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SUMMARY

AstraZeneca's Iressa has been linked to 125 cases of interstitial pneumonia and 39 deaths in Japan, leading to a label change but not market withdrawal. AstraZeneca has downplayed the significance of these reports, and U.S. oncologists do not appear to be not worried about this, with most suggesting it is something unique to Japan. However, FDA officials are likely to be more concerned, and they may require another trial before approving Iressa.

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THE SAFETY OF ASTRAZENECA'S IRESSA

The Oncologic Drugs Advisory Committee (ODAC) voted in September 2002 to recommend approval of AstraZeneca's Iressa (ZD-1839). However, since then at least 125 cases of interstitial pneumonia (IP) and 39 deaths in Japan have been linked to Iressa. On July 16, 2002, Japan approve Iressa, making it the first country to approve an epidermal growth factor receptor (EGFR) inhibitor. The Japanese Ministry of Health, Labor and Welfare ordered AstraZeneca to issue stronger warnings that the drug may have serious side effects, but it hasn't ordered the drug withdrawn from the market.

U.S. experts claim the background incidence of interstitial pneumonia is 2-4 of every 1,000 patients, with fatalities in 1 in 1,000 patients. This translates into an *expected* pneumonia rate of 0.2%-0.4% and *expected* death rate of 0.1%.

Annually, there are a reported 50,000 new lung cancer patients in Japan, with 43,000 dying. An AstraZeneca official told Dow Jones Newswires, "This side-effect was known to AstraZeneca throughout the drug's clinical development and was included on the original label for Iressa in Japan."

The statistics available on the Japanese cases indicate the incidence may be increasing and is at or above the upper limit of expectations:

- In mid-October 2002, the first 26 pneumonias and 13 deaths were reported with Iressa in Japan. At that time, about 7,000 patients had been treated there. That would be an *incidence* of about 0.37% pneumonias and 0.19% death. The *expectation* would be for 14-28 cases of pneumonia and seven deaths.
- By the end of October 2002, the toll had risen to 125 pneumonias and 39 deaths, out of an estimated 15,000 Japanese patients. This would be an *incidence* of about 0.83% pneumonias and 0.26% deaths. The expectation would be for 30-60 cases and 105 deaths.

What do these adverse events mean for FDA approval of Iressa?

THE JAPANESE VIEW

An official with the National Cancer Center said that as of October 30, 2002 (with three months on the market), about 15,000 patients in Japan had received Iressa. Among the other points he made are:

1. Japanese patients receive the same dose for which AstraZeneca is seeking FDA approval – 250 mg.

2. The incidence of interstitial pneumonia and deaths is becoming a concern in Japan and is likely to affect use of Iressa in Japan in the future.

3. The Japanese Ministry of Health is unlikely to further change the label of the drug or to withdraw it.

4. Asked if there is anything in the way that Iressa is given in Japan that might be adding to these cases (e.g., in combination with full-body radiation that might cause the rates to be higher than seen in the clinical trials), he said, "As with Herceptin (Genentech, trastuzumab), Iressa has been in patients with extremely poor PS, low SO2, etc. There were also a lot of drug-related deaths after the approval of Herceptin."

5. The details of the deaths are still being investigated.

This Japanese oncologist said that U.S. oncologists can learn from the Japanese experience. He advised that U.S. doctors only give Iressa to non-small cell lung cancer patients with good general health, including PS, SO2, etc., and warned that it should be prescribed by medical oncologists.

THE U.S. ONCOLOGY VIEW

U.S. oncologists do not appear to have lost their enthusiasm for Iressa. One expert said, "We've seen this (pneumonitis) with other drugs in Japan. With CPT-11 (Pfizer's Camptosar, irinotecan), there was a similar problem. There was interstitial pneumonitis reported with CPT-11 in Japan, but there have never been reports in the U.S. It turned out to be radiation pneumonitis or complications of therapy (in Japan). So, I don't believe these reports about Iressa…In Japan, they use a lot of radiation, and they call a lot of things interstitial pneumonia (IP) – but it is probably residual radiation pneumonitis, which occurs three to six months after radiation therapy…I haven't reviewed the (Japanese Iressa) cases, but I would recommend looking back to the Phase I reports for CPT-11. The only patients who got pneumonitis with CPT-11 in Japan were lung cancer patients, and that taints my assessment of this. I think the issue probably will die."

This appears to be a common U.S. view. Another expert said, "I don't think this (the pneumonia and deaths) is a concern. We've known Iressa could cause this. I don't think this is a big problem. I am interested in whether it was just pulmonary inflammation, but it doesn't give me pause. These are very sick patients and small numbers. It is a rare side effect, but we are seeing it because we are treating more patients."

INSIGHTS FROM THE FDA

A senior FDA official discussed how the agency views adverse event reports in foreign countries, and his comments appear to suggest that the FDA:

- Believes the Iressa efficacy rate (even at 10%) is sufficient for approval. Toxicity is the only remaining issue.
- May require another trial before approval, but a second advisory panel is unlikely.
- Considers the incidence rate of the side effects and deaths critical to its analysis of the problem.
- Believes that if something occurs in another country (whether Europe or Japan), it probably will occur eventually in the U.S.
- Assumes that adverse event rates are actually much higher than what is reported.
- Was impressed with patient testimonials about Iressa.

Following are this FDA official's comments in Question and Answer format.

QUESTION: When the FDA is reviewing an NDA, and the drug is already approved outside the US, how does the agency deal with adverse event reports from those other countries?

ANSWSER: "The only difference is if the side effect arises from a marketing situation -- arises from a larger population than in the case of a single trial. Everything about adverse events reported with a marketed drug make it more complicated; the description may or may not be very good, and the rate is likely to be lower than one sees in trials. If trials have 300 patients, and you don't see the side effect in two trials, but you see a respectable, believable rate in a similar-sized trial or with a marketed drug in another country, you need to wonder why that happened."

QUESTION: How do you view foreign adverse event data in this kind of situation, and what access does the FDA have to that data?

ANSWSER: "We take foreign data -- both for efficacy and toxicity -- perfectly seriously. Companies are obliged to tell us about adverse events in trials wherever they occur, and they also are obliged to tell us if a marketed drug in another country has a problem. Usually, it is the sponsor's obligation to get the data to us."

"Most of the adverse event data from a marketed drug comes via the company. Some comes directly from MedWatch, but that is still a minority (of reports). With foreign reports, the government has to tell someone or no one knows. I'm sure there are cases where we talk directly to a country, and sometimes companies look further (into the matter), and they are obliged to tell us about events in a timely way."

"You try to understand why that happens. Is it just because more of it (the drug) was used? Did it occur only in the foreign country or not? People look to see if the molecules are the same. We try to understand why it happened. Sometimes the dose is different, or it could have been taken with other drugs. If it is an important adverse event, what is the rate? That might affect our decision."

QUESTIONS: So, you would stop your review and take time to study the adverse events that occurred in the other country?

ANSWER: "Maybe. It depends on how serious and how overwhelming the data supporting the drug are. If we were still weighing the benefits and risks of something, we might have a new contribution to the risk. If we were looking at something, and there was no U.S. marketing experience, and we only knew of a high rate of something bad in another country, we would have to come to grips with it. We wouldn't have our own U.S. marketing experience to reassure us. I can think of two cardiovascular drugs from a couple decades ago where we were on the road to approval, and we discovered fairly late in the game that the marketing experience in Europe led to liver injury and other injuries, and both drugs were turned down because of what we learned."

QUESTION: Do you only get your information from the company, or do you contact the other country directly?

ANSWER: "We can call the Europeans."

QUESTION: Would you take an adverse situation like this to a second Advisory Panel?

ANSWER: "If the information merited that treatment, we could. If it is late in the game when we develop new adverse event information, and we want another view, we could. I'm positive we've done that in the past, but I can't think of an example. There is no impediment to doing that. Going back to the panel would mean we are no longer sure the drug merits approval because of new information. It is not different from getting the results from another study late in the course of something."

QUESTION: If you went back to the Advisory Panel a second time, would you bring experts from the other country to present?

ANSWER: "Theoretically, yes, and I believe that probably has happened in the past. That is more common where a drug has been on the market, and then we discover something. It is not too likely that we would discover something that hot in the course of a review. The review period is only six to nine months, but we could do any of those things. There is no rule against it…The point I'm trying to make is that while the timing is unwelcome to the company, it doesn't really alter what you do with the data. You do the best you can with the data. If there are spontaneous reports, and you don't have much information that is as useful as well-documented reports, well --- (then, that's what you have)."

QUESTION: Could you discuss the CPT-11 case as it relates to pneumonia seen in Japan?

"I don't know the irinotecan (CPT-11) situation that well. I don't remember the case. I don't know if that is a good example or not…The Japanese are smaller, but for the most part, people respond more or less the same across the world, though they might use different doses. But you try to think of the number of things that really had differential toxicity from one place to another, and it is a small list, which isn't surprising."

QUESTION: In oncology, do you accept more toxicity than in cardiorenal drugs?

"In cardiorenal, you mostly treat people without much seriously wrong, so a 0.5% intracranial hemorrhage rate would be an impossible side effect for an anti-hypertensive or an analgesic. You get some extra strokes with aspirin, but in the right population, you get a larger benefit. But you have to weigh the benefit and the risk."

"In oncology, in the treatment of an active tumor, a metastatic tumor, that is a fatal illness, and the long history is to accept a considerable toxicity, even potentially lethal toxicity in the hope of helping someone. People are working on less toxic groups of drugs that are less toxic to cells and inhibit something more specific. And you wouldn't accept a similar degree of toxicity in an adjuvant setting; a lot of those people don't even have cancer, so major toxicity is not acceptable there. In prophylaxis, you really don't want much toxicity at all because these are healthy people with no tumors, so you weigh the benefits against the risks."

"In oncology, we said we would approve drugs for refractory disease, where there are no other options, on the basis that they show tumor shrinkage in a reasonable fraction of patients.

That's not news here. We've approved about 11 drugs that way. We said we were going to do it, that is thought to be a good thing, and we have a guidance document on it. So, that is not news."

QUESTION: You haven't had to recall any of those drugs?

ANSWER: "No, we haven't had any recalls. Not all of the companies have done the (post-approval) studies they promised – yet. We are still hopeful on some of them. But some have done them. Irinotecan did its study, and that was an accelerated approval, which is something you do for a fast-track drug."

QUESTION: Is there pressure from doctors and patients to approve oncology drugs the way there is for HIV/AIDS drugs? Does the agency feel pressured?

ANSWER: "Fast-track approvals in oncology are more or less the same situation as in HIV. Virtually all the fast-track drugs have been AIDS or cancer drugs. In AIDS we want a six month reduction in viral load by a reasonable fraction, and in cancer, a response or possibly TTP – which is being discussed as an endpoint. Oxaliplatin (Sanofi's Eloxatin) has only a 10% response rate – no better than that – in colorectal cancer, where initial therapies have a higher response rate. (Sanofi) showed that oxaliplatin with 5FU, in a nicely controlled study, had reasonable evidence of effect on TTP, that was a surrogate endpoint. It has not yet shown that anyone feels better or lives longer. A surrogate endpoint is anything other than improved symptoms or survival, and that includes TTP, which is a surrogate. Time to symptomatic progression would be a clinical endpoint."

"The percent of cases, the incidence, and how many are fatal or nearly fatal matter. One in 1,000 matters. You have to weigh these things…The nature of the event and how it compares to the benefit it provides is important. It could make a difference whether you have a response rate, survival data, etc."

"There is no short answer here. The question is whether it still looks like a benefit to approve it."

"We have not felt more pressured lately to approve drugs, no, but remember there was tremendous enthusiasm for early approval of cancer drugs when this program first was approved…I don't see any increase in that. The oncology community obviously was very disappointed by the initial rejection of the ImClone drug (Erbitux, C-225), but they mostly blamed the company for not doing it very well."

"Look at the drugs we've approved recently. Oxaliplatin only has a 10% response rate, but it had a nice study that showed TTP that was not controversial, though there were complaints that we could have approved it sooner."

QUESTION: There were a lot of patients at the Iressa advisory panel in September 2002 and more who wrote in testimonials. How does that impact the FDA's decision process?

ANSWER: "Those individuals clearly felt their lives had been saved, so they came. I don't know whether that was unusual. It is not so common. Something like 12,000 patients were treated, and some felt the drug had helped them a lot. That doesn't strike me as a sign of increased militancy. Does it tell me companies will bring them to all advisory panels? I'm not so sure it is that easy to do that. These patients claim a very long and satisfactory response that is not common to have in most tumors."