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by Lynne Peterson

Quick Pulse

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Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

What is the Outlook for AstraZeneca's Iressa?

AstraZeneca's Iressa (gefitinib) was originally approved by the FDA in May 2003 under Subpart H (accelerated approval) for the treatment of patients with non-small cell lung cancer (NSCLC) who had failed two or more courses of chemotherapy. Companies who get drugs approved under Subpart H are required to do additional studies after approval to verify the expected clinical benefit, but AstraZeneca's post-marketing study (Trial 709 or ISEL) failed to show any survival benefit. The FDA now has the option to remove Iressa from the market.

Under Subpart H, the FDA can approve a drug based on an effect on a surrogate endpoint – e.g., the sign of a disease or the results of a laboratory test – that is considered reasonably likely to predict clinical benefit (improved symptoms or survival). Iressa's approval was based on data that indicated it led to a statistically significant shrinkage in tumor burden in ~10% of patients, which was expected to increase overall survival.

The FDA convened a meeting of the FDA Oncologic Drugs Advisory Committee (ODAC) on March 4, 2005, in Gaithersburg MD to discuss the negative results from Trial 709 and what that means for future use of Iressa. The purpose of the panel was not to recommend whether or not Iressa should remain on the market, but to advise the FDA on whether patients were being adequately informed of the negative news.

Only the top-line data from Trial 709 had been released before the panel meeting. AstraZeneca officials suggested the more complete data paint a less negative picture of Iressa. One official said, "We are looking at a trial that barely missed statistical significance…It is not that there wasn't benefit, but it didn't meet statistical significance."

FDA officials said they do not plan to make a decision about the future of Iressa until the complete dataset is available in June 2005. Dr. Richard Pazdur, Director of Oncology Drug Products at the FDA told the panel, "The FDA will not make a definitive decision on Iressa until the trial data are received and reviewed. In the interim, AstraZeneca has suspended promotion of Iressa, but will make the drug available to patients who appear to be benefiting from it...We are not here to vote on the ultimate regulatory fate of Iressa."

New Iressa Data

AstraZeneca officials said complete data from Trial 709 and Trial 503 will be filed with the FDA when the full analysis is complete, which is expected to be in about three months. Data through October 2004 from Trial 709 (ISEL) were provided to the panel, and an AstraZeneca official said that additional data, through

February 2005, found the median survival unchanged (p=.09) in the overall population and unchanged in the adenocarcinoma subset (p=.09).

AstraZeneca's interpretation of this data is that there is evidence of at least some activity of Iressa. In the briefing documents to the panel, AstraZeneca wrote: "AstraZeneca intends to continue to make Iressa available as an option for patients who are deemed appropriate…It is clear that Iressa is an active agent. It produces durable tumor responses and, based on the heterogeneity seen in Trial 709, appears to improve survival in some patient subsets (Asian origin and never smokers)."

Iressa Trial 709 (ISEL) Results

Measurement	Iressa 250 mg	Placebo	p-value
Primary endpoint: Median overall survival	5.6 months	5.1 months	Nss
One-year survival	27%	22%	Nss
Adenocarcinoma patients			
Median survival	6.3 months	5.4 months	p=.07
One-year survival	31%	17%	---
Other results			
Objective response rate (ORR)	7.7%	1.2%	p<.0001
Median time to treatment failure (TTF)	3.0 months	2.6 months	p=.0005
Quality of life			
Symptoms (lung cancer subscore, range 0-28)	16.9	16.4	p=.02
Overall quality of life (range 0–144)	83.8	82.3	p=.07
Trial outcome index (range 0-84)	47.5	46.5	p=.11

Trial 709 Safety Data

Measurement	Iressa 250 mg	Placebo
Rash (all grades)	35%	9%
Rash (Grade 3-4)	1.2%	0.2%
Diarrhea (all grades)	27%	9%
Diarrhea (Grade 3-4)	3.0%	1.0%
Nausea	17%	16%
Interstitial lung disease-like events	1.1%	0.9%

Response Rate by Subset Analysis *(Data through October 2004)*

Subset	Iressa 250 mg
Adenocarcinoma vs. non-adenocarcinoma	11.4% vs. 4.0%
Never smoked vs. ever smoked	17.2% vs. 5.2%
Refractory vs. intolerant	7.8% vs. 7.2%
1 prior chemo vs. 2 prior chemo	7.4% vs. 8.0%
PS 0-1 vs. PS 2-3	8.3% vs. 6.6%
Female vs. male	14.0% vs. 4.9%
Age <65 vs. age ≥65	7.1% vs. 8.7%
Asian vs. non-Asian	12.0% vs. 6.5%
No prior docetaxel vs. prior docetaxel	10.3% vs. 6.7%
All patients	**7.7%**

Ongoing Iressa trials include:

- **Trial 721:** A randomized, open-label, international, non-inferiority trial of Iressa vs. docetaxel (Sanofi-Aventis's Taxotere). So far 700 of a planned 1,440 patients have been randomized. An interim analysis will be available in May 2005, with a final survival analysis expected in November 2006.
- **Trial 503:** This is a comparison of Iressa and docetaxel, designed to be supportive of Trial 721. A clinical trial report will be available in May 2005.
- **Trial 710:** A double-blind, placebo-controlled, parallel group, randomized Phase III study on symptom improvement of Iressa vs. placebo plus best supportive care. This trial was closed in September 2004, in agreement with the FDA.
- **SWOG-0023:** A Phase III maintenance study of Iressa vs. placebo in patients with inoperable, locally advanced, Stage III NSCLC. So far 259 of 672 planned patients have been enrolled. Results are expected in 2008.
- **BR19:** A prospective, randomized, double-blind, placebo-controlled, Phase III adjuvant therapy study of Iressa vs. placebo in completely resected Stage IB, II, and IIIA NSCLC. So far 457 of 1,242 planned patients are enrolled. Data are expected in 2008.

Disseminating the Negative News

Approximately 15,000 patients are currently taking Iressa in the U.S., AstraZeneca estimated. FDA and AstraZeneca both have made efforts to inform patients, doctors, and the general public about the negative news on Iressa. FDA officials said the Agency has notified doctors and the public by:

- Sending an email to ASCO members notifying them of the study results and alternative treatments.
- Putting a letter/statement on the FDA website.

AstraZeneca's efforts have included:

- A press release.
- A Dear Doctor letter posted on the company website and sent to ~141,000 physicians and other healthcare providers.
- Advertisements in major medical and oncology journals.
- Teleconference between the company and patient advocate groups.
- Direct communications to known Iressa patients.
- Separate mailing to clinical investigators and the National Cancer Institute.

- Presentation of Trial 709 data at American Association for Cancer Research (AACR) meeting in April 2005 (pending abstract acceptance).
- Tracking new and total Iressa prescriptions every two weeks.
- Presentation of Trial 709 data at the World Conference on Lung Cancer (WCLC) meeting July 3-6, 2005, in Barcelona Spain (pending abstract acceptance).

FDA officials and panel members were not sure these efforts were enough.

- Dr. Robert Temple, who is Director of the FDA's Office of Medical Policy, Center for Drug Research and Evaluation (CDER), and also the Acting Director of Drug Evaluation 1 (which is in charge of oncology, neurology and cardiac drugs), said the FDA has had time to review the AstraZeneca materials and agreed they are "okay," but he commented, "I'm slightly nervous about them."
- The panel chair said, "What their (AstraZeneca's) intent is, in their gut and heart, in all fairness, is not really what this committee can deal with."
- Panel member Ralph D'Agostino PhD, a statistician, said, "I'm bothered by the presentation…Are they putting a letter out and then showing this presentation, which has a different bent to it?…What is the presentation to the field? Is it this letter, or are they spinning it? What are MDs being told?"

IRESSA PRESCRIPTIONS

One of the key issues for the FDA is whether or not AstraZeneca is continuing to promote Iressa despite the findings in Trial 709. An AstraZeneca official claimed total and new prescriptions for Iressa have significantly decreased:

- Total prescriptions down 49%.
- New prescriptions (defined as refills as well as new patients) down 58%.
- The company's market research reportedly indicates that 78% of clinical oncologists are aware of the Dear Doctor letter content, and 86% are modifying their treatment practice.

However, AstraZeneca officials also suggested the prescription data indicate some patients are benefiting from Iressa. One said, "The bottom line that the trial didn't meet statistical significance has not changed…We have not been able to get a source to define new patients, so we have to take new script data as indicative of what is happening in the marketplace… Every time a new script is written, it is listed as a new prescription…It is our belief, based on the duration of therapy, that the majority of scripts are now being written for patients prescribed Iressa prior to the results of (Trial) 709, so we deem they are benefiting…We did some market research in early February (2005) and established that physicians are aware of the results and are no longer choosing Iressa as the EGFR inhibitor of choice."

NEW PATIENTS GOING ON IRESSA

The FDA wants to allow patients already on Iressa to continue to have access to the drug, but officials are concerned about new patients starting on Iressa, except perhaps those who are intolerant to Tarceva (Genentech, erlotinib). Dr. Pazdur and Dr. Temple both appeared disturbed by AstraZeneca's presentation, which they seemed to view as less negative on Iressa use in ***new*** patients than they expected. Among their comments were:

- *Dr. Pazdur:* "It is new patients that we feel uncomfortable with…We are very interested in how many new patients are going on Iressa…When one EGFR inhibitor (Tarceva) shows a survival benefit, why would anyone use another EGFR inhibitor (Iressa) that hasn't shown a survival benefit? The rational choice would be the one with a survival benefit."
- *Dr. Temple:* "We never thought someone on the drug should lose access…But the study failed. These are after-the-fact subset analyses in a study that did not win. That is different from a subset analysis in a study that did win. Where do you come out on new patients being started on Iressa now?…Is your position that a person with this disease really should not be started on Iressa?…Is that your view?"
- *Dr. Temple:* "One might say you should use the drug with very similar properties that has been shown to improve survival (Tarceva). Are you saying something to the contrary? I don't think it is clear…I thought it was, but from your presentation, I don't think it is (clear)…I thought you thought one should use the drug that won, but I no longer perceive that from this presentation."
- *Dr. Temple:* "The pattern (of response) may be the same …but it may be this drug (Iressa) does not work as well (as Tarceva)…I think they (AstraZeneca) are more ambiguous now…Given the choice of two drugs now – one of which has successful clinical results, and the other doesn't, most of the time – people would suggest you use the one with the favorable results…I thought that was the direction AstraZeneca was urging people to go...and I'm not clear on that now."
- *Dr. Temple:* "Maybe mutation status will be overwhelming and knock everyone's eyes out, but at the moment you have no prospective data on these people."

Another panel member was concerned that the FDA might bar new prescriptions for Iressa. She asked FDA officials, "You are not suggesting that doctors should not be allowed to write new prescriptions for Iressa, are you?" Dr. Temple responded, "We don't control what doctors write. For someone on the drug and responding, it is not an issue…I am more concerned

(that AstraZeneca appears) more ambiguous now. We've been pushing, if anything, the idea that there are subsets of patients who are more likely to respond than others. That has been apparent from the beginning…All those differences were much more credible when a trials wins overall or in pre-specified subsets."

AstraZeneca experts defended prescribing Iressa to new patients:

- Dr. Mark Kris of Memorial Sloan Kettering Cancer Center, "You can't look at one piece of data…And this (Trial 709) is only one piece of data…It is important to put this in the context of what is available, especially after the failure of initial therapy…I interpret the whole of the data as consistent. It is extraordinary that, when you look at the responses, how consistent they are…There are some patients, those with an EGFR mutation, which the literature today says have an 89% chance of response…So, as a clinician, my first point is to find those people with an extraordinary chance of response – never smoking and probably Asians."
- Dr. Howard Burris of Tennessee Oncology, a group of 36 practicing oncologists, said, "We issued guidelines (for EGFR inhibitor use)…that patients being treated with Iressa should be continued…For those patients called appropriate for an EGFR inhibitor, Tarceva would be the preferred agent. If patients are intolerant of one or the other, switch to the other in the class…There is a belief that there is a subset who will benefit (from Iressa)."

PUBLIC COMMENTS

Witnesses argued both sides of the issue, some, like Public Citizen, demanding an immediate end to new patients going on Iressa, and others – including both patients and doctors – pleading for it to stay available.

In favor of continued marketing

Laurie Fenton, president of the Lung Cancer Alliance, said, "Alimta (Lilly, pemetrexed) and Tarceva are important arrows in our treatment quiver, but Iressa must also be recognized as an important weapon in this battle. Iressa has shown striking benefits in a subset of the population. Patients and their doctors need all, not limited, choices."

Rosalind Brannigan, a patient on Iressa, said, "I am responding to Iressa…When I asked my oncologist if I should switch to Tarceva, he said, 'Absolutely not.'"

Selma Schimmel, CEO of Vital Options International, a non-profit cancer communications and advocacy organization, said, "Patients deserve choice…and adequate safeguards that protect them from erroneous choices…How am I to respond to the man who tells me how he has read that Iressa has no survival advantage and that it is not being used in Europe, yet he will begin receiving it here? I have no reasonable and satisfactory answer…While Iressa should remain available to a defined population who are likely to benefit – or to patients already on it – a labeling change is necessary and now, not later, to avoid patient confusion and misperception."

Against continued marketing

Public Citizen's Dr. I. Peter Lurie told the panel that earlier in the day of the panel meeting his organization had filed a Citizen's Petition, asking the FDA to remove Iressa from the market. He said, "If this drug is not taken off the market on these grounds, it will make an absolute mockery (of the accelerated approval program)…We are asking that patients on the drug get it through IND status…In Europe, the marketing application has been withdrawn, and the Japanese Ministry is giving serious consideration to withdrawal…Even prior to approval there were studies that an FDA medical official described as 'unambiguously negative.'"

ADVISORY COMMITTEE DISCUSSION

The FDA's discussion points for the advisory committee dealt with whether or not AstraZeneca's effort to disseminate information on Iressa have been satisfactory, what lessons have been learned from the Iressa development process that might be applied to future drug development, and possible future Iressa studies. Several panel members commented that patients have been very upset over the idea of Iressa being withdrawn from the market. The patient representative on the panel, Sheila Ross, said, "We had calls from patients in a panic when they heard the news. They were discussing stockpiling the drug or buying it in Japan…(The FDA) and AstraZeneca helped to draft more plain English information to post on the (Lung Cancer Alliance) website…The process was more than adequate. Thanks to the FDA and AstraZeneca for all they did."

Panel member comments included:

- *Dr. Maha Hussain,* an oncologist with the University of Michigan: "I am concerned. If one of two drugs stands the test, and the other doesn't, to me, from a clinical standpoint, it doesn't make sense to use a drug that doesn't meet the test in a new patient…I think the package insert and the label have to change, reflecting a definitive trial that didn't work, though there are some subsets that seem to benefit. Considering industry uses the media to advertise these drugs, maybe the media should be used to contact patients to be sure patients heard about it."
- *Dr. Joanne Mortimer,* a breast cancer specialist at the University of California, San Diego: "It is a very thorny issue…I disagree with the classification that this is a negative trial. This is a negative trial, but there are extenuating circumstances."

- *Dr. Otis Brawley,* an oncologist at Emory University, wondered if Iressa should have been approved in the first place, "The development of this drug has been mishandled by AstraZeneca and by this committee…I voted for approval, so I take some of the blame…The fact remains that this drug has been available for several years, and we still don't know how it should be used…I was quoted in the press when I voted for this drug, saying this is lung cancer's tamoxifen in search of its estrogen receptor. The failure to totally find and categorize that estrogen receptor is the reason we are in the pickle we are in today…In defense of those who mishandled this: This was one of the first targeted therapies to come along, so we need to learn from our mistakes and go forward."
- *Dr. Alexandra Levine,* an oncologist at the University of Southern California: "I don't believe that there is no efficacy. I think the company has data to say there may be something there…We are hearing that Tarceva is a better drug…Is it fair to compare one drug to another when those issues are not presented to us? I am disquieted about that…After the accelerated approval, the company was asked to do three studies…If we are basing everything on one study, why were they asked to do two or three? Aren't we obligated to look at all of them in making our decision?" Dr. Temple responded, "The short answer is that this (Trial 709) was a very large study. You would expect it to detect overall survival if there was one, and the fact that it didn't tells you something."

There was no vote by the panel, but when members were polled, all but one agreed that the public has been adequately informed about the results of Trial 709. The dissenting panel member said, "I think physicians are well-informed, but I'm concerned when I hear patient advocates saying they are afraid their drug will be taken away."

THE OUTLOOK

There are several scenarios that could play out including:

1. **Labeling change.** The FDA's Dr. Temple suggested that a labeling change may be likely for Iressa, perhaps suggesting that another drug (Tarceva) be used before Iressa. He added, "We don't do that lightly. It doesn't force doctors, but it encourages them." Dr. Pazdur said the FDA will be discussing internally a review of the package insert for Iressa.
2. **Second-line therapy.** The FDA also could decide to designate Iressa as second-line therapy. The FDA also does not take that step lightly, but there are examples where that has been done.
3. **Withdrawal.** Finally and more drastically, the FDA could order Iressa withdrawn from the market, with the likely exception of supplying patients already on the drug.

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