Oncologic Drugs Advisory Committee
DRAFT MINUTES
September 24, 2002

The 72nd meeting of the Oncologic Drugs Advisory Committee was held in the Kennedy Ballroom at the Holiday in at 8777 Georgia Avenue, Silver Spring, Maryland. Approximately 475 people were in attendance. The meeting was chaired by Donna Przepiorka, MD, PhD.

Open Public Hearing

Carl Dixon – The Kidney Cancer Association
Rick and Jan Lesser – Redondo Beach, California
Abbey S. Meyers – National Organization for Rare Disorders, Inc. (NORD)
Carolyn R. Aldige - Cancer Research Foundation of America
Susan Nelson – Perris, California
Anita Johnston – East Norwich, New York
Gloria Caruso – Tampa, Florida
Robin Prachel – National Patient Advocate Foundation
Melissa Mahoney – Virginia Beach, Virginia
Janine Hutchison – Las Cruces, New Mexico
Adriane Riddle – San Bernardino, California
Blanche Taylor and Laura Tirpak – Sparta, New Jersey
Charles H. Riley – Tarrytown, New York
Erica Hurtz – The Wellness Community

NDA 21-399, IRESSA® (gefitinib), AstraZeneca Pharmaceuticals LP

- indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer who have previously received platinum-based chemotherapy

Sponsor Presentation	**AstraZeneca Pharmaceuticals LP**
IRESSA® (ZD1839) Monotherapy for NSCLC Introduction and Rationale for Clinical Development	George Blackledge, M.D., Ph.D., MB, F.R.C.P. Clinical Vice President of Oncology
Recurrent Non-Small Cell Lung Cancer	Frances A. Shepherd, M.D., F.R.C.P.C. Director, Division Medical Oncology University of Toronto
IRESSA® (ZD1839) Efficacy	Ronald B. Natale, M.D. Medical Director Cedars Sinai Comprehensive Cancer Center
IRESSA® Safety Profile	Alan B. Sandler, M.D., F.A.C.P. Associate Professor of Medicine Vanderbilt University

FDA Presentation

Introduction and Regulatory Background	Grant Williams, M.D.

	Deputy Director Division of Oncology Drug Products, FDA
Review of the Clinical Trials	Martin Cohen, M.D. Medical Reviewer, FDA
Statistical Analysis	Rajeshwari Sridhara, Ph.D. Statistical Reviewer, FDA
Summary	Grant Williams, M.D.

Questions to the Committee

Introduction

AstraZeneca has submitted a marketing application for the above indication for consideration of accelerated approval. Before the Agency's action on this application, results became available from ZD1839 studies in patients with previously untreated NSCLC. Two large randomized trials failed to show clinical benefit from the addition of ZD1839 to standard first-line cisplatin-based regimens. The Agency had expected that if ZD1839 received accelerated approval in refractory NSCLC, these trials would provide the post-approval evidence of ZD1839 clinical benefit. Evidence of clinical benefit is required for the conversion of the application status from accelerated approval to full approval. Presently, the Agency must consider the relevance of the tumor response data from the single-arm ZD1839 trials of patients with refractory NSCLC. Given the lack of ZD1839 clinical benefit in patients with previously untreated NSCLC, the dilemma is whether a 10% response rate in a 3rd line treatment is reasonably likely to predict clinical benefit.

The regulations and results are discussed in more detail below.

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Regulatory Background

Regular marketing approval of oncology drugs requires substantial evidence of efficacy from well-controlled clinical trials. Guidance promulgated in the 1980's indicated that efficacy for cancer treatment should be demonstrated by prolongation of life, a better life, or an established surrogate for at least one of these. In 1992, Subpart H was added to the NDA regulations to allow *accelerated approval* (AA) for diseases that are *serious or life-threatening* where the new drug appears to provide *benefit over available therapy*. AA can be granted on the basis of a *surrogate endpoint* that is *reasonably likely to predict clinical benefit.* After AA, the applicant is required to perform a post-marketing study to demonstrate that treatment with the drug is indeed associated with clinical benefit. If the post-marketing study fails to demonstrate clinical benefit or if the applicant does not show *due diligence* in conducting the required study, the regulations describe a process for rapidly removing the drug from the market. After AA of oncology drugs, clinical benefit has often been evaluated in patients with less refractory tumors, i.e., in first or second-line treatment settings.

Results of single-arm studies of chemotherapy resistant/refractory NSCLC

Response rate claims

Study 0039 evaluated ZD1839 treatment in 216 NSCLC patients, including 139 patients with tumors resistant or refractory to cisplatin and taxotere. These 139 patients were considered to have no *available therapy*. In this population, response rate serves as the surrogate endpoint for the AA claim. The response rate was 10.1% (95% CI: 5%,17%)

Symptom improvement claims

Patient symptoms were evaluated with the Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L). This subscale is composed of seven 4-point questions that are summed for a total of 28 possible points. The applicant claims that clinical benefit is demonstrated by individuals showing a 2-point improvement on the LCS of 28 day duration. The applicant finds that approximately 40% of patients in Study 39 derive such benefit, and that the benefit correlates with response and survival. The FDA believes these results are not reliable because there is no concurrent, randomized, blinded control arm and a prospective plan for collecting and analyzing data on supportive care products (e.g., oxygen and pain medications) did not exist.

Results from randomized clinical studies in first-line treatment of NSCLC

Recently, the applicant provided FDA with analyses of two trials evaluating standard chemotherapy plus or minus ZD1839 in first-line treatment of NSCLC. These results are relevant because the FDA must determine whether a 10% ZD1839 response rate is reasonably likely to predict clinical benefit. The FDA must consider all available information on a drug product prior to making a regulatory decision. The lack of ZD1839 clinical benefit in the closely related first-line NSCLC setting must be considered in the FDA's regulatory decision-making process.

Approximately 350 patients per arm were entered on each trial. Adequate follow-up (about 240 events per arm) has been provided. Neither Study 14 nor Study 17 showed survival benefits for the addition of ZD1339 to chemotherapy.

Study 14 Survival

	At Risk	Events	Median in Months	1-year
500 mg ZD1839	365	243	9.9	44%
250 mg ZD1839	365	248	9.9	42%
Placebo	363	236	11.1	45%

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Study 17 Survival

	At Risk	Events	Median in Months	1-year
500 mg ZD1839	347	246	8.7	38%
250 mg ZD1839	345	232	9.8	42%
Placebo	345	247	9.9	42%

Depending on the number of patients entered and subsequent events, detection of a small survival benefit may be difficult. However, for active drugs, a difference in response rate difference may be detected in these situations. In Study 14 and 17, the addition of ZD1839 to chemotherapy did not result in a significant improvement in response rates:

	Study 14 Response Rate	**Study 17 Response Rate**
500 mg ZD1839	49.7%	32.1%
250 mg ZD1839	50.1%	35.0%
Placebo	44.8%	33.6%

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Questions to the Committee:

1. The FDA believes the relevance of the symptom improvement data discussed above cannot be adequately evaluated without a randomized, blinded study with an adequate control arm (the two doses of ZD1839 show no difference in efficacy and are thus not adequate). Do you agree?

   YES – 9 NO – 5

   The Committee felt that the data supported only a soft claim of symptom management, and that a randomized, controlled trial with a "no drug" arm (either placebo or best supportive care) would be required for substantial evidence.

2. Given the lack of clinical benefit in two large studies of ZD1839 in combination with standard first-line NSCLC chemotherapy, is the Study 0039 response rate of 10% in 139 patients with resistant or refractory NSCLC reasonably likely to predict ZD1839 clinical benefit in NSCLC?

   YES – 11 NO – 3

   The Committee indicated that, for NSCLC in the third line setting where there are no viable treatment options, a 10% response rate is meaningful, and shows evidence of biologic activity of the drug. The reason for failure of the first line trials remains unexplained, and requires further study.

3. More than 12,000 NSCLC patients have received ZD1839 under an expanded access protocol. Please discuss what position FDA should take on ZD1839 expanded access if marketing approval of ZD1839 is not granted at this time.

   There are concerns about the effects of both accelerated approval and the expanded access program on patient accrual for confirmatory studies, and the Committee suggests that patients who qualify for any ongoing studies be ineligible for the expanded access program.

4. Regardless of whether ZD1839 is granted accelerated approval for treating NSCLC, additional trials may be needed. Please discuss potential study designs to demonstrate that ZD1839 provides clinical benefit to NSCLC patients.

   The Committee agreed that timely, randomized, adequate and well-controlled studies will be necessary to determine the efficacy of the drug and the best way to utilize it. Suggestions included trials of ZD1839 versus chemotherapy in the first line, stratification studies to determine which patient subset derives the most benefit, and cross-over studies. Careful thought is especially urged in avoiding the problems inherent to crossover studies.