

# Public Citizen

Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group  
Joan Claybrook, President

March 4, 2005

Lester Crawford, DVM, Acting Commissioner  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville MD, 20857

Dear Dr. Crawford:

Public Citizen, representing 150,000 consumers nationwide, petitions the Food and Drug Administration (FDA) to remove the drug Iressa (gefitinib; AstraZeneca) from the market immediately.<sup>1</sup> Iressa was approved in May 2003 under the agency's accelerated approval program that allows for the expedited review and approval on the basis of a clinical or surrogate endpoint that is "reasonably likely . . . to predict clinical benefit,"<sup>2</sup> if the drug is for a serious or life-threatening condition. The law also states that "approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit." FDA did require such a study and that study (Iressa Survival Evaluation in Lung Cancer Study or ISEL) has now been completed; it failed to show that Iressa has any efficacy in improving survival in patients with non-small cell lung cancer.<sup>3</sup> As a result, Iressa's application for approval in Europe has been withdrawn.

The accelerated approval law also states that the FDA may withdraw approval of a fast track product "if a postmarketing clinical study fails to verify clinical benefit."<sup>4</sup> We, therefore, call on you to withdraw Iressa from the market. Any unapproved uses of Iressa can be explored using the experimental Investigational New Drug (IND) mechanism. (The IND is the procedure used to study drugs before approval to ensure that their safety and efficacy meets certain standards before marketing.)

<sup>1</sup> The authority for this petition can be found in the Federal Food, Drug and Cosmetic Act 21 U.S.C. Section 355(e)(3) and 21 C.F.R. 10.30

<sup>2</sup> 21 Code of Federal Regulations. Part 314.510.

<sup>3</sup> <http://www.fda.gov/bbs/topics/news/2004/new01145.html>

<sup>4</sup> 21 Code of Federal Regulations. Part 314.530.

2005P-0094



CP1

On May 5, 2003, Iressa was granted accelerated approval for the treatment of non-small cell lung cancer (NSCLC) in patients who had failed at least two other treatment regimens (third-line therapy). The surrogate endpoint used for approval was tumor shrinkage of at least 50%; this occurred in approximately 10% of treated patients in an uncontrolled (no placebo group) phase II study.

In our May 1, 2003 letter to the FDA,<sup>5</sup> we urged that Iressa not be approved because 1) in the pivotal trial, only 10% of third-line therapy patients responded to treatment (as measured by tumor shrinkage), 2) two large Phase III trials with Iressa as first-line therapy (no treatment prior to Iressa) had been completed and were clearly negative with respect to survival, and 3) there were already 473 reports of acute interstitial pneumonia in NSCLC patients in Japan, of whom 173 had died. These deaths were thought to be directly linked to Iressa treatment.

### APPROVAL HISTORY

The pivotal trial on which the accelerated approval of Iressa was based was a Phase II study of Iressa as third-line therapy. Two doses of Iressa (250 mg/day and 500 mg/day) were tested, but there was no control group against which to measure safety or effectiveness.

In addition to the Phase II study, two Phase III trials had also been completed before approval; these were first-line therapy trials. In principle, this group should have been even more responsive than patients given third-line therapy. According to the FDA Medical Officer, "A widely accepted medical oncology principle is that for each chemotherapy regimen failed, the probability of responding to a subsequent regimen decreases."<sup>6</sup> Nevertheless, there were "no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival."<sup>7</sup> In spite of this, FDA granted an accelerated approval to Iressa.

### POST-APPROVAL STUDY

On December 17, 2004, the FDA announced that another Phase III trial the FDA had required as a condition of approval was complete and had failed to show a survival advantage: patients taking Iressa did not live any longer than those taking a placebo pill. This Phase III study (ISEL) enrolled 1,692 patients with advanced NSCLC who had failed either one or two prior chemotherapy regimens (i.e., very similar to the only group for whom Iressa was approved). Patients were split into two groups: 250 mg Iressa plus best supportive care or placebo and best supportive care.

---

<sup>5</sup> <http://www.citizen.org/publications/release.cfm?ID=7242>

<sup>6</sup> FDA Medical Officer briefing document.

<http://www.fda.gov/ohrms/dockets/ac/02/briefing/3894b1.htm>

<sup>7</sup> Iressa drug label

According to the briefing documents posted in advance of the Oncologic Drugs Advisory Committee Meeting of March 4, 2005, the one-year survival with Iressa in ISEL was 27% compared to 22% for the placebo group ( $p=0.11$ , log rank test).<sup>8</sup> The company has done a number of additional analyses, some post-hoc. For example, the company presents a Cox regression that claims statistical significance; its purpose was to adjust for differences between the two trial groups at baseline, even though the company acknowledges that because the trial was randomized, such differences were minimal. A number of subanalyses were also done (the total number is not disclosed), among which Asian ethnicity, adenocarcinoma histology (Cox regression only), and non-smoking status predict survival. Such subanalyses should not obscure the fact that overall no benefit of Iressa upon survival could be demonstrated in the analysis done as planned in the protocol or that there is currently no way to know who might respond.

The FDA, instead of removing the drug from the market as the law authorizes the agency to do when no survival benefit is shown by post-approval studies, told patients to "consult with their physicians as soon as possible" and consider switching to either of two alternative therapies (Taxotere [docetaxel] or Tarceva [erlotinib]) that had demonstrated improved survival.<sup>9</sup>

On the same day that FDA announced the results of ISEL (December 17, 2004), AstraZeneca issued a "Dear Doctor Letter" to physicians in the U.S. reporting Iressa's lack of improved survival. The company stated: "AstraZeneca urges you to consider other treatment options in the recurrent non-small cell lung cancer patient population."<sup>10</sup> Keeping a drug on the market while effectively telling people to avoid taking it is not an adequate public health response.

There has been international fallout from the failed ISEL study:

- 1) On January 4, 2005, AstraZeneca withdrew its marketing application for Iressa in Europe based on the drug's failure to prolong the lives of patients with NSCLC.<sup>11</sup>
- 2) On January 20, 2005, a panel of Japanese scientists submitted the results of an emergency investigation into Japanese adverse reaction reports to the Japanese Ministry of Health and Welfare. These post-marketing data linked Iressa to 1,473 adverse event reports and 588 deaths in Japan alone, raising the possibility, according to an official spokesman for the ministry, that Iressa could be withdrawn.<sup>12</sup>

---

<sup>8</sup> AstraZeneca. Oncologic Drugs Advisory Committee (ODAC) Meeting Briefing Document. March 4, 2005. Available at: [http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4095B2\\_01\\_01-AstraZeneca-Iressa.pdf](http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4095B2_01_01-AstraZeneca-Iressa.pdf).

<sup>9</sup> <http://www.fda.gov/bbs/topics/news/2004/new01145.html>

<sup>10</sup> <http://www.iressa-us.com/dr.pdf>

<sup>11</sup> <http://www.astrazeneca.com/pressrelease/4442.aspx>

<sup>12</sup> Lewis L and Irving R. AZ cancer drug could be banned in Japan. London Times, January 21, 2005.

## HEALTH RESEARCH GROUP ANALYSIS

An epidemic of interstitial lung disease has now begun in the U.S., mimicking that in Japan. In our own analysis of the FDA Adverse Event Reactions database, we found 144 reports of interstitial lung disease, including 87 deaths for which Iressa was considered the primary suspect. These data cover only the first 17 months of post-marketing use, from approval in May 2003 through September 2004. These are certainly underestimates since, ordinarily, at most, 10% of adverse events are reported to FDA, and we used only one search term (interstitial lung disease) when many related (but less specific) terms could also have been used.

## MECHANISM OF ACTION

Iressa is thought to work by binding to the epidermal growth factor receptor (EGFR), a protein that is present on the surface of most cells and helps regulate cell growth. Iressa, by binding to and blocking EGFR action, would presumably inhibit growth.

There is a growing interest in identifying the 10% of patients who benefit from Iressa in terms of tumor size. Recent experiments have provided evidence that some patients have a change (mutation) in their DNA such that Iressa binds more tightly to EGFR than in patients without mutations.<sup>13,14,15</sup> However, these were post-hoc results from a small subset of patients; patients have never been tested prospectively and the positive predictive of a test for mutations has not been calculated.

The identification of the responder group is much more complicated than just looking for mutations, however, since some patients who respond lack these mutations. Even patients who do respond do so for only a limited time before relapsing. Research is therefore ongoing as to the identity of mechanisms for relapse, including the search for additional mutations.<sup>16,17</sup> According to Bruce Johnson (a researcher in the field), "there are at least 20 different mutations in the EGF receptors in human lung cancers, and we don't know if the same drug

---

<sup>13</sup> Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *New England Journal of Medicine* 2004;350:2129-39.

<sup>14</sup> Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497-1500.

<sup>15</sup> Pao W, Wang TY, Riely GJ, et al. KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. *2005 PLoS Med* 2(1):e17.

<sup>16</sup> Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *2005; PLoS Med* 2(3):e73.

<sup>17</sup> Kobayashi S, Boggon TJ, Dayaram T. et al. EFGR mutation and resistance of non-small-cell lung cancer to gefitinib. *New England Journal of Medicine* 2005;352:786-92.

works as well for every mutation."<sup>18</sup> It is noteworthy that in Iressa Phase II trials, EGFR expression per se did not predict response.<sup>19</sup> Clearly, much research needs to be done before anyone can know who might benefit.

The manufacturer agrees with the complexity of the DNA issue, saying, "new mutations are being discovered on an ongoing basis" and "the clinical significance of different mutations needs to be demonstrated."<sup>20</sup> AstraZeneca has also acknowledged that, "mutations alone do not provide an explanation" and that "other factors must have a role in determining sensitivity to gefitinib." What those factors might be is a crucial unanswered question

AstraZeneca added that the current method for detecting DNA mutations is "time-consuming, complicated, and costly," and that "While more user-friendly technologies are likely to emerge, validation of these techniques will be required."<sup>21</sup> Although there are tests in development, FDA can not say when they might be available for research outside the research setting.<sup>22</sup>

The FDA pharmacology reviewer pointed out additional dangers in Iressa's use: "Despite claims to the contrary, in both the NDA [New Drug Application] and the literature, the data does not support the concept that ZD1839 [Iressa] binds specifically at the EGF Receptor" <sup>23</sup> He noted that plasma concentrations of Iressa are high enough in humans to inhibit six or more other growth factor receptors, putting patients at risk for additional non-specific adverse effects. Just as alarming was his observation that, "in all tested animal species, the difference between a chronic dose that caused relatively little toxicity and one that was lethal was less than twofold . . . consistent with clinical results [i.e., sharply increased toxicity in patients with a small increase in dose]."<sup>24</sup> He added that giving such a toxic drug safely is extremely difficult as there was "insufficient evidence to accurately characterize such a [dose-response] curve."

---

<sup>18</sup> Twombly R. Failing survival advantage in crucial trial, future of Iressa is in jeopardy. *Journal of the National Cancer Institute* 2005;97:249-50.

<sup>19</sup> AstraZeneca. Oncologic Drugs Advisory Committee (ODAC) Meeting Briefing Document. March 4, 2005. Available at: [http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4095B2\\_01\\_01-AstraZeneca-Iressa.pdf](http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4095B2_01_01-AstraZeneca-Iressa.pdf).

<sup>20</sup> <http://www.iressa.com/iressaHCP/index.asp?did=9898&aid=12836&l1=6&ch=>

<sup>21</sup> <http://www.iressa.com/iressaHCP/index.asp?did=9898&aid=12836&l1=6&ch=>

<sup>22</sup> Vastag B. Research unveils the 'who' and 'why' of gefitinib. *Journal of the National Cancer Institute* 2004;96:1352-1354.

<sup>23</sup> Pharmacology Review. [http://www.fda.gov/cder/foi/nda/2003/21-399\\_IRESSA\\_Pharmr\\_P1.pdf](http://www.fda.gov/cder/foi/nda/2003/21-399_IRESSA_Pharmr_P1.pdf).

<sup>24</sup> Pharmacology Review. [http://www.fda.gov/cder/for/nda/2003/21-399\\_IRESSA\\_Pharmr\\_P2.pdf](http://www.fda.gov/cder/for/nda/2003/21-399_IRESSA_Pharmr_P2.pdf), p.66.

## CONCLUSIONS

With its clinical efficacy in prolonging life in first-, second-, or third-line therapy NSCLC patients now disproved, Iressa should again become an experimental drug. Iressa combines several negatives: lack of specificity in binding to different EGFRs, a small step between a safe and toxic dose, and an inability to determine which patients will benefit. Its use puts all patients at risk for a serious and potentially fatal lung disease that is occurring with a relatively high incidence. Moreover, Iressa is no longer the only oral drug for NSCLC. In November 2004, Tarceva, another oral EGFR inhibitor that actually has positive survival data, became available for second-line therapy.<sup>25</sup> Leaving Iressa on the market increases the likelihood that patients will be diverted from an effective therapy (Tarceva) to an ineffective therapy, endangering their lives.

Changing the label to include genetic testing is not an alternative until the science advances to the point that such testing can reliably distinguish a group that benefits from Iressa. Until it becomes clear what that group is, NSCLC patients should not be put at risk for another potentially fatal disease and diverted from effective therapy. Iressa should return to IND status to encourage investigations to take place that might identify sub-populations in which the drug is actually effective in improving survival. Patients currently taking the drug could continue to receive the drug under AstraZeneca's compassionate use program.

While the European marketing application was withdrawn immediately upon the receipt of the ISEL results, the company has managed to drag the process out in the more lucrative U.S. market. While new Iressa prescriptions per week are down from a peak of 1114 in August 2004 to 331 in mid-February, this is still a large number of patients for a drug with no proven benefit but clear risks. Instead of acting to protect patients by removing the drug from the market, the FDA instead scheduled an Advisory Committee meeting and has now apparently agreed to reach no decision at that meeting. AstraZeneca continues to demand more time for further analysis of the ISEL results and additional data. Haste seems not to be a consideration: the EGFR outcomes analysis will be complete on March 21, 2005, conveniently less than three weeks after the Advisory Committee meeting. It is no small irony that a drug that received its approval under an accelerated approval mechanism should now be subject to such delaying tactics.

---

<sup>25</sup>As of February 28, 2005, the FDA had not made its reviews of Tarceva available for analysis.

**ENVIRONMENTAL IMPACT STATEMENT**

Nothing requested in this petition will have an impact on the environment.

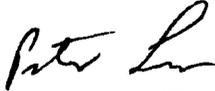
**CERTIFICATION**

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners that are unfavorable to the petition.

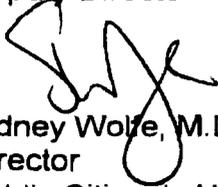
Yours sincerely,



Elizabeth Barbehenn, Ph.D.  
Research Analyst



Peter Lurie, M.D., M.P.H.  
Deputy Director



Sidney Wolfe, M.D.  
Director  
Public Citizen's Health Research Group