Oncologic Drugs Advisory Committee
March 13, 2006

Summary Minutes of the Oncologic Drugs Advisory Committee
Meeting on March 13, 2006:

The committee met to discuss pre-clinical requirements and phase 1 trial design issues for the development of oncologic products in the morning session and new drug application (NDA) 20-509, S-039, Gemzar (gemcitabine hydrochloride) for injection, Eli Lilly and Company, proposed indication for use in combination with carboplatin for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy during the afternoon session.

The summary minutes for the March 13, 2006 meeting of the Oncologic Drugs Advisory Committee were approved on April 5, 2006.

I certify that I attended the March 13, 2006 meeting of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/s/ /s/

Johanna Clifford, M.Sc., RN
Executive Secretary, ODAC

Silvana Martino, D.O., Chair, ODAC

The meeting of the Oncologic Drugs Advisory Committee was held in the Ballrooms at the Gaithersburg Hilton, 920 Perry Parkway, Gaithersburg, MD. Approximately 200 people were in attendance. The meeting was chaired by Silvana Martino, D.O.

The committee met to discuss pre-clinical requirements and phase 1 trial design issues for the development of oncologic products.

Attendance:
Oncologic Drugs Advisory Committee Members Present (voting):
Bruce Cheson, M.D., Maha Hussain, M.D., David Harrington, Ph.D., Pamela Haylock, M.D., Silvana Martino, D.O.(Chair), Michael Perry, M.D., Maria Rodriguez, M.D., Gregory Reaman, M.D.

Oncologic Drugs Advisory Committee Consultants (voting):
Susan Bates, M.D., Ralph D'Agostino, Ph.D., Tito Fojo, M.D., Ph.D., Eric Kodish, M.D., Chris Takimoto, M.D., Ph.D.

Oncologic Drugs Advisory Committee Consultants (non-voting):
Edward Sausville, M.D.

Industry Representative (non-voting):
Antonio Grillo-Lopez, M.D.

Oncologic Drugs Advisory Committee Members Absent:
Ronald Bukowski, M.D., James Doroshow, M.D., Joanne Mortimer, M.D.

FDA Participants:
Richard Pazdur, M.D., Robert Justice, M.D., Patricia Keegan, M.D., M. David Green, Ph.D., John Leighton, Ph.D., DABT

Open Public Hearing Participants:

Guest Speaker:
James Green, Ph.D., DABT, Senior VP, Biogen Idec, Inc.

The agenda proceeded as follows:

Opening Comments	Richard Pazdur, M.D., Director Office of Oncology Drug Products, CDER, FDA
Requisite Non-clinical Data for first-in-human studies.	**David Jacobson-Kram, Ph.D., D.A.B.T.** Associate Director for Pharm. & Tox. OND/CDER/FDA
Drug Review	**John Leighton, Ph.D.**

	Pharmacology/Toxicology Team Leader DOOP, CDER, FDA
Industry Perspective	**James Green, Ph.D.** Vice President, Biogen Idec, Inc.
Biologics Review	Martin **David Green, Ph.D.** Supervisory Pharmacologist DBOP, OND, CDER, FDA
Nonclinical Perspective on Initiating Phase 1 Studies for Biolgical Oncology Products: Case Examples	**Anne M. Pilaro, Ph.D.** Expert Toxicologist, DBOP OODP, OND, CDER, FDA
Non-Clinical Studies for Initiating Phase I studies in Oncology: Small Molecules vs. Biologics	**David Ross, M.D., Ph.D.** Medical Officer

Break

Open Public Hearing

Questions from the Committee

Questions to the Committee & Committee Discussion

Questions to the Committee

<u>Background</u>

FDA and the International Conference of Harmonization (ICH) Guidance documents provide recommendations for non-clinical testing of small molecule drugs and biologics under development for human use. These guidances outline general principles and are not tailored to drug development for a specific medical condition. While the ultimate goal of all non-clinical testing is to characterize adverse drug effects and the pharmacokinetic profile in order to guide safe use in human subjects, the amount of non-clinical safety data needed to support initiation of clinical testing differs, based on the proposed use and patient population(s). The non-clinical data must be sufficient to permit FDA to conclude that the patients are not exposed to unreasonable risks.

Not only will the patient population dictate the amount of non-clinical data necessary to support clinical testing, but the product class is also a factor in determining both the type of studies conducted, and the amount of non-clinical data required to initiate clinical testing. Biotechnology-derived drugs such as monoclonal antibodies differ from small molecular weight drugs in their biology, pharmacodynamics, pharmacokinetics, and potential for cumulative toxicity. Moreover, the pharmacologic and potential toxic effects of biologics may differ qualitatively and/or quantitatively from effects seen with small molecular weight drugs, may be more apparent with increasing exposure, may not be identified by routine non-invasive tests

typically used to monitor toxicity in clinical trials (e.g., urinalysis, chemistry profile, or ECG), and may not be readily reversible. The FDA considers all these factors when advising sponsors about the design of their non-clinical safety programs for oncology drugs and biologics. The Agency believes an individualized, science-based approach to non-clinical testing requirements across different product classes of anti-tumor therapies is appropriate.

Meeting Questions:

FDA seeks the Committee's advice regarding approaches to non-clinical safety data that will facilitate development of drugs and biological products for the treatment of cancer while safeguarding patient safety.

1. For most drug development programs, FDA recommends that the duration of non-clinical studies match the duration proposed for the clinic, an approach supported by the ICH M3 Guidance document. However, an abbreviated duration of non-clinical testing is generally acceptable for small molecule drugs under development as anti-tumor therapies. An abbreviated dosing duration has also been proposed for selected biological products intended as anti-tumor treatments. Please discuss scenarios where the duration of non-clinical studies:

   a. may be abbreviated relative to the clinical duration.
   b. should match the duration of the proposed clinical study.

   In your response, please address the anticipated non-clinical parameters (*e.g.*, PK/PD, toxicity profiles) that should be considered in determining the minimum duration of toxicity testing.

   The FDA noted that a non-clinical study of three month duration will generally suffice to support the clinical dosing of biologic products with long half-lives for an unrestricted period of time. Before initiation of a clinical study with such a biologic, FDA requests that animal studies be conducted based on the proposed duration of clinical dosing (1:1 dosing); FDA feels that animal studies are relevant and show sufficient predictability in terms of toxicity and dose determination. The committee felt that it was important to characterize risks to subjects and was divided in their advice regarding the timing of studies of longer duration.. Some members felt it would be advantageous to abbreviate the non-clinical trials in order to reduce costs and expedite the time to initiation of clinical trials; however, the majority of the committee felt that this should be addressed on a case by case basis and agreed that for some products, initial clinical studies will require a longer duration of non-clinical studies, given the potential for cumulative toxicity and long exposures..

   The question was revised by the panel to state, "should the agency require 3 month toxicology data to be available before a patient is placed on a Phase I/II trial?" An informal vote was taken on this question. The consensus of the committee was that 3 month toxicology studies should not be required before a patient is begun on the trial. Some members felt strongly that 3-month non-clinical studies should be ongoing and

conducted in parallel with the clinical trial while others felt such studies could be performed later, if at all.

2. The FDA has received applications that do not provide adequate non-clinical data to support continuation of dosing for an extended duration in a phase 1 clinical study. Please discuss the following:

   a. In what clinical setting and/or patient population (*e.g.*, refractory disease, indolent disease status, no prior treatments) would the risk of continued treatment in the absence of long-term non-clinical safety data be considered acceptable?

      The committee felt patients should be discontinued from study in the event of unacceptable toxicities or progressive disease. However, the concern is for patients who fall into the category of either not meeting the criteria for objective tumor response (partial or complete response) but also not meeting the criteria for progressive disease, thus pursuing the study without clinical evidence that the patient is deriving benefit, compounded with the issue of unknown toxicities to that patient. The committee felt that, in this scenario, patients and their clinicians should determine whether treatment should make their own determination regarding the benefits of continued dosing in the face of the unknown risks.

   b. Where extended non-clinical safety data are unavailable for long-acting biologic therapeutics (e.g., monoclonal antibodies), FDA believes that continued dosing in the phase 1 study is appropriate only in patients who have demonstrated an acceptable benefit:risk (*e.g.*, objective tumor responses or symptomatic improvement). Should extended non-clinical testing be available prior to allowing continued dosing in patients who have not had clear evidence of benefit? Please discuss the following scenarios: the patient with stable disease, the patient with progressive disease. [Voting]

      The committee discussed, at length, the clinical value of stable disease in the context of end-stage cancer as opposed to patients with better prognoses. The committee felt overall that the clinician and patient should discuss the patient's condition, treatment side effects, and available options, in making a decision as to whether the patient should continue dosing.

      The committee suggested that if a patient is allowed to continue dosing, the study should be designed to show that the drug is active in that patient or having some pharmacologic effect, such as that the target is being reached, or at least having an impact on the disease's biology itself.

   c. How should patients who continue dosing in the absence of supporting non-clinical data be informed of the limitations of the non-clinical data and potential risks? Should they sign a new consent form, and if so, what should be conveyed (*e.g.*, the lack of information about cumulative/delayed onset toxicity, the lack of information on how best to monitor patients, the potential for irreversible toxicity)? What additional information should the sponsor obtain during the clinical study to minimize the risks to the study subjects in the absence of supporting non-clinical safety data (e.g., interim reports of ongoing non-clinical studies)?

Data was not presented as to how common this issue (i.e., patients continuing on study for more than 1-3 months) actually is. The committee agreed that patients who enter phase 1 studies should be informed of the potential risks, however, given that the committee assumed that patients in phase 1 studies come off study in 2-4 months, due either to toxicity or progressive disease, short term non-clinical studies may be sufficient. The committee noted that an informed consent for Phase 1 studies should note that the goals are scientific not patient treatment and that the long term effects are, in fact, not known. In addition, the committee noted that obtaining a new consent form after initiation of the study would be burdensome for the investigators, so incorporating this information into the original consent form was a more appealing alternative than re-consenting study subjects.

The session adjourned at approximately 12:00 noon.

The meeting of the Oncologic Drugs Advisory Committee was held in the Ballrooms at the Gaithersburg Hilton, 920 Perry Parkway, Gaithersburg, MD. The afternoon session began at approximately 1:00 p.m. Approximately 150 people were in attendance. The meeting was chaired by Silvana Martino, D.O.

The Committee was convened to discuss new drug application (NDA) 20-509, S-039, Gemzar (gemcitabine hydrochloride) for injection, Eli Lilly and Company, proposed indication for use in combination with carboplatin for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.

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Attendance:

Oncologic Drugs Advisory Committee Members Present (voting):
Bruce Cheson, M.D., David Harrington, Ph.D., Pamela Haylock, RN, Maha Hussain, M.D., Silvana Martino, D.O.(Chair), Joanne Mortimer, M.D., Michael Perry, M.D., Gregory Reaman, M.D., Maria Rodriguez, M.D.

Oncologic Drugs Advisory Committee Consultants (voting):
Ralph D'Agostino, Ph.D., Harry Long, M.D., Stacy Nerenstone, M.D., Martha Solanche, M.D.,

FDA Participants:
Richard Pazdur, M.D., Robert Justice, M.D., John R. Johnson, M.D., Martin Cohen, M.D. .

Committee Members Absent:
Ronald Bukowski, M.D. James Doroshow, M.D., Joanne Mortmer, M.D.

Open Public Hearing Participants:
Selma Schimmel, Founder and CEO, Vital Options
The Wellness Foundation
George Ashkar, Ph.D.

The agenda proceeded as follows:

Opening Remarks	Richard Pazdur, M.D., Director Office of Oncology Drug Products, FDA
Sponsor Presentation	**Eli Lilly & Co.**
Introduction and Objectives	Richard Gaynor, M.D. Vice President, Oncology Lilly Research Laboratories
Manangement of Ovarian Cancer	Robert Ozols, M.D., Ph.D. Sr. Vice President, Medical Science Fox Chase Cancer Center
Efficacy of Gemzar/Carboplatin combination	Allen Melemed, M.D. Associate Medical Director, Oncology Eli Lilly and Company
Robustness of Efficacy Results	Daniel Sargent, Ph.D. Director, Cancer Center Statistics Mayo Clinic
Safety Results and Patient Benefit	Richard Gralla, M.D. President, Multinational Association of Supportive Care in Cancer Director, IASLC
Risk/Benefit Overview and Conclusion	Tate Thigpen, M.D. Professor of Medicine University of Missippi School of Medicine
FDA Presentation Gemzar Review	**Martin Cohen, M.D.** Medical Officer, OODP, CDER, FDA & **John R. Johnson, M.D.** Medical Officer OODP/CDER/FDA
The Role of Covariates in Clinical Trials	**Ralph D'Agostino, Sr., Ph.D.** Boston University Boston, MA

Break

Open Public Hearing

Questions to the Committee and Committee Discussion

Background

Gemzar was studied in a randomized Phase 3 study of 356 patients with advanced ovarian cancer that had relapsed at least 6 months after first-line platinum-based therapy. Patients were randomized 1:1 to receive either Gemzar in combination with carboplatin (GC) or carboplatin (C) alone. The Gemzar/carboplatin combination improved progression-free survival (HR 0.72, p=0.0038, median 8.6 months for GC and 5.8 months for C) with no apparent effect on survival (HR 0.98, p=0.898) at a cost of increased toxicity, mainly anemia, neutropenia and thrombocytopenia, requiring increased RBC and platelet transfusions and increased use of granulocyte stimulating factors and erythropoietic agents. Independently assessed tumor response rates were Gemzar/carboplatin 46.3% and carboplatin alone 35.6%.

The main issue is whether this improvement in progression-free survival (PFS) without a demonstrated survival advantage and with the toxicity described above is sufficient basis for approval of this supplemental NDA. An important consideration is that the combination of paclitaxel and carboplatin has been shown in a randomized controlled trial (RCT) to prolong survival in this setting. In addition there is strong suggestive evidence from a RCT that liposomal doxorubicin prolongs survival in this population.

Questions to the Committee

1. Does the committee agree that there are chemotherapy regimens that have been shown in randomized controlled trials (RCTs) to prolong survival in the patient population for the proposed indication, i.e. patients with advanced ovarian cancer that has relapsed 6 months or more after completion of platinum-based chemotherapy?

   Outside of a clinical trial, the committee agreed that the primary drug for treatment in this group of patients is carboplatin. The panel noted that there are 6-8 agents that show activity in this disease and will give the patient 2-3 months of survival with each drug. However, toxicities such as neuropathy is considered to be a serious side effect. Considering this adverse reaction, the consensus for treatment was to provide consecutive single agent as opposed to combination therapy..

2. If given after progression, subsequent chemotherapy or cross-over may confound survival analyses and may obscure the demonstration of a survival improvement. Are there chemotherapy regimens that have been shown in RCTs to prolong survival if given after progression in the same patient population as in the Gemzar RCT?

   The committee felt that with no survival advantage seen, single agents used sequentially was the preferred treatment as opposed to combination therapy because it is more toxic.

3. In the Gemzar RCT, PFS was improved in the combination group without an apparent survival improvement (HR 0.72, median 8.6 months for GC and 5.8 months for C, LR p=0.0039). However, there was no apparent effect on survival (HR=0.98, p=0.898, medians 17.97 months for GC and 17.31 months for C). Eighty percent of the survival events have occurred.

   Is the demonstrated increase in PFS without an effect on survival and with the observed toxicity a sufficient basis for regular approval of Gemzar in combination with carboplatin

for treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy?

Given discussions of the committee regarding PFS over OS in this setting for approval, the committee felt that the sponsor was not able to provide evidence of OS. A vote was taken to give the product full approval. The results are as follows:

Yes – 2 ***No – 9*** ***Abstain - 1***

The meeting adjourned at approximately 4:30 p.m.