FOOD AND DRUG ADMINSTRATION
Center for Drug Evaluation and Research
Oncologic Drugs Advisory Committee Meeting
March 4, 2005

Iressa

Questions to the Committee

Background

Iressa (gefitinib) was originally approved by the FDA on May 5, 2003, as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies. Partial tumor responses occurred in 15 of 142 evaluable patients for a response rate of 10.6 percent (95CI: 6-16.8 percent) overall. Responses occurred in 9 of 66 patients receiving 250 mg/day (13.6 percent) and in 6 of 76 patients receiving 500 mg/day (7.9 percent). Median duration of response was 7.0 months (range 4.6 -18.6+ months). Iressa was approved under accelerated approval regulations. These regulations allow approval based on a surrogate end point reasonably likely to predict clinical benefit and require subsequent demonstration of clinical benefit in further investigations. As an approval condition, AstraZeneca committed to conduct a randomized trial examining the Iressa effect on survival in patients with advanced NSCLC who have received 1 to 2 prior chemotherapy regimens (ISEL Trial 0709).

AstraZeneca notified the United States Food and Drug Administration (FDA) on December 16, 2004 that a large randomized study comparing Iressa plus best supportive care (BSC) to placebo plus BSC failed to demonstrate a survival advantage for Iressa in the treatment of NSCLC patients who have received 1 to 2 prior chemotherapy regimens (ISEL Trial 0709). AstraZeneca reports that Trial 0709 enrolled 1,692 patients from 210 study centers in 28 countries. The last patient was enrolled on August 2, 2004, and the data cut-off was October 29, 2004. The two treatment arms were well balanced for demographic and disease-related patient characteristics. Iressa treatment was not associated with a significant survival improvement in the overall population HR=0.89 (95%CI: 0.78, 1.03, p=0.11) with a median survival of 5.6 months for Iressa-treated patients and 5.1 months for placebo-treated patients.

The FDA has not yet received complete data from this trial. The FDA management plan is rapid communication of the above trial results to health care professionals and patients concurrent with expeditious completion of the trial analyses by AstraZeneca, including the effect of EGFR status determined by the Dako Kit on efficacy. 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, and pointed out that other treatments with positive survival data should be considered, but will continue to make the drug available to patients who appear to be benefiting from Iressa treatment.

Iressa

(Questions to the Committee Continued)

Background Cont.

The following actions have been taken to communicate the most recent Iressa information to health care professionals and patients.

- AstraZeneca press release of ISEL study results
- Approximately 141,000 Dear Doctor Letters
- AstraZeneca Sales Force distribution of Dear Doctor Letter
- Dear Doctor Letter posted on AstraZeneca website
- Patient Advocate groups notified
- AstraZeneca communications to known patients
- Clinical Trial Investigators and NCI notified
- ASCO E-Mail from FDA
- Information posted on FDA website
- AACR and WCLC abstracts
- Journal placement of Dear Doctor Letter
- Advertisements on a continuing basis in all issues of the 10 most read oncology journals urging physicians to consider treatment options other than Iressa (see attachment)
- AstraZeneca is tracking total and new Iressa prescriptions every two weeks to ensure that the above communications are resulting in decreased Iressa use.

This is a revised version of an FDA statement originally issued December 17, 2004. Information on Alimta was added to the fourth paragraph.

FDA Statement

FOR IMMEDIATE RELEASE
Statement
December 17, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Statement on Iressa

The FDA today released the following statement regarding the failure of a clinical trial of Iressa (gefitinib) to show an overall survival advantage in treating patients with lung cancer:

The Food and Drug Administration (FDA) learned yesterday from AstraZeneca that a large clinical trial comparing Iressa (gefitinib) with placebo in patients with non-small cell lung cancer who had failed other courses of cancer therapy showed no survival benefit from taking Iressa.

Patients currently taking Iressa should consult with their physicians as soon as possible; patients should not change their therapy without first consulting with their physicians.

Alternative therapies are available. FDA has approved Taxotere (docetaxel) and Tarceva (erlotinib), both of which have been shown in studies to improve survival in patients with non-small cell lung cancer whose cancer has progressed while on previous therapies. Alimta (pemetrexed) has received an accelerated approval based on the surrogate endpoint for this use but has not yet demonstrated any survival benefit.

FDA approved Iressa on May 2, 2003, under the Agency's accelerated approval (Subpart H) program, for the treatment of patients with non-small cell lung cancer who had failed two or more courses of chemotherapy. The accelerated approval provisions in FDA's regulations allow the agency to approve a drug for marketing based on an effect on a surrogate endpoint -- such as a 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 was approved because the data from clinical trials showed that it caused significant shrinkage in tumors in about 10% of patients, and this was thought likely to increase patients' overall survival time.

One requirement for drugs approved under the agency's accelerated approval program is that the sponsor must study them further after approval to verify the expected clinical benefit. After the approval of Iressa in 2003, AstraZeneca conducted a study in approximately 1700 patients to determine whether the drug would in fact prolong survival in comparison to patients taking placebo. The results announced today indicate that the drug did not prolong survival. Under FDA's accelerated approval program, the Agency has the authority to remove a drug from the market if a postmarketing clinical study fails to verify clinical benefit. After FDA has evaluated the recent study results, FDA will determine whether Iressa should be withdrawn from the market or if other regulatory actions are appropriate.

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Physicians are urged to consider treatment options other than IRESSA®

AstraZeneca
life inspiring ideas

December 17, 2004

Subject: IRESSA® (gefitinib) ISEL study results
A double blind, placebo controlled, parallel group, mulitcentre, randomised, Phase III survival study comparing IRESSA® (gefitinib) (250mg tablet) plus Best Supportive Care versus placebo plus Best Supportive Care in patients with Advanced NSCLC who have received one or two prior chemotherapy regimens and are refractory or intolerant to their most recent regimen.

Dear Doctor,

I am writing to inform you that AstraZeneca has just analyzed the top-line data from the ISEL trial, a trial which compared IRESSA® (gefitinib) to placebo in advanced non-small cell lung cancer patients who had progressed or could no longer tolerate chemotherapy.

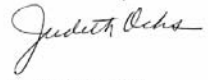
The trial was closed to randomization on August 2, 2004 with 1692 enrolled patients. The analysis of the primary endpoint of the study shows that IRESSA did not significantly prolong survival in the overall population (HR 0.89, p=0.11, Median 5.6 vs 5.1 months for IRESSA and placebo respectively), or in patients with adenocarcinoma (HR 0.83, p=0.07, Median 6.3 vs 5.4 months for IRESSA and placebo respectively). In addition, an unconfirmed objective response rate for IRESSA of 8.2% was observed, which did not translate into an overall statistically significant survival benefit. There is no methodological explanation for these study findings and analysis of EGFR status and other biomarkers is still underway for ISEL and other ongoing studies.

AstraZeneca is providing the ISEL data to you in a rapid fashion to enable you to best treat your current and future patients. In light of positive survival data with other agents including another oral EGFR inhibitor, AstraZeneca urges you to consider other treatment options in the recurrent non-small cell lung cancer patient population. Individual patients currently on IRESSA and doing well may be part of a patient group that might derive benefit from IRESSA. AstraZeneca plans to evaluate further which patient groups may derive benefit from IRESSA.

These top line results are currently being reviewed and discussed with the FDA. Full results of the data will be available in the first half of 2005 and publicly presented as soon as possible. For those individual patients whom you feel are benefiting and deem appropriate, AstraZeneca intends to continue to make the drug available. At this time, AstraZeneca is suspending promotion of Iressa while these trial data are further analyzed.

Please do not hesitate to contact the AstraZeneca Cancer Support Network at 866-992-9276 for further clarification of your questions.

Yours sincerely,



Judith Ochs, MD
Senior Medical Director, Clinical Development
Oncology Clinical Research
AstraZeneca

Please see Brief Summary for IRESSA on the other side of this journal ad.

(Questions to the Committee Continued)

Discussion Points

1. Discuss whether the content of the information communicated by the FDA and AstraZeneca on Iressa is satisfactory. Should any other information be communicated?

2. Discuss whether the target audiences and the selected means of communication are satisfactory. Should any other audiences or means of communication be used?

3. Discuss "lessons learned" from the Iressa development process that might be applied to future drug development, e.g., Iressa dose selection for the ISEL trial.

4. Discuss possible future Iressa studies in NSCLC, including
   -targeting of subgroups of patients
   -use of Iressa in combination with other agents