteoporosis. The investigator said she hopes this data will encourage them to change their minds, "To me, this drug is particularly of value to women with osteoporosis."

Asked in which women Evista is an appropriate preventive agent for breast cancer, an investigator said, "That answer is unclear to me…Are we now ready to use this drug specifically for breast cancer prevention even in the type of patient studied (in CORE)? I would say I am not sure we are quite ready to do that…The data has to go to the FDA for approval…and two larger studies are underway, both of which have finished accrual and in the next few years will yield data…Along with the 10,000-patient RUTH trial...and the 19,000-patient STAR trial…will come the answer." Another source said, "I would take something to prevent breast cancer, but not Evista until the STAR results are available. If Evista were approved for breast cancer prevention, I would take it based on this data."

Evista CORE Trial Results

Measurement	Placebo	Evista in CORE
Primary endpoint #1: Incidence of invasive breast cancer per 1,000 women/years (in years 4-8)	5.2	2.1 (a 59% reduction, p<.001)
MORE+CORE incidence of invasive breast cancer per 1,000 women/years	4.2	1.4
CORE incidence of invasive breast cancer	1.6%	0.7%
VTEs		
Clot to lungs	0.6% (p=.048)	0.2%
PE death	1 patient (Nss)	0
Venous clots (MORE+CORE)	47 patients	13 patients
Leg clots	1.1% (Nss)	0.8%
VTE overall	1.7% (p=.094)*	1.0%

*clinically significant

MILLENNIUM'S Velcade (bortezomib): Better than dexamethasone in multiple myeloma

The Phase III, confirmatory, APEX trial found Velcade to be more efficacious than high-dose dexamethasone in relapsed multiple myeloma. This was an international, randomized, 14-month, 669-patient trial. The trial was terminated one year early after the DSMB concluded the pre-specified interim analysis showed a statistically significant improvement in TTP in favor of Velcade, and the dexamethasone patients were given Velcade. An investigator said, "The difference in survival was statistically significant even with ~50% of patients crossing over from dexamethasone to Velcade…We wonder if Velcade is working by methods other than protea-some inhibition." The quality of life analysis is still ongoing.

Phase III APEX Trial Results

Measurement	Velcade n=327	High-dose dexamethasone n=330	p-value
Primary endpoint: TTP	5.7 months	3.6 months	<.0001
Overall survival	13 deaths	24 deaths	N/A
Deaths at median follow-up of 244 days	48	81	N/A
Incidence of Grade ≥3 infections	6.7%	10.6%	N/A
Grade 4 adverse events	11%	13%	N/A

NOVARTIS'S Femara (letrozole): A genetic marker predicts response

A study done in Spain found that CYP19 single nucleotide polymorphisms (SNPs) can predict the efficacy of Femara in metastatic breast cancer patients. A researcher predicted SNPs may help determine use of all aromatase inhibitors in breast cancer. He said, "The presence of a SNP on the 3'UTR of the CYP19 aromatase gene is associated with improved treatment efficacy and may help in selecting patients for letrozole therapy." No CYP19 test is commercially available at this time, but he believes a blood assay may be able to be developed.

Measurement	With a SNP	Without a SNP	p-value
Mean time to disease progression	525 days	196 days	Log rank p=.02

The MA-17 trial looked at letrozole use after five years of tamoxifen treatment. The trial, which was stopped early because of the benefits of Femara, didn't make it clear how long to give an aromatase inhibitor after tamoxifen since the whole trial did not get five years of aromatase inhibitor therapy. An expert said, "MA-17 suggests patients – especially node positive patients – should be considered for a sequential aromatase inhibitor, but it is not clear that patients should switch."

Results of MA-17 Femara Trial

Measurement	Femara 25 mg QD n=2,575	Placebo n=2,582	p-value
DFS at 2.4 years	93%	87%	.00008
Recurrences	2.4%	4.1%	N/A (a 43% risk reduction)
Contralateral breast cancer	0.5%	1.0%	N/A
Overall survival at 2.4 years	96%	94%	.25
Estimated 4-year DFS	93%	87%	N/A

PFIZER'S Aromasin (exemestane): Better survival than tamoxifen but slight worsening in BMD

A two-year, randomized, placebo-controlled study of Aromasin in 147 postmenopausal women, found Aromasin moderately increases bone loss and bone mineral density compared to placebo, and osteoporotic patients did worse in terms of their osteoporosis with Aromasin. However, no patients who had normal BMD at baseline became osteoporotic during the trial – either on drug or on placebo. In addition, the number of women who became osteopenic was the same in both arms of the trial.

A researcher said combining a SERM with Aromasin is absolutely contra-indicated, but bisphosphenates are a different story. He said, "Our data suggest that if a patient is going to be exposed to exemestane, then it is a good idea to have a BMD measurement at baseline. If that is normal, the patient should be handled at follow-up and treated in the same way as other postmenopausal women."

2-Year Exemestane Results

Measurement	Aromasin 25 mg n=62	Placebo n=66	p-value
Evaluated for BMD	62	66	---
Withdrawals of adverse events	9 patients	3 patients	---
Lifetime risk of fracture	20%	23%	Hazard ratio: 1.15
Primary endpoint: **BMD loss at 12 months**			
Spine	-2.17%	-1.84%	Nss
Femoral neck	-2.72%	-1.48%	<.05
Change in T-score at 2 years			
Spine	-.30	-.21	N/A
Femoral neck	-.21	-.11	N/A
Adverse events			
Hot flashes	30%	25%	N/A

Results of the randomized, open label, 371-patient, Phase III EORTC-10951 trial in metastatic breast cancer were presented, comparing Aromasin to tamoxifen. Median follow-up was 30.6 months.

- The survival data is not yet mature, with only 163 deaths (44%), but at this time point, there was no improvement in overall survival with Aromasin.
- There was a 4.7% absolute benefit for patients who switched to exemestane instead of continuing on five years of tamoxifen.
- On progression free survival, the two curves separated in the first 15 months (p=.05), and then came together (p=.121).
- Both arms of the trial were well tolerated: There was more arthralgia/myalgia with Aromasin (10% vs. 4%) but more edema, constipation, hot flashes, vaginal bleeding, and vaginal discharge with tamoxifen.
- Aromasin was associated with a 32% reduction in risk of recurrence, and a 56% reduction in contralateral breast cancer.

Aromasin EORTC-10951 Trial

Measurement	Aromasin 25 mg n=2,362	Tamoxifen 20 mg n=2,380
Primary endpoint: Median PFS	9.9 months	5.8 months
PFS at 6 months	66%	49%
PFS at 12 months	42%	31%
Overall response	46%	31%
Complete response (CR)	8%	3%
Local recurrence only	21%	33%
Distant recurrence	114 patients	174 patients
Discontinuations due to toxicity	1 patient	2 patients
Arthralgia	10%	4%

1-Year TEAM Study Results

Measurement	Aromasin 25 mg n=495	Tamoxifen 20 mg n=502
Mean hot flash score		
Baseline	~6	~7
At 3 months	~8	~10
At 12 months	5.4	7.1
Other Results		
Vaginal discharge	13%	29%
Vaginal dryness	48%	41%
Bone/muscle aches	---	Better
Hot flashes	No difference	
Bone loss and fracture	---	Better
Vaginal bleeding	No difference	
Mood alteration	No difference	

Comparison of Aromatase Inhibitors in Various Trials (not head-to-head)

Measurement	AstraZeneca's Arimidex (anastrazole) vs. placebo	AstraZeneca's Arimidex (anastrazole) vs. placebo	Novartis's Femara (letrozole) vs. placebo	Pfizer's Aromasin (exemestane) vs. placebo
Number of patients	170 vs. 182	340 vs. 328	453 vs. 454	182 vs. 189
OR	21 vs. 17	33 vs. 33	30 vs. 20	46 vs. 31

An Aromasin researcher argued that Aromasin is better tolerated and has a better anti-tumor effect than tamoxifen in first-line metastatic breast cancer, but the benefit, in terms of PFS and response, seems to be of the same magnitude as other aromatase inhibitors.

PFIZER'S CP-675,206: A hint of efficacy in malignant melanoma

First-in-human data on this CTLA-4 monoclonal antibody in 39 patients with malignant melanoma were presented. Researchers concluded: "CTLA-4 blockage with a single dose is feasible and well-tolerated. Three of six patients obtained major responses with non-disabling and self-resolving toxicity." Other findings included:

- Mean half-life of 22.2 days.
- No antibody formation.
- Increase in plasma concentration at higher doses.
- All toxicity was manageable and reversible. More than 50% of patients at 10 mg/kg and 15 mg/kg developed dermatitis at different sites and with different severity. Diarrhea was the DLT, occurring in more than 50% of patients at 10-15 mg/kg. The diarrhea resolved after three months, and in patients where Grade 3 diarrhea was observed, it actually slightly responded to lomodil and other supportive measures…It is of interest that it is self-resolving, and I think it will be most related to the median half-life of the antibody."
- DLT is diarrhea at 10 mg/kg. Antihistamines did not relieve the symptoms, but immunosupressives were not needed. A researcher said, "Some of the patients at low doses developed progression after therapy…The most impressive results are those at 15 mg/kg, but we also find that the DLT is diarrhea at 10 mg/kg."
- 10 of 12 patients had an enhanced tetanus skin test response.

TELIK'S Telcyta (TLK-286): Surprisingly little hoopla over fairly promising results in ovarian cancer

Data from two Telcyta ovarian cancer trials were presented in posters at ASCO. A researcher noted that there is very little hair loss with Telcyta. He also noted that there was one PR

that relapsed at eight months, but this was a clear cell patient, which historically has the worst prognosis.

Telcyta in Ovarian Cancer

Measurement	Telcyta	Historical Rate
Study 1: single agent		
CR	19%	0.8%
Study 2: combination with 50 mg/m^2 docetaxel		
ORR	46%	56% carboplatin 46% docetaxel
PR	46%	---
SD	31%	---
TTP	28 months	9 months

Two Phase III trials will determine the future of this agent.

- A Phase III trial of single-agent Telcyta (1000 mg/m^2 every three weeks) vs. Iressa in refractory ovarian cancer is ongoing, with the primary endpoint overall survival. It is enrolling 440 patients and was described as "on target."
- The pivotal Phase III trial of ~200 patients in combination with carboplatin is expected to start soon in ovarian cancer. Company officials would not say whether the Telcyta will be dosed at 750 mg or 960 mg in this trial, and they would not discuss the trial design, which they said would be revealed later this summer.

A small triplet study of carboplatin, docetaxel, and Telcyta is also planned. A researcher said the label, if all goes well, is likely to be Telcyta in combination with carboplatin.

GENETIC MUTATIONS AND RESPONSE TO EGFR INHIBITORS: A way to predict response to Iressa and maybe Tarceva

The news that EGFR inhibitor response is linked to gene mutations was a hot topic at ASCO, and the finding raised almost as many questions as it answered. Doctors generally agreed that the findings applied equally to Tarceva and Iressa, though Genentech officials and Tarceva researchers tried to differentiate the two drugs. However, doctors were divided on what these findings mean for the clinical use of Iressa and Tarceva.

The Science

Two recently published studies in the New England Journal of Medicine reported that patients with a specific EGFR mutation responded to Iressa, while patients without the mutation did not respond to the drug. These findings were a hot topic at the meeting, and one expert called this perhaps the most significant development in lung cancer.

***Massachusetts General Hospital*:** In one 16-patient study, 8 of 9 Iressa responders had mutations in the EGFR gene, compared to no mutations in 7 patients who did not respond. Researchers had reviewed a study of 275 chemo-refractory NSCLC patients treated with single agent Iressa. They found 25 (9%) with a major clinical response, and tumor samples were obtained from nine of these. The other responders either had not granted consent or had been diagnosed by fine needle aspiration so there was no archival material to review. The researchers found mutations in Exon 19 and Exon 21 in responders. No mutations of Exon 18-24 were found in breast, ovary, kidney, head & neck, brain, prostate, or colon cancer patients. One researcher said, "It looks like (NSCLC) mutation receptors appear more sensitive to Iressa, nearly 10-fold more sensitive."

The researchers also looked at mutations in a small set of Erbitux patients, analyzing Exons 18-19-21. Two mutations were identified: one in a patient with SD, and another in a patient who had progressed. The suggestion was that mutation positivity may not be a prognostic factor for Erbitux.

The conclusions were:

- Mutations determine responsiveness to Iressa for a large majority of patients with a major response.
- Mutations are not the entire story, but the majority of patients with a response will have mutations.
- Mutation may not have the same role in monoclonal antibodies (e.g., Erbitux).
- Overall survival of mutation-positive patients treated with Iressa is >20 months.

***Dana-Farber Cancer Institute*:** A study compared 58 Japanese and 61 American NSCLC patients found mutations in 15 of the Japanese patients but only one American patient. Of the 9 patients who received Iressa, all five who responded had mutations and none of the non-responders had mutations.

They also looked at Tarceva patients from a Phase II study, and found:

- 2 of 4 PR had Exon 19 deletions, and 2 had no mutations
- 1 patient with minor response had a mutation
- 5 SD patients had no mutations
- 1 of 8 patients with disease progression had a mutation of Exon 19

A look at the Tarceva TRIBUTE trial patients, found 29 mutations (frequency of 12.7%), and 199 patients without a mutation. The researcher concluded that mutation may not only indicate response but also survival.

These researchers concluded mutations are:

- More frequent in adenocarcinoma, women, and Japanese patients
- More sensitive to Iressa
- Important for NSCLC survival
- Found in patients who respond to both Iressa and Tarceva

Measurement	Mutation	No mutation
Median TTP		
Chemotherapy alone	6.6 months	5.4 months
Chemo+Tarceva	12.5 months	4.6 months
Median survival		
Chemotherapy alone	N/A	11.7 months
Chemo+Tarceva	N/A	9.6 months

Gene sequencing. A researcher said the whole gene was sequenced and only the reported Exon mutations were found, but he said they are "re-looking" at the data to be sure. He outlined some of the key mutation findings:

- Somatic mutations in EGFR were found in 12% of patients with NSCLC.
- The mutations are more common in women, patients with adenocarcinoma, and patients from Japan.
- Eighteen different mutations were identified, but all cluster in the tyrosine kinase domain.
- The mutant EGFR receptor is turned off by lower Iressa concentrations (50 times lower) than the wild type EGFR is.
- Mutant but the not wild type EGFR receptor is important for survival of NSCLC cells.
- EGFR mutations were found in 7 of 7 patients who responded to Iressa, but in 0 of 6 who progressed on treatment.
- Mutation response probably does not change over time. However, another expert said it is possible that a patient might become mutation positive, but he did not think a patients could lose positivity once they had it.

The Meaning of the Mutations

Since these studies were published, these and other researchers have taken additional looks at mutations and EGFR inhibitors. So far, Iressa responses have been linked to mutations of Exon 18-19-21, and Tarceva to mutations of Exon 18-19-21-23. However, there were some Tarceva patients with stable disease and even some responders who were not mutation positive. A speaker said, "Not all patients who respond (to Iressa and Tarceva) have mutations, but the response rate to chemotherapy+Tarceva is greater in patients with mutations. No mutation was identified in patients who develop stable disease.

In reviewing the mutation data, a speaker concluded, "I think this rate of mutation in metastatic NSCLC might be an underestimation because:

- The entire gene has not been sequenced in all these tumors…We saw an Exon 23 mutation in Tarceva...and that has not been sequenced.
- Most of the DNA extracted from diagnostic tumor material was obtained at variable times before the development of metastatic disease.
- Zero of 13 patients with mutations progressed on Iressa… but I wouldn't be surprised if soon we see some, so that number may not be zero soon."

In the BR-21 trial, Tarceva prolonged survival in patients with incurable NSCLC…Is the impact on survival explained completely by a robust response to mutations?…If you consider a 10% mutation rate, it is hard to explain this data…Genentech did a simulation analysis in which they assumed a 10% mutation rate, and you have to have some patients with a moderate benefit, not just a large benefit, to get the survival results…The implication is that Tarceva still benefits patients who may not have mutations…I propose there are three or more groups of lung cancers:

- EGFR mutants who achieve great benefit from EGFR inhibitors.
- Mutations we missed who respond to EGFR inhibitors.
- No clinical benefit with EGFR inhibitors. It may be easier to identify this no clinical benefit group than those who do benefit."

Clinical Implications

The clinical implications of the Iressa EGFR mutations include the potential for:

- ***Diagnostic testing to predict a response***. If a patient has this mutation, it might be a good idea to treat with Iressa early, first-line – or to take Iressa as adjuvant therapy after surgery or chemotherapy/XRT. Another expert said, "Mutation positivity would be more important in going to earlier treatment…But there are mutation negative patients who respond. The data sets are not perfect. There are more negative responders with Iressa than with Herceptin…People will start thinking of selecting patients – females, non-smokers, etc. – who will do better with small molecules. They could tell them they have a choice of chemotherapy or Tarceva, or they could use Tarceva first-line." A third expert said, "I think we are going that (Herceptin) way…but amplification is also important with this mutation."
- ***Designing second generation inhibitors.***
- ***Understanding resistance.***
- ***Defining other solid tumors*** with activating mutations in EGFR.

Among the unanswered questions about the mutations are:

- ***Are all mutations equivalent?***
- ***What is the story in patients with stable disease?***
- ***Is the EGFR inhibitor toxicity different in patients with a mutation?***

➢ ***What relationship is there between other EGFR inhibitors and the mutations?*** An expert said, "I believe we'll see the same mutation response with Tarceva as Iressa…Tarceva has a similar mutation in the same area."

➢ ***Are there mutations in other malignancies that indicate a response to the small molecule EGFR inhibitors?*** It appears that the mutation may only predict response to the small molecule EGFR inhibitors, and not monoclonal antibodies (e.g., Erbitux). An expert said, "We presented an abstract looking at cetuximab (Erbitux)…and in the 14 patients we looked at, there did not appear to be a relationship to response and mutation…But those are very small numbers." Another expert said, "It is possible that the effect of the small molecules will be similar, though that is not proven…Antibodies bind to the extracellular domain, so there may be a different story for those."

The mutations have potentially serious implications for clinical use of these agents, and it is possible that mutation positivity may become to EGFR inhibitors what HER2 positivity is to Herceptin use in breast cancer, but that is at least a few years away – if it ever happens. There currently is no commercially available test for the mutations, but several academic centers are doing the test, including Massachusetts General Hospital and Dana-Farber Cancer Institute. An expert said, a commercial test will require either DNA sequencing or a chip-type assay, but he predicted a commercial test will be developed and could be available as soon as summer 2005. Another expert said, "To validate a commercial test would require more studies and more patients. A company is not likely to do this, but there is a lot of interest by academia."

Several doctors were asked how the gene mutation news will affect their use or choice of an EGFR inhibitor. Among their comments were:

- "I won't test for mutations before giving Iressa yet. That kind of work will be in future trials. It is not yet at that level of validity."
- *2004-2005 President of ASCO:* "Iressa was approved on what many thought was fairly flimsy data…but we have seen stunning responses in a minority of patients…This (mutation) will allow us to target the therapy…That is the ultimate in personalizing medicine."
- *2003-2004 President of ASCO:* "Why give something with a low chance of response when there are so many other treatments in development."
- *Massachusetts*: "I had a patient who switched doctors because I wouldn't give her Iressa because she was too refractory. She got it, had stable disease for two months and now thinks I was a bad doctor. So, there will be a lot of patient pressure to prescribe Iressa, even in mutation negative patients."
- *Netherlands*: "The mutation is good for selecting patients for studies, but it is not ready to be used in clinical practice. Some patients respond who are mutation negative, so you can't really deny the drugs to patients."
- "If patients are mutation positive, then they would get the drug first-line. If they are mutation negative, then they would still get the drug, but as they are used today…Mutation negative patients may need to get a higher dose…You could use a lower dose in mutation positive patients, but there is no reason to do that – unless you wanted to cut pills to save money."

Should patients be screened for mutations? Among the comments on this topic were:

- "I don't know, and there is no test…It is unlikely there will be a test for all the Exons…And there is limited tissue available in most patients (because of biopsy by fine needle aspiration)…Would non-smoker female patients with adenocarcinoma and more advanced disease consent to a larger biopsy? I think so, and they might be eligible for first-line therapy (with an EGFR inhibitor)."
- "Surgical specimens should be screened if possible."
- "If there is a correlation of mutation with gene amplification, it could allow the use of FISH as a screening test. That is more doable than sequencing…and that would be very powerful."
- "The effect of Tarceva on survival cannot be solely explained by mutation."
- "It is unlikely that EGFR mutations alone explain all the benefit with (Iressa or Tarceva)…This is exciting data, but caution is required because the clustering was only done with four sensitive and six resistant cell lines…We need to validate these findings in the clinic with responders and non-responders…How predictive are cell lines of clinical behavior?…It would be of interest to focus on the subgroup of patients with clinical benefit who do not have activating mutations…There are probably other determinants of response in addition to mutations."
- "We know patients respond to Iressa and Tarceva…and the response rate is 12%-15%, depending on the population. But who responds? We know women, patients with adenocarcinoma, and non-smokers seem to do better…EGFR expression levels probably don't predict response."

Among the questions raised about these findings: ***Does the dose matter?***

- Could Iressa dose escalation improve therapy for mutation negative patients? One expert thought this might be a good idea, but another said, "I would argue that most responders probably have a mutation, so it is not likely a dose escalation would help." A third researcher said, "The ongoing Tarceva trial, where patients are dosed to rash…may partly answer that."
- Is a lower dose reasonable for mutation positive patients?

TAMOXIFEN VS. AROMATASE INHIBITORS FOR BREAST CANCER:
Mounting evidence for aromatase inhibitors

NIH has advised against giving tamoxifen to breast cancer patients for more than five years because the NSABP B-14 trial found that, at 10 years, uterine cancer was increased with longer duration tamoxifen treatment. A speaker said, "The problem with this study is that it was in node negative patients."

So, the question is how to choose between tamoxifen and an aromatase inhibitor? A speaker said, "There are some subgroups where you may want to think of an aromatase inhibitor from the get-go: in general, the aromatase inhibitor is better than tamoxifen or placebo in node negative patients… Hot flashes tend to be a little better with an aromatase inhibitor than with tamoxifen, and there is less uterine cancer, vaginal discharge, and vaginal bleeding, but there are more osteoporotic fractures with an aromatase inhibitor." Another speaker said, "There is mounting evidence that tamoxifen is less potent than third generation aromatase inhibitors in post-menopausal disease. The large, inter-national, ongoing ATTOM and ATLAS trials should tell us if five years of tamoxifen is optimal." A third expert said, "All three aromatase inhibitors appear to have similar toxicity."

DIAGNOSTICS

AGENCOURT BIOSCIENCE:
Ready to test for EGFR mutations now

An EGFR mutation test is not years away, as some experts have suggested. Agencourt, which is known for its reagents for purifying nucleic acids and for genomic project sequencing, has a gene sequencing test available ***now*** for looking for EGFR mutations. The test currently can only be marketed for research purposes. That is, the company can't call it a diagnostic test until it gets CLIA certification, which reportedly is not far away. A company official predicted the test will be commercially available within six months as a service, not a kit. That means doctors will be able to send tissue samples in to Agencourt for analysis at Agencourt.

The EGFR assay is a pre-validated sequencing assay that identifies genetic alterations within Exon 18-24. The cost for a single test currently is about $1,000, but doctors/hospitals that send in multiple samples at the same time or that commit to a larger number of tests per month or year will get a "drastic" volume reduction, a source claimed. Discounts begin with two samples, and the price goes steadily down with volume.

So, today, if a patient wants to know mutation status, the sample can be sent to this lab. The patient, upon finding out status, could request or reject Iressa. However, the doctor and company can't call this a diagnostic test for lung cancer mutation. It's a bit of a semantic and marketing situation.

At an EGFR mutation session, a case was made that:

1. Tarceva is less mutation-related than Iressa because Tarceva trials have shown mutation negative patients with stable disease.
2. It is too early to base clinical treatment decisions on mutations.

However, most experts believe that Iressa and Tarceva are like Coke and Pepsi – more similar than different. After the EGFR mutation session, the president of ASCO said,

- "If gene amplification is related to gene mutation, then we could do FISH and that would be very powerful. There is data circulating that suggests that is the case."
- "The mutations will affect clinical practice when a test is available."
- "Mutation negative patients may have un-found mutations."
- "We will be using the EGFR inhibitors like Herceptin in less than five years."
- "I agree the Tarceva benefit isn't entirely explainable by the mutation; there has to be some other effective...but I think Iressa would have had exactly the same results in a similar trial."
- "I'm not convinced yet that there is a difference between Iressa and Tarceva (on survival)."
- "The mutation may be determined by germ line. The genetic environment may play a role."

Another expert said:

- "The association of mutation and survival is similar with both Iressa and Tarceva."
- "The mutation will affect clinical trials design now, but not clinical practice yet."

ARCTURUS' Paradise Reagent System:
A very promising test

Many breast tumors fail to respond to tamoxifen or they develop early resistance to the drug, but it has not been possible until recently to identify which women will fall in these categories. Arcturus' technology earned high praise at AACR, and it was featured again at ASCO. The company found that the ratio of HOXB13 to IL17BR can predict whether women are tamoxifen responders or not.

The technology does not require fresh samples; RNA can be extracted from formalin-fixed biopsy samples that are up to five years old. Genetic analyses can be done on these formalin-fixed samples to find the HOXB13:IL17BR ratio. And that is what the North Central Cancer Treatment Group did. They looked at 60 frozen tumor samples for which

clinical follow-up information was available. An investigator said the findings support the initial Arcturus discovery and have "implications for personalized medication." He added, "We don't claim this will change treatment, but it will help oncologists think of patients differently…This may help us identify patients at risk."

An Arcturus official said several centralized labs are developing a test that will be available this summer. However, before the test is likely to be used to direct patient treatment, an expert said there needs to be a large, randomized clinical trial.

Japanese Patients:
Respond differently to chemotherapy

A chemotherapy regimen commonly used to treat NSCLC is more effective – but more toxic – in Japanese patients than in American patients. This was the finding of a comparison of two Phase III trials – the Japanese FACS study to the SWOG S-0003 trial. The comparison found that there are genetic differences in chemotherapy drug metabolism.

Both trials used a common treatment regimen (paclitaxel plus carboplatin) and had patients with similar characteristics, but the paclitaxel dose was slightly lower in Japan because the patients could only tolerate a lower dose, and, despite that lower dose, they still had more toxicity – double the neutropenia and five times the febrile neutropenia compared to the SWOG patients.

A researcher said, "The results of clinical trials outside the U.S. cannot always be extrapolated to the U.S." Among the things that could cause this genetic difference are:

- Cytochrome P450
- Polymorphisms in the MPR1 gene
- SXR gene

Measurement	Japanese FACS 200 mg/m² paclitaxel n=145	American S-0003 225 mg/m² paclitaxel n=185
Survival at one year	51%	37%
Mean survival	12 months	9 months
Completed 3 cycles	24%	100%
Completed 6 cycles	11%	36.5%
Neutropenia	69%	26%
Febrile neutropenia	16%	3%
Neuropathy (Grade 3-4)	5%	16%
CR/PR	32%	34%

Regulatory Perspective:
Confusion, confusion, and more confusion

ASCO held a Reimbursement Forum, and there was standing room only for this session. The general mood reflected significant concern and confusion. At times, speakers made comments that elicited gasps from the audience.

ASP. In April 2004, reimbursement of 85%-90% of AWP went into effect for infused drugs, but the physician fee for doing infusions was increased (to $217.25 average). The net effect of these changes is pretty much a wash for oncologists – but only for 2004. Starting in 2005, doctors will get paid ASP (re-adjusted quarterly) plus 6% for infused drugs, and the ASP calculation will consider all non-government sales (including rebates and discounts). Hardest hurt are likely to be smaller clinics and independent oncologists.

What the ASPs will be for 2005 is uncertain, and that uncertainty is making planning very difficult for oncologists. The first look at the ASP schedule is due in August or September 2004, and in 2005 CMS will issue a proposed rule on how ASPs are to be calculated. Right now, each manufacturer is using its own system to calculate ASP; there are no standards. Thus, the speculation is that ASPs will be lower than they probably should be.

Infusion Payments.

- 2004: $217.25
- 2005: $172.14
- 2006: $150.00

Physician fee schedule. There is likely to be big battle between the AMA and CMS over this.

- 2004: up 1.5%
- 2005: up 1.5%
- 2006: projected decreases of 5%

Timeline.

- **2005**. Drug reimbursement will decrease, administrative fee decreases. CMS to release ASPs, which will help doctors and ASCO with planning.
- **2006**. ASCO is pushing for:
  - Infusion codes for each day a drug is administered.
  - New codes for monoclonal antibodies.
  - New codes for venous access devices.
  - A physician management code.

ASCO's proposal – though there is little optimism that it will succeed – is for CMS to:

1. Maintain reimbursement in 2005-2006 at the 2004 levels, creating a floor in reimbursement levels for infusion fees.
2. Ensure ASP plus 6% is ***not*** below market prices.

The outlook for modifications. There appears to be little political will to "rescue" oncologists from these changes. The Republicans don't want to reopen this issue before the presidential election. The Democrats consider it too hot an issue to touch. ASCO reportedly has been told by the White House "not to push it." Thus, ASCO leaders had little confidence any changes in the proposed reimbursement will be made this year.

Off-label drug usage. CMS appears to be very concerned about off-label drug usage and wants to "get a handle on this." By law CMS must pay for all on-label drugs and for off-label usage where the use is listed in the compendia. The clear suggestion, however, was that CMS is looking for ways to restrict reimbursement of off-label drugs.

New Medicare Drug Benefit (Part D). This may increase the volume of physician visits. The Bush administration reportedly wants this to look like a PBM.

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