Trends-in-Medicine

September 2005
by D. Woods

Quick Pulse

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

FDA Advisory Committee Recommends Approval of Pancreatic Cancer Drug

Bethesda, MD
September 13, 2005

The FDA's Oncologic Drugs Advisory Committee (ODAC) voted 10-3 to recommend approval of OSI Pharmaceuticals/Genentech's Tarceva (erlotinib) in combination with Lilly's Gemzar (gemcitabine) for treatment of pancreatic cancer, despite concerns about marginal efficacy and severe toxicity.

OSI is seeking approval for the proposed indication for first-line treatment, in combination with gemcitabine, of patients with locally advanced, unresectable, or metastatic pancreatic cancer. The proposed dose is 100 mg QD in combination with gemcitabine at the standard approved dose and schedule.

OSI officials said that its study met the primary endpoint, and they argued that pancreatic cancer patients need another option to treat their disease. However, an FDA official pointed out that the Tarceva/Gemzar combination adds only marginal efficacy (clinically and statistically) while adding severe toxicity. He said the Tarceva/gemcitabine arm has a higher incidence of:

- Grade 3/4 toxicity (regardless of causality and treatment related).
- Serious adverse events (regardless of causality and treatment related).
- Discontinuation due to adverse events (regardless of causality and treatment related).
- Toxic deaths.
- Refusal of therapy.
- Death on treatment or within 30 days of last treatment.

The Company Perspective

OSI's Vice President for Medical Affairs and Translational Research, Dr. Pablo Cagnoni, told the panel, "Tarceva, when added to the current standard of care, gemcitabine, provides the first statistically significant and clinically meaningful increase in survival compared with gemcitabine alone." Another OSI speaker argued that pancreatic cancer patients have limited treatment options, with gemcitabine the only FDA-approved treatment. He added that pancreatic cancer is the fourth-leading cause of cancer-related deaths, with a five year survival rate of <4%.

A speaker described the OSI randomized, placebo-controlled study of Tarceva + gemcitabine in patients with locally advanced, unresectable, or metastatic

pancreatic cancer. The trial met the primary endpoint of overall survival. Key secondary endpoints were progression-free survival, response rate, quality of life (in selected countries), tumor epidermal growth factor receptor (EGFR) status with outcomes, and safety. Sample size initially was 800 patients with accrual over nine months, with a minimum follow-up of 2.8 months. The sample size was modified to 450 patients during the study, with an extension of follow-up to 18 months, and no change in the number of deaths for event-driven analysis.

The hazard ratio (HR) for death was 0.80, with a statistically significant p-value of 0.018. The assumption of proportional hazards was satisfied. The median survival for the Tarceva arm was 6.24 months, compared to 5.91 months for the placebo arm**.** However, the OSI speaker said that the median may be inappropriate as a measure for overall survival. The one-year survival rate was 23% for Tarceva patients versus 17% for the placebo arm.

Overall Survival Robustness Analyses by Intent to Treat (ITT)

Analysis	HR	p-value
Stratified log-rank (485 deaths)	0.80	0.018
Cox model with stratification factors + gender	0.80	0.015
Cox model with stratification factors + other prognostic factors (gender, pain intensity, age, race, prior chemo, region, baseline albumin)	0.81	0.023
Stratified log-rank, censored at 1st anticancer therapy (341 deaths)	0.80	0.039
Stratified log-rank (381 deaths)	0.80	0,034
Stratified log-rank (551 deaths, June 2005)	0.81	0.016

Overall Survival – Robustness Analyses (100 mg Cohort)

Analysis	HR	p-value
Stratified log-rank (485 deaths)	0.81	0.028
Cox model with stratification factors + gender	0.81	0.028
Cox model with stratification factors + other prognostic factors (gender, pain intensity, age, race, prior chemo, region, baseline albumin)	0.82	0.048
Stratified log-rank, censor at 1st anticancer therapy (341 deaths)	0.80	0.050
Stratified log-rank (381 deaths)	0.82	0,059
Stratified log-rank (551 deaths, June 2005)	0.82	0.028

The tumor response for patients with measurable disease at baseline was described as similar in the two arms, and the speaker added that the global quality of life measure was no different from the placebo arm, despite problems with diarrhea. A speaker concluded that the study met the primary endpoint, but the secondary efficacy endpoints used statistics and medical values that were "inappropriate." He also said the robustness of survival benefit:

- Does not depend on the statistical analytical approach used.
- Remains statistically significant in multivariate analyses.
- Cannot be explained by benefit from subsequent anticancer therapy.
- Persists with additional follow-up.
- Persists when ineligible patients are excluded.

The results were not considered statistically significant in terms of EGFR status. The survival benefit by adding Tarceva to Gemzar does not seem to affect EGFR status. In conclusion, a speaker said that, for the 100 mg cohort, Tarceva + Gemzar resulted in:

- Statistically significant 23% improvement in overall survival (HR=0.81).
- Statistically significant 30% improvement in PFS (HR=0.77).
- No difference in response rates, but an improvement in disease control rate (CR + PR + SD).
- No detrimental effect on global quality of life, compared with placebo plus gemcitabine.

An OSI official said that Tarceva does not compromise the dose intensity of concomitant Gemzar. Selected adverse events included fatigue, rash, diarrhea, infection, decreased weight, and stomatitis. More patients in the Tarceva + Gemzar arm experienced rash and diarrhea. Overall, the rate of Grade 3 events was balanced, but Grade 4 events occurred more in the Tarceva arm (22%) than the placebo arm (16%).

The most frequent serious adverse event was fever. The remaining serious adverse events were infrequent, with minor differences between the arms. Interstitial lung disease (ILD)-like cases reported as serious adverse events in the 100 mg and 150 mg cohorts were evaluated, and a speaker reported that three patients died, and four patients recovered. Five deaths were attributed to protocol treatment in the 100 mg cohort (all in the Tarceva + Gemzar arm). Two died of pneumonitis, two died of non-neutropenic sepsis, and one died of central nervous system (CNS) bleeding.

Serious Adverse Events
(occurring in ≥2% of patients) in the 100 mg cohort

Serious adverse event	Tarceva + Gemzar n=259	Placebo + Gemzar n=256
Fever	8%	7%
Pneumonia	4%	3%
Sepsis	4%	2%
Cellulitis	2%	0
Vomiting	3%	4%
GI hemorrhage	3%	3%
Fatigue	3%	3%
Deep vein thrombosis	3%	1%
Pulmonary embolism	2%	2%
Thrombosis	2%	2%

In summary, the presenter said that treatment with Tarceva at 100 mg/day in combination with Gemzar was tolerated by most patients. Rash and diarrhea were reported more often in the Tarceva arm. He said that ILD-like serious adverse events were infrequent, and that the hematologic toxicity of gemcitabine was not increased with Tarceva added.

An OSI consultant made the company's concluding remarks. He said, "The therapeutic benefit is both statistically significant and clinically meaningful, including a:

- 23% increase in overall survival.
- 30% increase in progression-free survival.

He added that a point estimate, such as median survival, does not accurately capture this benefit. The speaker admitted that the Tarceva + Gemzar combination resulted in modest or infrequent toxicities, but he insisted the magnitude of toxicity is substantially less than what has been observed when other cytotoxic agents are added to Gemzar.

- Primarily rash and diarrhea.
- Rare episodes of ILD-like events.
- No worsening of global quality of life.

The FDA Perspective

An FDA staffer said that while some analyses showed statistically significant differences between the treatments, there was no "clinically meaningful" differences between tumor shrinkage, duration of tumor response, or survival. The median survival for patients on Tarceva was seven months compared to about six months for patients on placebo. No differences were seen in tumor size reduction.

The FDA saw major protocol violations in the area of pathological confirmation (i.e., no pathological report, lack of confirmation of malignancy, other primary tumor, or metastatic without proof of pancreatic origin). He concluded that the Tarceva combination added marginal efficacy and added severe toxicity. The median survival rate for the Tarceva groups was about 12 days longer than the placebo group, which the FDA speaker said was of questionable significance.

The results for all secondary endpoints were no different between the two arms except for survival by EGFR, which was 10 days longer for the Tarceva group compared to placebo. He said that:

- Mixed results do not confirm a quality of life benefit.
- Worse diarrhea ($p < 0.001$) with the Tarceva + Gemzar combination.
- Tarceva + Gemzar combination worse in some variables (i.e., cognitive functioning, fatigue, dyspnea, appetite, global quality of life,) while improved in other categories (i.e., pain, sleep, social functioning, constipation).
- Combination worse in global health status (32% vs. 25%).

Strokes were also a significant concern in the Tarceva arm. The FDA reviewer said that there were six patients in the Tarceva group (2.3%) with strokes compared to none in the placebo group. Five of these stroke patients were ischemic, and one was hemorrhagic. Median time to stroke was 24 days. The speaker suggested that the strokes may be due to the combination of Tarceva + Gemzar. Severe adverse events included thrombotic and pulmonary events. Toxicity was higher for the Tarceva arm than the placebo arm:

- Grade 3/4 (regardless of causality and treatment related).
- Serious adverse events (regardless of causality and treatment related).
- Discontinuation due to adverse events (regardless of causality and treatment related).
- Toxic deaths.
- Refusal of therapy.
- Death on treatment or within 30 days of last treatment.
- Most frequent adverse events in the Tarceva arm were rash and diarrhea.
- The Tarceva group had a higher incidence of ILD-like disease.
- Other severe adverse events were higher in the Tarceva + Gemzer arm – stroke, TTP, MI, arrhythmias, edema, renal failure, bleeding, disorders, ileus, pancreatitis, odynophagia, and neuropathy.

PA3 Trial: Death on Therapy or Within 30 Days of Therapy

Measurement	Tarceva + Gemzar n=81	Placebo + Gemzar n=68
Toxicity from protocol treatment	2.5%	0
Combination of pancreatic cancer and therapy	3.7%	0
Other conditions	12.3%	13.2%
Other primary malignancy	1.2%	0
Pancreatic cancer	80.2%	86.8%

The FDA speaker said that the study appeared to meet the criteria for single study effectiveness. Multiple endpoints, primary and secondary, are positive. He said that the trial shows the drug adds marginal efficacy, clinical and statistical, while adding toxicity. Adverse events, including higher incidence of strokes, are a safety concern.

Public Comment

During public comment, patient advocates asked the panel to approve the drug, saying that pancreatic cancer patients need more options. One patient advocate said, "An extra day, or a week, or a month means a lot to patients and their families."

PANEL DISCUSSION

Following are selected comments on various topics from the panel discussion.

FDA: "I'd like to address the one trial versus two trial thing again. We have to make sure that we understand that there are many instances where the FDA has accepted one trial, and we have numerous examples where we have approved drugs on the basis of one trial. Oncology is a bit different from other therapeutic areas. We have secondary endpoints that frequently corroborate the primary endpoint. It's difficult to develop drugs in oncology, where we don't have good predictive models. So, to do two large trials in a certain disease is somewhat difficult and somewhat onerous to ask sponsors to do. In our past experience in approving drugs, including this drug's first approval, approval was based on one randomized trial which showed a survival benefit. Another thing is how much survival constitutes clinical benefit? That is a very difficult question for any of us to answer. I'm sympathetic to the views expressed by our patients who have come to the microphone. In general, we say publicly that we look at any meaningful benefit in terms of survival. This endpoint is often a difficult endpoint to achieve. To say that x amount of days is a benefit, and x minus 2 days is not a benefit may not be the most appropriate conversation to be having. The thing is, do we truly have a true finding and is it a clinical benefit in terms of the toxicity? – not what is x number of days of benefit."

Cost effectiveness

Panel member: "Even in the most optimistic scenario, we're talking 21 days, and if it's $100 a day, can society afford this amount of money for this amount of gain? Or should we be looking for a better drug?"

FDA: "We are not supposed to be talking about money or how much a drug costs. A decision regarding this drug should be made on the basis of safety and efficacy that is presented to you, not on any cost considerations…"

Panel member: "Question withdrawn."

Adverse events

Panel member (oncologist): "We seem to have spent a lot of time talking about increased complications and rash and response."

OSI: "In this trial, it is true that if you look at the patients who dropped Tarceva, ~283, they divided into three groups of equal size with Grade 1-2-3 rash. This phenomenon of a rash seen with benefit is a hypothesis-generating analysis. The ability to generate a rash may be because you generate better performance. In terms of thromboembolic disease, the incidence is higher."

Panel member (oncologist): "Pancreatic cancer itself is associated with an increased risk of clots. More people happened to be on Coumadin in the Tarceva arm compared to placebo. That might have explained the increased clots."

Survival and the risk:benefit ratio

Panel member (patient advocate): "Can you tell me how this drug compares to the other combinations that we see all the time with pancreatic patients, from a median survival standpoint?"

FDA: "Those comparisons are very, very dangerous to make. This data did not go through the same scrutiny that this NDA did, so we may be comparing apples and oranges here. It was a background information package that there may be other therapies out there. Furthermore, there is no comparative efficacy standpoint when we're talking about clinical benefit. One has to demonstrate an effect on survival, not that it is any better than anything else. So it's a very tenuous situation."

Panel member (patient advocate): "Then I guess you don't want to discuss the toxicity of those other combinations?"

FDA: "No, that data have not been approved. They have to show that they are safe and effective."

Panel member (oncologist): "What I've been struggling with is that I do get concerned about the magnitude of the change and certainly with regard to risk:benefit ratio."

OSI: "With new data in the 100 mg cohort, it is true that the median survivals appear to be two weeks. But…the two pinch together very closely at the median. Statisticians have been preaching that we should not use means. Most survival curves contain quite a bit of censoring. It turns out that the average, the mean as we know it, is equivalent to the area underneath the survival curves. So the mean survivals here are 8.7 versus 6.2. That turns out to be a five week difference in the mean survival, calculated this way…So, you should probably think that the benefit is in the neighborhood of five to six weeks."

Another OSI official: "In pancreatic cancer, usually you expect results to be negative. Having said that, most improvements in oncology are incremental. When you have a horrible disease like pancreatic cancer, the absolute improvement is only one to two months, so do you penalize people who have these aggressive diseases by asking for a higher survival rate? Does this mean that we have to use triple therapy? I think that's a good thing. I, personally, am hopeful that if we target all the pathways that we know are over-expressed, we'll have a better chance of controlling the disease."

First OSI official: "Does this represent progress? I believe it does."

Panel member: "They set up to increase survival, and they showed it."

Panel member (oncologist): "What's interesting about this data is the fact that there is, at some level, positivity…What's happening here is that we're seeing some small incremental benefit, but I would hope to pursue next whether the patient shouldn't get concomitant therapy."

Panel chair: "In all fairness, as a clinician, I am having a very hard time making a judgment on this…Is it two minutes? Is it

five days? Is it 12 weeks? If that (survival) and quality of life are the issues, then it isn't clear to me why I'm sitting here."

Panel member (oncologist): "None of us can put a statement on a week or a month. You can't do that. The survival of pancreatic cancer is six months. If we say to the company we want a year, we want five years, that's not fair. So if there's an improvement of a month, I think that's valid."

Panel member (hematologist/oncologist): "But it doesn't come without a price. You're coming with increased toxicity. There are problems associated with it, and what really bothers me is lack of improvement in quality of life. That's my concern – where's the drug effect?"

OSI: "That's a valid concern. The drug effect comes from what I think of as a staged migration. The absolute survival that you see is pretty much the same with Tarceva + Gemzar or placebo if you have progressive disease or with stable disease."

Patient advocate: "I haven't seen too many patients just on gemcitabine. Typically, it's (given) in combination with something else – one of the platins…And the quality of life varies from patient to patient on all those combinations, and, frankly, the quality of life isn't particularly good. But I haven't heard anyone say I prefer to die rather than just have diarrhea. What I'm seeing in the stats is that there is an improvement in survival. It's slight, but it gives you an opportunity to be around for the next clinical breakthrough, for the next clinical trial."

Chemotherapy and AstraZeneca's Iressa (gefitinib)

FDA: "We wanted a public discussion of it pure and simple. I have a question about the use of Tarceva with chemotherapy. If you know something about lung cancer, this is a giant elephant in the room…A similar drug, Iressa, also did two first-trials, and those were negative. So, we had four first-line trials in lung cancer that were completely negative when these EGFR molecules were combined with chemotherapy. This caused some in the field to say, 'Maybe we should use these drugs in chemotherapy…Do you think this is the best route to use this drug as scheduled? Should it be given in sequential use?' What's going on? Why does it work in this situation but not in a lung cancer situation?"

Quality of life

Panel chair: "What bothers me is that the quality of life wasn't made better by something that prolongs survival. As a human being, if I have pancreatic cancer, I'm uncomfortable. Yet, no one has suggested that I'm going to have better quality of life. I'm just going to have diarrhea and rash. Help me to understand this?"

OSI speaker #1: "The quality of life was a secondary endpoint. These were exploratory analyses, and probably no definitive conclusions could be drawn. The suggestion is that things are a little bit better in the early part of the curve. And it looks like there's no harm from adding it."

OSI speaker #2: "When you talk about the possibility that additional life gain may be tainted by toxicity, that may actually not be the case."

Panel member (hematologist/oncologist): "This is a positive study in a tough disease…I don't think we should be the judge of what a patient should choose. All of the drugs are toxic; some kill patients. A lot of the side effects appear to be manageable, but there are other drugs being used daily that have life-threatening side effects. So, I think the quality of life is at least no worse."

Panel member (oncologist): "I agree. If the drug were available, it's up to the patient and the physician. I wasn't overwhelmed by the toxicity, although I was concerned about the incidence of stroke. We need more information, but it's up to the patient and, yes, there was a statistical increase in survival."

Panel member (hematologist/oncologist): "Do you have data on the number of days the patient spent in the hospital during the drug course related to toxicity or not?"

OSI: "There was an effort to collect duration of hospitalization during the study but, as you can imagine, patients who are hospitalized but don't have a discharge date…It's not something we've looked at."

Other issues and comments

Panel member (oncologist): "What are the company's plans for the drug if it is approved or not approved?"

OSI: "A large study in Europe is built on the findings of the study. In addition, there are a number of other trials and depending on those results, future studies may be considered."

Panel member (oncologist): "I didn't hear you say anything about the sequential use of these drugs, did I?"

OSI: "We're still discussing how to design those studies. Building sequential regimens is not a simple way to address this issue. We are looking at it in lung cancer, however."

FDA: "We talked about the classical chemotherapy studies, but the big question is can we identify a subset of patients which can respond to this therapy? We have to have a momentum, and I hope the committee would agree to make this a priority as far as other studies that need to be looked at. We're talking about a small benefit, regardless of how we want to cut it. But, truly, if we could identify the population that is most likely to respond…"

FDA Questions to the Panel

Question 1: *Is the Tarceva survival effect in Study PA3 statistically persuasive?* **Unanimously YES**

A biostatistician on the panel commented, "The data, even with the question in terms of how many events the study was originally designed for, are persuasive and hold up."

Question 2: *Is the size of the Tarceva survival effect in Study PA3 clinically important?* **YES by a vote of 11 to 2**

The panel's biostatistician said, "So many of the studies I'm involved in are four or five point scales and we talk about clinical significance from 3.2 to 3.4. This is survival. It's hard to say that survival is trivial, but survival is extremely impressive." The panel chair added, "I'm going to give it a yes, but it's a very qualified and heavy-hearted yes."

Question 3: *Is the Tarceva risk:benefit ratio in Study PA3 favorable?* **YES by a vote of 11 to 2**

Question 4: *The FDA guidance on when evidence of efficacy from a single trial without independent confirmation is adequate for marketing approval indicates that the study must be statistically persuasive (very low p-value) such that it would be unethical to repeat the trial. Is a confirmatory trial recommended prior to approval?* **NO by a vote of 12 to 1**

Comments prior to the vote included:

- *Hematologist/oncologist:* "It would be unethical to do another study."
- *Oncologist:* "I think the results are disappointing. We don't need another trial to confirm that. What we need is another, better drug – another, better trial."
- *Chair:* "I recognize the difficulty of these patients, the problems, yet I feel like I'm approving something where I'm still sitting here scratching my head wondering if it's valuable or just another thing to offer. When someone says your survival is improved, that's usually the end of the sentence. We usually don't add how many days. But there are ways in which we…get people to buy things. We're going to be selling the drug and not explaining to people what it is that they're buying out of this. That bugs me a lot with this drug."
- *Biostatistician:* "I'm concerned that, while it's statistically significant, it's not a huge value. There are questions about the p-value and safety...I'm going to vote to approve it."
- *FDA:* "I don't have to lecture you on historical databases…I don't even know if we have that – that would be a matched control situation…Why do you think we ask in other therapeutic areas to do two trials? Generally it's because there might be some interest we have to verify the results, to replicate the results. Are you uncertain about these results? The statistical validity?...The question is – is an additional trial needed before approval of a drug?"
- "We are beating ourselves about the toxicity of this particular compound, which may be manageable compared to other combinations which may have much greater toxicity. I would see that there are additional studies required to confirm the benefit of lesser toxicity."
- "I think this is the wrong way to look at this drug. I think we're making the Iressa mistake again. We need to learn which patients may benefit, etc. I think we're putting out an inferior regimen on the streets, and I think if you want to do a second trial, and if you look at patients looking at informed consent and see that you're looking at ten days, you're not going to get a lot of takers."
- "The last thing we want to see is another marginal study. But I think looking in the face of such a bad disease that we're looking on bad data. But I'd like to see a trial with a better design or better drugs. This drug may or may not be part of the next active regimen. This is really just the next step."
- "I don't believe we need another trial. I would be in favor of Phase IV testing after approval."
- *Chair:* "I'm still bothered by the fact that one study with such little difference between the two arms is putting this through and maybe we should think about that…I'm arguing the basic human principle of: Is one study what everything is based on? Is that it? Is that what science is all about? If we aren't the right people to make these judgments, who in the hell is? If you've ever watched someone dying of pancreatic cancer, even a few more days isn't it…Maybe we should be confirming that it has marginal benefit, or maybe it doesn't have any."
- "That gets into the ethics and utilization of patient resources. If you've shown a marginal benefit in a deadly disease, at the end of the day you'll find a marginal benefit but you won't have taken the field forward. That's subjecting patients to more disappointment. We need to move on. We all agree it's marginal."
- "Yes, we have approved regimens, but not with this minimal benefit…That's one thing that's troubling us. There was no improvement in quality of life. Did we know what the baseline was? If it was okay, that's fine. But if it was poor to begin with, and that's what you're prolonging, then what's the point? So, do we have that information?" An OSI official responded: "20% had performance status 2. The rest had performance 0-1."
- *FDA:* "If you take a look at the number of drugs that have a label on quality of life, they're woefully few. So not having quality of life data isn't surprising to me."
- "If the patient has a tumor mass, and it hasn't changed, we say the patient has stable disease. But is that a clinically positive endpoint? I don't think it is. If we don't know what it was when it started, and it hasn't changed, we don't know if it's good for the patient."

Question 4: *Is this sNDA approvable?*
YES by a vote of 10 to 3

♦