

COMMENTS

of the

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

to the

FOOD AND DRUG ADMINISTRATION

Concerning

LABELING OF IRESSA (GEFITINIB)

Daniel J. Popeo
David Price
WASHINGTON LEGAL FOUNDATION
2009 Massachusetts Ave., N.W.
Washington, D.C. 20036
(202) 588-0302

July 25, 2005

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WASHINGTON LEGAL FOUNDATION

2009 MASSACHUSETTS AVE., N.W.

WASHINGTON, D.C. 20036

(202) 588-0302

July 25, 2005

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

Re: Labeling of Iressa (Gefitinib)

Dear Dr. Crawford:

The Washington Legal Foundation (WLF), the Abigail Alliance for Better Access to Developmental Drugs, the Lorenzen Cancer Foundation, and the Lung Cancer Alliance are submitting these comments to voice our opposition to the FDA-mandated relabeling of Iressa (gefitinib) announced on June 17, 2005.

Iressa, a cancer drug approved by regulatory authorities in 36 countries, 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. Iressa was approved in the United States in May 2003 under the FDA's accelerated approval program. It was approved for the treatment of patients with locally advanced or metastatic non-small cell lung carcinoma after failure of platinum-based and docetaxel chemotherapies.

The revised label for Iressa states that it is to be used only for the "continued treatment" of patients "who are benefiting or have benefited from Iressa." This action effectively limits the use of Iressa in the United States to the approximately 4,000 patients currently being treated with

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it.¹ As detailed below, we believe this limitation on the availability of Iressa will harm lung cancer patients in the future who have no other approved treatment options and who may benefit from this medicine, and that it sets an unsound precedent.

It should be noted that 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 thousands of patients of the treatment that is best for them.

I. Interest of Commenters

Commenters WLF, Abigail Alliance, and Lorenzen Cancer Foundation previously submitted comments on April 20, 2005, in opposition to Public Citizen, Inc.'s petition for the withdrawal of Iressa from the market. Commenter Lung Cancer Alliance testified before the Oncologic Drugs Advisory Committee (ODAC) on March 4, 2005, in opposition to restrictions on the availability of Iressa and has written multiple letters to FDA on this subject.

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.

¹ <http://www.iressa-access.com/news.asp>.

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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 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 either as a stand-alone therapy or in combination with other therapies.

Commenter Lung Cancer Alliance is a national non-profit organization dedicated solely to advocating for people living with lung cancer or those at risk for the disease. Its initiatives aim to educate public policy leaders of the need for greater resources for lung cancer research while changing the face of lung cancer and reducing the stigma associated with the disease.

II. Aggregated Clinical Trial Results Concerning Iressa's Efficacy Do Not Justify A Blanket Action to Withhold Iressa From All New Patients

FDA's action on the labeling of Iressa is apparently based on the results of the Survival Evaluation in Lung Cancer Study (ISEL), also known as Trial 709, which did not find a statistically significant improvement overall under its primary analysis in survival of patients with non-small cell lung cancer treated with Iressa who had undergone one or two prior chemotherapy regimens and were refractory or intolerant to their most recent regimen.

These findings (as well as those of the SWOG 0023 study, to similar effect) do not warrant the FDA's action in this matter. 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 in the primary analysis simply reflects the averaging of the subgroups of patients who respond very positively to Iressa (roughly 10%, as indicated by multiple studies) 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. It beggars belief that terminally ill patients would be denied a drug, one that may be their last hope, on this hyper-technical basis.

If a drug is safe and is effective for some patients – as Iressa clearly is – that is the end of the FDA's inquiry. While clinical trial results suggest that Tarceva will show better results for the majority of patients in need of a third-line treatment, this is hardly a reasonable basis to

withhold a drug from *all* new patients when it is indisputably extending the lives of patients today.

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. AstraZeneca is conducting additional testing to identify the biomarkers that predict response which will build on the work already done by others. In the interim, Iressa should remain available to non-small cell lung cancer patients for whom it represents the best available care – who are not limited only to those patients already on the drug and experiencing clinical benefit, but also future patients who do not respond to or cannot tolerate other third-line treatments such as Tarceva. Physicians treating this terminal illness need more choices, not fewer.

III. At A Minimum, Iressa Should Be Labeled For Use By Patients In Subgroups For Which It Has Been Shown To Confer A Benefit

Apart from the FDA's overreliance on aggregate statistical findings, this action by the FDA is flawed on its own statistical terms. Analysis of two subgroups – Asian patients and non-smokers – *did* reveal a statistically significant effect on survival.² In the highly refractory population studied by the trial, Iressa showed a 33 percent reduction in the risk of death in never-

² Indeed, according to the new FDA-mandated label, response rates were “highly variable in subgroups of the

smoking patients compared to a placebo, and a 34 percent reduction in the risk of death in Asian patients compared to a placebo.³ These results are consistent with Phase II data and with findings from overseas.⁴ That the availability of Iressa has been curtailed even for new patients in these groups is inexplicable and is difficult to square with the FDA's professed commitment to evidence-based medicine.

The FDA appears to have forsworn reliance on this subgroup data on the ground that the primary analysis at the *aggregate* level did not show a statistically significant effect. At a March 4, 2005, ODAC meeting, Dr. Robert Temple, Associate Director for Medical Policy for FDA's Center for Drug Evaluation and Research, dismissed the subgroup findings as "after-the-fact subset analyses in a study that did not win."⁵ Dr. Temple suggested, "All of these differences [in subgroups] in a trial are much more credible when the trial wins overall or when you have specified that as the primary endpoint."⁶ Dr. Richard Pazdur, head of the Office of Oncology Drug Products within CDER, similarly noted, "The Iressa data is somewhat subject to questions about these subsets, because they did not win on their primary endpoint, so looking at these subsets could be statistically ambiguous or criticized."⁷ To dismiss statistically significant results at the subgroup level simply on account of a lack of statistical significance at the aggregate level, however, is a pure *non sequitur* as a matter of statistical methodology.

treated population," with previous or current smokers showing a response rate of 4.6%, but nonsmokers showing a response rate of 29.4%. The disparate response rates of Asians vs. non-Asians are not noted in the revised label.

³ Transcript, Oncologic Drugs Advisory Committee, March 4, 2005, Vol. II ("ODAC Transcr."), p. 34. Available for download at <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4095T2.htm>.

⁴ ODAC Transcr., pp. 33, 74.

⁵ ODAC Transcr., p. 72.

⁶ ODAC Transcr., pp. 83-84.

To the extent that FDA refuses to rely on the subgroup findings because they are not “prospective,”⁸ that too is unsound. These subanalyses *were* pre-planned⁹ and, as noted, are consistent with other study findings. Even if they were purely retrospective, to disregard the subanalyses outright on that basis 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.

IV. The FDA’s Action Is Unnecessary In View of the Sponsor’s Effective Program To Make Physicians Aware of The Relevant Facts

No one disputes that the sponsor, AstraZeneca, has aggressively disseminated cautionary information to physicians in the wake of the ISEL results. AstraZeneca’s program has included a press release of the study results, “Dear Doctor letters,” journal placements of the “Dear Doctor” letters, notification of patient groups, abstracts at meetings, and advertisements in all issues of the 10 most widely-read oncology journals urging physicians to consider options other than Iressa.¹⁰ A physician told ODAC, “I have got more notice about this drug than I have credit card applications, so they have clearly done a good job in saturating the medical community, at least the lung cancer doctors.”¹¹ In addition, the Oncology Nursing Society distributed information to

⁷ ODAC Transcr., p. 115.

⁸ ODAC Transc., p. 74.

⁹ ODAC Transcr., pp. 30-31.

¹⁰ ODAC Transcr., p. 13.

¹¹ ODAC Transcr., pp. 122-23.

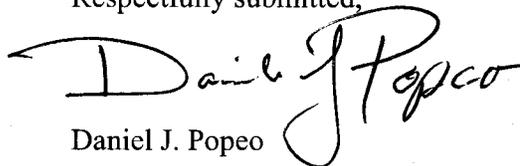
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its more than 30,000 member nurses.¹² In view of the widespread distribution of information about Iressa's limitations, it is appropriate to treat the decision to prescribe Iressa as a matter within a physician's discretion, like the many issues presented in the practice of medicine that require consideration of risks and potential benefits in light of the individual patient's circumstances.

CONCLUSION

The Washington Legal Foundation, the Abigail Alliance for Better Access to Developmental Drugs, the Lorenzen Cancer Foundation, and the Lung Cancer Alliance respectfully request that the FDA allow Iressa to be labeled for use by lung cancer patients who have no other approved options remaining.

Respectfully submitted,


Daniel J. Popeo


David Price

WASHINGTON LEGAL FOUNDATION
2009 Massachusetts Ave., N.W.
Washington, D.C. 20036
(202) 588-0302

Counsel for Commenters

¹² ODAC transcr., pp. 137-38.