Oncologic Drugs Advisory Committee
December 16, 2003

This is the final report of the ODAC meeting held on December 16, 2003. A verbatim transcript will be available in about 2 weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder03.html#OncologicDrugs

All external requests should be submitted to the Freedom of Information office.

The 75th meeting of the Oncologic Drugs Advisory Committee was held in the CDER Conference Room 5630 Fishers Lane, Room 1066, Rockville, Maryland. A webcast was available the Ramada Inn, 1775 Rockville Pike, Rockville, MD. Approximately 120 people were in attendance in the CDER Conference Room and approximately 50 people at the Ramada Location. The meeting was chaired by Donna Przepiorka, MD, PhD.

Open Public Hearing
Mark Scott – Astra Zeneca Oncology

The committee met to discuss general issues on clinical trial design and endpoints in the morning session. The afternoon session was devoted to non-small cell lung cancer endpoints as a follow-up to issues discussed at an April 15, 2003 FDA Workshop.

The Agenda proceeded as follows:

Call to Order	Donna Przepiorka, M.D., Ph.D. Chair, Oncologic Drugs Advisory Committee
Introduction of Committee	
Conflict of Interest Statement	Johanna Clifford, M.S., RN, BSN Executive Secretary, Oncologic Drugs Advisory Committee
Opening Remarks	Grant Williams, M.D., Deputy Director Division of Oncology Drug Products Center for Drug Evaluation and Research, FDA
General Regulatory Background	Ann Farrell, M.D., Medical Team Leader Division of Oncology Drug Products Center for Drug Evaluation and Research, FDA
Endpoints for Past Approvals	Ramzi Dagher, M.D., Medical Team Leader Division of Oncology Drug Products Center for Drug Evaluation and Research, FDA
Selected Issues in Oncology Trial Design	Grant Williams, M.D., Deputy Director Division of Oncology Drug Products Center for Drug Evaluation and Research, FDA

Clarification Questions to Presenters

Break

Open Public Hearing

Questions for Discussion

Lunch

Non Small Cell Lung Cancer Regulatory Background	Martin Cohen, M.D., Medical Officer Division of Oncology Drug Products Center for Drug Evaluation and Research, FDA
FDA/ASCO Non Small Cell Lung Cancer Workshop Summary	Paul Bunn, M.D. Professor and Director University of Colorado Cancer Center Denver, Colorado
Quality of Life and Patient Reported Outcomes as Endpoints in Clinical Cancer Trials	Richard Gralla, M.D. President, Multinational Association of Supportive Care in Cancer New York, New York

Clarification Questions to Presenters

Break

Open Public Hearing

Questions for Discussion

Adjourn

Meeting Questions– Session I

Background

Sponsors must demonstrate that drugs are safe and must provide substantial evidence of effectiveness from "adequate and well-controlled clinical investigations." Such effects could include important clinical outcomes (e.g., survival), symptomatic improvement, or effects on established surrogate endpoints, such as blood sugar, blood pressure, or blood cholesterol, and all of these endpoints have often been used as a basis for approval.

In oncology, survival is the gold standard for clinical benefit, but the FDA has accepted other endpoints for cancer drug approval. Given the toxicity of cancer drugs, approval required evidence of improvement in survival or in a patient's quality of life, e.g., improved physical functioning or improved tumor-related symptoms. Other endpoints have been accepted in specific clinical situations. Disease-free survival has been accepted as an adequate endpoint for adjuvant cancer treatment when a large proportion of patients with recurrence was symptomatic. Durable complete response was considered an acceptable endpoint in testicular cancer and acute leukemia because the untreated conditions were quickly lethal or even in some chronic leukemias and lymphomas, where it was clear that

remission would lead to less infection, bleeding, and blood product support. Response rates have been considered as endpoints for regular approval in specific settings when other factors were taken into consideration, such as response duration, relief of tumor-related symptoms, and drug toxicity

With this background in mind, please discuss issues relating to the following endpoints:

Survival

1. Discuss the role of survival as an endpoint. Consider in your discussion 1) the importance of whether existing therapies prolong survival and 2) the potential confounding of survival results by patient crossover or where several subsequent therapies may also affect survival.

The committee felt that survival should always be assessed but need not always be the primary endpoint. The committee acknowledged that in some cases, crossover could obscure detection of a potential survival benefit.

Time to tumor progression (TTP)

TTP has been proposed as an endpoint for regular approval, but has not been rigorously validated as a surrogate for survival. As noted below TTP has important attributes, yet difficulties exist with its use.

Pros

- TTP is a measure of tumor effect in all patients, rather than measuring effect in a subset of patients.
- Progression is widely viewed by oncologists and patients as an indicator of worsening necessitating a change in therapy.
- Tumor progression is in the direct causal path of morbidity and death.

Cons

- TTP is an indirect measure of patient benefit.
- The clinical meaning of small TTP difference is unclear.
- Reliability in an unblinded setting has been questioned.
- TTP findings are difficult for independent review groups and for FDA to verify.

2. Discuss whether clinical settings exist where TTP improvement should be considered an established surrogate for clinical benefit and should support regular drug approval. Identify the factors that determine when TTP is an adequate endpoint for drug approval.

   Factors to be considered in your discussion include reliability in measuring the endpoint, relationship of disease progression to death, established benefit of available therapy, drug toxicity, and whether progressing patients are symptomatic. (Clinical scenarios highlighting these factors are listed in the appendix).

First, all committee members preferred inclusion of deaths in the TTP endpoint, i.e., they preferred progression free survival (PFS) to TTP. Most committee members felt that an improvement in PFS was clinical benefit, but that whether to TTP as a regulatory endpoint depended upon many factors, such as treatment toxicity, the ability to measure TTP without bias, the size of theTTP benefit, the toxicity of treatment, and the effectiveness of other available therapy. The committee did not feel that measurement of TTP at a single time point was an attractive option until the concept had been studied further.

Disease-free survival

FDA has stated that disease-free survival (DFS) can support regular drug approval in cancers where the majority of recurrences are symptomatic. Others propose that prolongation of DFS should support regular approval in all clinical settings because a delay in cancer detection or a delay in the need for toxic cancer treatment is of clinical benefit.

3. Discuss whether DFS is generally an adequate endpoint for approval of cancer drugs or whether additional evidence is needed, such as data demonstrating (or suggesting) that DFS is a survival surrogate.

4. Consider whether the adequacy of DFS varies with the clinical setting. For instance, consider the following clinical scenarios:

   A. No standard adjuvant therapy exists. Treatment with investigational drug shows superior DFS compared to an unproven control regimen.

   B. Treatment with investigational drug shows prolongation of DFS compared to highly effective standard therapy (that imparts a survival benefit).

   C. Treatment with investigational drug shows non-inferior DFS compared to highly effective standard therapy (that imparts a survival benefit).

The committee felt that prolongation of DFS is a clinical benefit, not just a surrogate for survival. Even so, when deciding whether to accept DFS as a primary endpoint, the FDA should weigh the benefit from delay in tumor detection versus the toxicity of treatment. In evaluating treatment toxicity, effects on functionality are of most interest, not minor toxicities or minor changes in QOL scales. Whether DFS would be an appropriate primary endpoint for a particular setting should be made on a case-by-case basis. Survival should be assessed in all studies.

Meeting Questions – Session II

First-line NSCLC treatment setting: approval based on demonstrating superior TTP

Considering the pros and cons of TTP discussed in the morning session:

1. For approval of drugs for first-line treatment of advanced lung cancer, could a TTP benefit of a new drug compared to a standard first-line regimen justify regular drug approval? (Assume the standard control arm has a known small [2-month] survival benefit.)

The question was rephrased to address locally advanced and metastatic disease as separate entities. As such, the question to the committee read, would you consider progression free survival as an appropriate endpoint for full approval for the patient with metastatic NSCLC?

Yes – 11 No – 08

Please note that all but one of the lung cancer consultants voted no on this issue. Dr. Temple suggested that data should be examined to assess whether patients are symptomatic at the time of recurrence. If they were, this would strengthen the case that PFS is a clinical benefit measure in this setting.

The committee then addressed the question with respect to the inoperable, locally advanced setting, asking the committee to vote on whether they would use progression-free survival as a primary endpoint for approval.

Yes – 4 No - 15

2. If the answer to question 1 is yes, describe the TTP evidence that would suffice:

   a. Discuss the magnitude of TTP improvement that would be clinically relevant.

   b. Given the difficulties with measuring TTP, should FDA's evidentiary requirements (number of trials, required significance level) be greater for TTP than for survival?

   c. If TTP is the primary endpoint should trials be blinded? If not, should progression be verified by blinded central reading of scans?

3. In addition to the TTP finding what, if any, survival evidence would be needed?

   a. Should trials rule out a survival decrement of some size?

   b. Should trials be powered to detect a realistic improvement in survival even if survival improvement is not an approval requirement?

4. If an improvement in TTP would not support regular approval, could it support accelerated approval?

The committee felt that under the considerations discussed, they would support AA, if a clinically significant effect on TPP were documented.

Yes – 18 No - 0 Abstain – 1

First-line NSCLC treatment setting: approval based on demonstrating non-inferiority in survival

5. When designing a non-inferiority (NI) trial, the active control treatment should have demonstrated a consistent treatment effect in numerous trials. The effect should be reasonably large and precisely defined. A critical assumption (the constancy assumption) is that the treatment effect of the active control will also exist in the planned NI trial setting.

   a. FDA believes that data from existing active control regimens for NSCLC are insufficient to support the design of NI trials based on survival. Do you agree?

   b. Discuss the potential effect on the NI survival analysis of crossover or change to other available treatment.

The committee statisticians stressed that in any NI trial it is important that the active control have well-documented, substantial historical benefits demonstrated in multiple randomized studies and that are precisely estimated. Furthermore these active control effects should also be expected to be found in the NI trial setting. This aspect of NI design is known as the constancy assumption. The committee agreed that current data on survival effects of most NSCLC treatments did not meet these standards.

First-line NSCLC treatment setting: approval based on non-inferiority (NI) analyses of TTP and/or RR

6. Could approval be based on NI analyses of RR and/or TTP in situations where a NI analysis of survival cannot be performed? Examples would be when there are insufficient patient numbers to allow a survival NI analysis or when there is confounding of the survival analysis by crossover.

   Specifically, address the following situation:

   A less toxic experimental drug demonstrates non-inferiority of both RR and TTP compared to the standard toxic regimen. The standard toxic regimen has previously demonstrated an estimated 2-month survival benefit in one trial comparing it to best supportive care. In the current trial data 95% confidence intervals cannot establish whether the experimental therapy retains the survival benefit of the standard regimen.

The committee felt that it is very complicated to perform a NI on a surrogate endpoint as described in this question. Further information would be required to respond adequately, in terms of functional relationships with respect to the fractions of the benefit in TTP that translates into the fraction of the survival benefit.

After a committee statistician explained the difficulties with NI studies using surrogates, the committee expressed little enthusiasm for this approach. The committee statisticians stressed that in any NI trial it is important that the active control have well-documented, substantial historical benefits demonstrated in multiple randomized studies and that are precisely estimated. Furthermore these active control effects should also be expected to be found in the NI trial setting. This aspect of NI design is known as the constancy assumption.

The surgical adjuvant setting

7. FDA has stated that disease-free survival (DFS) can support regular drug approval in cancers where the majority of recurrences are symptomatic. Others propose that prolongation of DFS should support regular approval in all clinical settings because a delay in cancer detection or a delay in the need for toxic cancer treatment is of clinical benefit.

   a. In NSLC, should a DFS improvement from adjuvant chemotherapy support regular drug approval? If so, clarify why you consider DFS an established surrogate for clinical benefit in this setting:
      - Because it delays the detection of cancer and treatment?
      - Because it delays symptoms?
      - Because it delays death?

   b. If not, could a DFS improvement support accelerated approval? Would a survival advantage ultimately be required for conversion to regular approval?

The experts on the panel suggested that adjuvant therapy has yet to play a role in lung cancer. However, the committee agreed that DFS can be used as a primary endpoint. There are currently 2 studies underway.

Symptoms and QOL in lung cancer studies

Symptom-based endpoints have served as the basis of approval for several drugs including drugs for local treatment of obstructing endobronchial cancer. However, difficulties exist with using such endpoints in cancer treatment,

including lack of blinding and missing data.

7. Do lung cancer settings exist where symptom-based endpoints can serve as the primary endpoint for approval? If so, discuss suitable symptom-based endpoints.

The committee had concerns about the length of the QOL instruments (21+ questions). They emphasized the merits of using very targeted symptoms scales such as the Lung Cancer Symptom Scale (LCSS).

8. Discuss the role of HRQOL as a drug approval endpoint.

   a. In the NSCLC setting, are HRQOL results meaningful in single arm studies?

   b. In randomized studies are HRQOL results meaningful without blinding?

   c. Should HRQOL instruments be routinely included in lung cancer studies? If so, which instruments?

The committee felt that long HRQOL instruments should be used sparingly in lung cancer patients who are often experiencing lung cancer symptoms. They recommended shorter targeted scales.