Summary Minutes of the
Oncologic Drugs Advisory Committee
December 16, 2008
Location: Hilton Washington DC North/Gaithersburg, The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the December 16, 2008 Meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on _December 31, 2008_____.

I certify that I attended the December 16, 2008 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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Nicole Vesely, Pharm.D.	Janice Dutcher, M.D.
Designated Federal Official, ODAC	Acting Committee Chair

The Oncologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 16, 2008 at the Hilton Washington DC North/Gaithersburg, The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsors. The meeting was called to order by Janice Dutcher, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Nicole Vesely, Pharm.D. (Designated Federal Official). There were approximately 225 persons in attendance. There were three speakers for the Open Public Hearing session.

Issue: The committee will discuss biologics license application (BLA) 125084, trade name ERBITUX (cetuximab), ImClone Systems, Incorporated, and BLA 125147, trade name VECTIBIX (panitumumab), Amgen, Incorporated, in the context of K-ras as a predictive and/or prognostic biomarker in oncology drug development.

Attendance:

Oncologic Drugs Advisory Committee Members Present (Voting):
Jean Grem, M.D., David Harrington, Ph.D., Michael Link, M.D., Gary Lyman, M.D., M.P.H., Virginia Mason, R.N., Ronald Richardson, M.D., Wyndham Wilson, M.D.

Oncologic Drugs Advisory Committee Member Present (Non-Voting)
Gregory Curt, M.D. (Industry Representative)

Special Government Employee Consultants (Temporary Voting Members):
Ralph D'Agostino, Ph.D., Jo-Ellen De Luca, Janice Dutcher, M.D. (Acting Chair), William Funkhouser, M.D., Ph.D., Joanne Mortimer, M.D., George Netto, M.D., Ronald Przygodzki, M.D., Derek Raghavan, M.D., Ph.D., Richard Simon, D.Sc., Xiao-Hua Andrew Zhou, Ph.D.

Oncologic Drugs Advisory Committee Members Not Present:
S. Gail Eckhardt, M.D.
Margaret Tempero, M.D.

FDA Participants (Non-Voting):
Richard Pazdur, M.D., Patricia Keegan, M.D., Robert O'Neill, Ph.D., Ruthann Giusti, M.D., Robert Becker, M.D., Ph.D.

Designated Federal Official:
Nicole Vesely, Pharm.D.

Open Public Hearing Speakers:

Robert Erwin
Carlea Bauman
David Apelian, M.D., Ph.D., M.B.A.

The agenda was as follows:

Call to Order and Introductions	**Janice Dutcher, M.D.** Acting Committee Chair Oncologic Drugs Advisory Committee
Conflict of Interest Statement	**Nicole Vesely, Pharm.D.**

	Designated Federal Official
Opening Remarks	**Richard Pazdur, M.D.** Director, Office of Oncology Drug Products (OODP), Office of New Drugs (OND), CDER, FDA

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FDA Presentation	**Ruthann Giusti, M.D.** Medical Officer, Division of Biologic Oncology Products, OODP, OND, CDER, FDA
Sponsor Presentation Role of K-ras Mutation Status In Optimizing Selection of Colorectal Cancer Patients for Treatment with Erbitux® (Cetuximab)	**ImClone Systems Inc.** **Hagop Youssoufian, M.D.** Senior Vice President, Clinical Research and Development ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company
Sponsor Presentation Introduction and Overview	**Amgen, Inc.** **Paul Eisenberg, M.D., MPH**, Senior Vice President, Global Regulatory Affairs & Safety, Amgen Inc.
KRAS as a Predictive Biomarker for Vectibix®(panitumumab) Monotherapy	**David Reese, M.D.,** Executive Director, Global Clinical Development, Amgen Inc.
FDA Presentation Prospective vs. Non-Prospective Design in Companion Drug/Diagnostic Studies	**Robert Becker, Jr., M.D., Ph.D.** Chief Medical Officer, Office of In Vitro Diagnostics (OIVD), CDRH
Some Considerations for Statistical Design, Analysis, and Interpretation for Biomarker Classifier Based Clinical Trials in Establishing Efficacy in Support of Regulatory Marketing and Promotional Claims	**Robert O'Neill, Ph.D.** Director, Office of Biostatistics (OB), Office of Translational Sciences (OTS), CDER, FDA
Questions to the Presenters	
Open Public Hearing	
Questions to ODAC and ODAC Discussion	
Adjourn	

Questions to the Committee:

Today's discussion focuses on the type and amount of data needed to support product labeling using biomarkers. In the following discussions, we are assuming that prospective studies intended to establish the clinical usefulness of the biomarker have not been performed and that decisions are being requested that require a retrospective analysis of a completed, or on-going, clinical trial(s). For the following series of questions, assume that appropriate tumor sample acquisition and handling procedures were used, the assay for the biomarker has acceptable analytical validation, and clinical data would be obtained from randomized, controlled clinical trials. This discussion applies to studies which met the pre-specified primary study endpoints and would not be intended as a mechanism to salvage failed trials.

Topic 5: (Zhou & Przygodzki) –WAS ADDRESSED AS FIRST QUESTION POSED TO COMMITTEE
Please discuss the importance of timing and rigor in determining the analytic performance of the companion diagnostic test.

- *Committee members agreed that it was ideal to have an analytically validated test prior to starting a study, however it was also noted that this is very often not the case.*

- *A few committee members mentioned that tissue sample ascertainment should be 100%, however many other members noted that this was impractical.*

- *Overall, committee members agreed that steps should be taken for sponsors to hold/store all samples from studies.*

Please see the transcript for detailed discussion.

Topic 1: (D'Agostino & Lyman)

When would it be appropriate to limit use of a drug to a subgroup based on retrospective analysis of one or more studies that were not designed to examine this subgroup? In your response, please discuss the factors to be considered, including:

- Claims to be made: efficacy vs. safety (differences in risk:benefit) for the drug
- Claims to be made for effectiveness and safety of the companion diagnostic test
- Number of studies (replication of finding)
- The proportion of the intent-to-treat entire population in which biomarker results are available. What fraction of missing biomarker data in this entire population would preclude a decision regarding effects in a subgroup?

- *It was noted that the retrospective analyses should be hypotheses driven with defined statistical plans prior to blinding the outcome of the study, detailing adequate sample size required in the subgroups, adequate power to test the hypothesis,and planned adjustments for multiplicity.*

- *It was mentioned that having a convenience sample may be problematic and the goal should be to ascertain 100% of baseline tissue samples. One committee member noted that ascertainment of samples is important, however since it is unlikely to have full ascertainment, it is best to determine how the samples that are available were ascertained.*

- *It was noted to look at consistency across subgroups in the analysis as this is important.*

- *One committee member mentioned that two prospective-retrospective studies would need to be done and be adequately powered within the subgroups.*

- *Another committee member noted that the studies must be focused, use a validated analytical test and have an ample number of patients.*

- *One committee member noted that K-ras is a very important topic to patients and it is important to keep patient's samples and determine how many samples would be needed for the future.*

Please see the transcript for detailed discussion.

Topic 2: (Harrington & Richardson)
When would a prospective study, designed for the purpose of examining treatment effects on a pre-specified subgroup, be needed to establish treatment effects in this group?

- *It was noted that ascertainment is important in all clinical trials and that data should be accessible for those trials that show negative results or do not meet their primary endpoint as much of this information does not reach peer-reviewed publications.*

- *Committee members agreed that data should be available from trials that don't meet their primary endpoint.*

- *Some committee members agreed with the prior statement that two prospective-retrospective studies would need to be completed.*

- *Members disagreed as to whether it was possible to have 100% ascertainment of tissue samples with one member noting that this may not be as practical in the community setting. Members also felt that the more tissue ascertainment, the greater the validity of the study.*

- *A few members noted that having repeated results in multiple studies was necessary.*

- *It was noted by one member that ascertainment would not introduce bias as long as the tissue samples are representative of the patients in the study. It was also repeated that it is important to know the details of the ascertainment and how the samples that were collected were ascertained.*

- *Committee members disagreed on the importance of discordance between PFS and OS with a few commenting that study design may be a reason for the discordance.*

- *Several members noted example cases when a prospective study would be needed to establish treatment effects in this group including: 1) instances where science has changed substantially and the intermediate end point has changed and 2) instances where important endpoints were contradictory.*

Please see the transcript for detailed discussion.

Topic 3: (Harrington & Raghavan)
Discuss the properties of clinical studies, originally designed for non-selected populations, that would make such studies unsuitable for demonstrating efficacy in a biomarker subgroup. Discuss in your answer potential problems associated with the failure to perform stratified randomization based on biomarker status, failure to pre-specify statistical adjustments for multiplicity, and incomplete ascertainment of biomarker ("convenience sampling").

- *It was noted that FDA should propose guidelines when the Critical Pathway does not apply.*

- *Committee members re-emphasized their responses to previous questions noting that adequate power would be needed in the study as well as a sample size large enough to detect a statistical difference.*

Please see the transcript for detailed discussion.

Topic 4: (Simon & Grem)
When is it acceptable to limit future enrollment to a biomarker selected subset of an actively accruing clinical trial based on external information (e.g., results from another study)? What would be the primary analysis population? Would the answer depend on the proportion of unselected patients, i.e., those enrolled prior to the study modification?

- *Committee members agreed that there is no simple answer to this question.*

- *Committee members noted that changing the study endpoints mid-stream may pose complications and caution is advised in removing patients in certain settings.*

Please see the transcript for detailed discussion.

The meeting adjourned at approximately 3:30 p.m.