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**COMMENTS**

**of the**

**WASHINGTON LEGAL FOUNDATION,  
ABIGAIL ALLIANCE FOR BETTER ACCESS  
TO DEVELOPMENTAL DRUGS, AND  
LORENZEN CANCER FOUNDATION**

**to the**

**FOOD AND DRUG ADMINISTRATION**

**Concerning**

**PUBLIC CITIZEN, INC. PETITION  
FOR WITHDRAWAL OF IRESSA (GEFITINIB)  
*(Docket No. 2005P-0094)***

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April 20, 2005

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April 20, 2005

Dr. Lester Crawford  
Acting Commissioner  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

**Re: Public Citizen, Inc. Petition for Withdrawal of Iressa (Gefitinib)  
(Docket No. 2005P-0094)**

Dear Dr. Crawford:

The Washington Legal Foundation (WLF), the Abigail Alliance for Better Access to Developmental Drugs, and the Lorenzen Cancer Foundation are submitting these comments to voice our opposition to the Public Citizen, Inc. petition for the immediate withdrawal of Iressa (gefitinib).

As detailed below, we believe granting this petition would be harmful to many terminally ill patients for whom Iressa has been approved as third-line therapy for refractory disease, and who have benefited from this medicine. Additionally, we are concerned that such an action by FDA would set an unfortunate and life-threatening precedent with regard to other targeted therapies, which may also show ambiguous results when assessed vis-à-vis an entire patient population but are nonetheless of great value to some patients.

In considering Public Citizen's petition, we urge that FDA bear two points in mind. First, Public Citizen does not even claim to represent cancer patients, oncologists, or any other group with direct knowledge of and involvement in medical research or the terminally ill patient's

struggle for life. Second, more people die from lung cancer than from any other type of cancer. According to the American Cancer Society, an estimated 173,770 patients were diagnosed with lung cancer in 2004, and an estimated 160,440 patients died from it that year. Hence, even though Iressa provides a documented benefit only to a subset of patients, the large universe of non-small cell lung cancer patients means that the withdrawal of such a therapy may deprive tens of thousands of patients of the treatment that is best for them.

## **I. Background**

Iressa (gefitinib) was approved in May 2003 under the agency's accelerated approval program. It has been approved for the treatment of patients with locally advanced or metastatic non-small cell lung carcinoma after failure of platinum-based and docetaxel chemotherapies. Iressa is a targeted therapy that inhibits the epidermal growth factor receptor tyrosine kinase (EGFR-TK) that is expressed on the cell surface of many cancer cells.

Commenter WLF is a nonprofit public interest law and policy center based in Washington, D.C., with supporters nationwide. Since its founding in 1977, WLF has engaged in litigation and advocacy to defend and promote individual rights and a limited and accountable government, including in the area of patients' rights.

Commenter Abigail Alliance for Better Access to Developmental Drugs is a nonprofit organization based in Arlington, Virginia, dedicated to helping terminally ill patients obtain access to the medicines they need. Abigail Alliance was founded in 2001 by Frank Burroughs, who is now its president. The group is named for Burroughs's daughter, Abigail, an honors

student at the University of Virginia. Abigail died of cancer on June 9, 2001, after she was stymied in her efforts to obtain new cancer drugs that her oncologist believed could save her life, but which were still in clinical trials. Abigail Alliance has numerous members and supporters who are suffering from terminal illness or who have lost family members to terminal illness.

Commenter Lorenzen Cancer Foundation is a nonprofit organization based in Monterey, California, providing assistance to patients fighting pancreatic cancer. The Foundation maintains a large database of clinical trials of pancreatic cancer therapies, as well as current medical news, to aid these patients and their physicians in keeping up to date on the range of available treatment options for pancreatic cancer. The chairman of the Foundation is Lee Lorenzen, who founded it in response to the diagnosis and subsequent passing of his brother Gary Lorenzen due to metastatic adenocarcinoma of the pancreas. Iressa is undergoing multiple clinical trials specifically for pancreatic cancer (two for adenocarcinoma of the pancreas and one for neuroendocrine tumors) either as a stand-alone therapy or in combination with other therapies.

## **II. Public Citizen's Arguments Concerning Iressa's Efficacy in Improving Survival Do Not Justify An Immediate Withdrawal**

Public Citizen argues that the Iressa Survival Evaluation in Lung Cancer Study (ISEL) "failed to show that Iressa has any efficacy in improving survival in patients with non-small cell lung cancer." But there is no serious dispute that Iressa does, in fact, dramatically benefit some patients with non-small cell lung cancer. The lack of statistical significance simply reflects the averaging of the subgroups of patients who respond very positively to Iressa with the patients

who do not. The statistical results at issue were based on a total number of deaths in the trial of 632 of 1,129 patients getting Iressa (56%) and 337 of 563 getting a placebo. If the number of deaths in the placebo arm had been 340 – three more – the survival rate in the Iressa arm would have been statistically significant.<sup>1</sup> It beggars belief that terminally ill patients would be denied a drug, one that may be their last hope, on this hypertechnical basis.

A key reason this drug received approval in the first place was the testimony of patients who had clearly received very substantial clinical benefit. Oncologists who use the drug report that it works well, and sometimes dramatically, for a small percentage of patients, in rare cases extending their lives by years. The statistics do not reflect that direct observational data. The ODAC in 2002 and FDA in 2003 recognized Iressa's value to those patients; FDA should recognize it again by rejecting Public Citizen's petition and allowing Iressa to remain on the market with appropriate labeling. AstraZeneca is conducting additional testing to identify the biomarkers that predict response which will build on the work already done by others. Moreover, leaving Iressa on the market preserves its availability to non-small cell lung cancer patients for whom it represents the best available care – for example, those already on the drug and experiencing clinical benefit, or future patients who run out of other options.

Public Citizen concedes that analysis of some subgroups did reveal a statistically significant effect on survival, namely Asian ethnicity and non-smoking status. Public Citizen

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<sup>1</sup> In a simple comparison of the proportion of patients dying in each treatment arm, an additional 7 deaths for placebo-treated patients in the overall population and an additional 3 deaths in the adenocarcinoma population for placebo-treated patients would have been sufficient to yield  $p < 0.05$  in the respective 15 analyses. This is reflected in the supportive Cox regression analysis, which, after covariate adjustment for the same pre-specified factors as in the stratified log-rank test, achieved statistical significance for both patient populations (overall population: HR

downplays these results, however, on the ground that “[s]uch 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.” But these subanalyses *were* pre-planned. Even if they had not been, to disregard the subanalyses outright because they do not coincide with “the analysis as planned in the protocol” would be an extreme case of form over substance; it is true that retrospective analyses may harbor some statistical bias, but in the real-world context of the treatment of terminal illness, insisting on perfect information is pedantry and is a formula for paralysis-by-analysis. The fact that “there is currently no way to know who might respond” (apart from the above subgroups) is true of pharmaceuticals in general and is hardly a reasonable basis to remove a drug that is indisputably extending the lives of patients today.

### **III. Public Citizen’s Arguments Concerning the Possible Side Effects of Iressa Do Not Justify An Immediate Withdrawal**

Public Citizen states that it has carried out an analysis based on the FDA Adverse Event Reactions database, and claims to have found 144 reports of interstitial lung disease, “including 87 deaths for which Iressa was considered the primary suspect.” Public Citizen does not provide any explanation of how it arrived at its results or how it related its findings to the occurrence of ILD in non-small cell lung cancer patients in general. In any case, Public Citizen’s conclusions disregard the fact that interstitial lung disease (ILD) is a known complication in lung cancer

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0.86, 95% CI 0.76 to 0.995, p=0.0419; adenocarcinoma population: HR 0.81, 95% CI 0.66 to 0.98, p=0.0298).

patients. This very issue was already considered extensively by the FDA, resulting in a four-month delay while AstraZeneca compiled and submitted, and FDA reviewed, all available data from all the clinical trials and the expanded access program, before Iressa was approved initially. Indeed, in the ISEL trial on which Public Citizen relies with regard to survival, ILD incidence was similar in both the Iressa and control arms. It should be noted that Japanese authorities have now twice sided with the FDA in deciding that Iressa's benefits outweigh whatever ILD-related risks are presented.

#### **IV. Iressa Must Be Assessed In Light of the Risk-Benefit Profile of Terminally Ill Patients Who Have Already Tried Other Therapies**

Every drug carries a risk of side effects; aspirin is available over the counter even though it causes some patients to bleed to death from gastric injury. What is critical in assessing a drug is the relationship of its risks and its benefits. Non-small cell lung cancer patients are at risk for a variety of complications and face a near certainty of death. In comparison, Iressa appears to be a reasonably safe drug with mild side effects and a low response rate. With suitable warnings, it is proper to make a drug with this risk/benefit profile available to terminally ill patients.

Granting Public Citizen's petition under these circumstances would go far toward undermining the concept of fast-track approval. Indeed, if the FDA were regularly to withdraw drugs on the basis of incomplete knowledge about their mechanisms of action or the specific subgroups for which they are effective, or on the basis of risks that are reasonable in the context of the illness being treated, pharmacy shelves in the U.S. would soon be stocked very sparsely.

It is thus unsurprising that the idea of withdrawing Iressa has been publicly criticized by practitioners before ODAC and elsewhere. Dr. Thomas Lynch of Massachusetts General Hospital told the Boston Globe, “I think the FDA should allow continued use of the drug. . . . To take it off the market would harm patients deriving benefits from it.”<sup>2</sup> Defending the FDA’s decision to approve Iressa, Dr. Lynch stated, “It would have been criminal had they not approved this drug.” Karmanos Cancer Institute director Dr. John C. Ruckdeschel has observed, “It would be incredibly stupid for ODAC to pull that drug, or to recommend pulling that drug. People are using it, people are benefiting from it, let them use it for God’s sake.”<sup>3</sup>

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<sup>2</sup> Raja Mishra, *Smart Drug For Lung Cancer Patients May Be Pulled From Market; Iressa Helps Small Portion of Patients*, Boston Globe, April 5, 2005, p. E1.

<sup>3</sup> Paul Goldberg, *Avastin Improves Lung Cancer Survival, Opens Options For New Combinations*, Cancer Letter, April 1, 2005, p. 7.

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## **CONCLUSION**

The Washington Legal Foundation, the Abigail Alliance for Better Access to Developmental Drugs, and the Lorenzen Cancer Foundation respectfully request that the FDA continue to monitor the risks and benefits of Iressa and deny the petition for immediate withdrawal of Iressa from the market.

Respectfully submitted,

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