



Waiver to Allow Participation in Food and Drug Administration
Advisory Committee Meeting

DATE: November 14, 2008

TO: Randall W. Lutter, Ph.D.
Deputy Commissioner for Policy
Food and Drug Administration

THROUGH: Vince Tolino _____ /S/
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

Michael F. Ortwerth, Ph.D. _____ /S/
Director, Advisory Committee Oversight and Management Staff
Office of Policy, Planning, and Preparedness

FROM: Igor Cerny, Pharm.D. _____ /S/
Director, Advisors and Consultants Staff
Center for Drug Evaluation and Research

Name of Advisory Committee Member: Jean Grem, M.D.

Committee: Oncologic Drugs Advisory Committee

Meeting Date: December 16, 2008

Description of the Facts on Which the Waiver is Based:

Type, Nature, and Magnitude of Financial Interest(s):

Dr. Jean Grem is an investigator at the Eppley Cancer Center at the University of Nebraska Medical Center (UNMC) for the following cooperative group trials. She does not receive any personal remuneration for her work on these studies. The trials involve Erbitux and/or competing products to Erbitux (cetuximab) and Vectibix (panitumumab), the products to be discussed in the context of the types of studies and data needed to establish K-ras mutational status as predictive of response to drug therapy or as prognostic biomarker in colon cancer.

- Eastern Cooperative Oncology Group (ECOG-E4203) "Phase II Study of Treatment Selection Based Upon Tumor Thymidylate Synthase Expression in Previously Untreated Patients with Metastatic Colorectal Cancer." The drugs under study include oxaliplatin, leucovorin, 5-fluorouracil, bevacizumab, and irinotecan, competing

products to Erbitux (cetuximab) and Vectibix (panitumumab). This study is funded primarily through ECOG, a cooperative research group funded by the National Cancer Institute (NCI) through the cooperative group mechanism. UNMC has a subcontract with [REDACTED] to conduct the laboratory study portion.

- Cancer and Leukemia Group B (CALGB-C80405) "Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with Bevacizumab, or Cetuximab (Erbitux), or with the Combination of Bevacizumab and Cetuximab (Erbitux) for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum." The trial has been temporary suspended.
- ECOG-E5202 "Phase III Randomized Study Comparing 5-FU, Leucovorin and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers."
- ECOG-N0147 "Randomized Phase III trial of Oxaliplatin plus 5-Fluorouracil (5-FU)/Leucovorin With or Without Cetuximab (Erbitux) After Curative Resection for Patients with Stage III Colon Cancer."

The majority of the research expenses for the above studies are paid by the National Cancer Institute through the cooperative group program mechanism. The University receives core support from the Cancer and Leukemia Group B (CALGB) Foundation for general study expenses for all studies the University participates in through CALGB. The Cancer and Leukemia Group B Foundation is a nonprofit, tax-exempt foundation formed for the primary purpose of supporting the clinical trials and laboratory research of the CALGB clinical trials cooperative group.

The magnitude of each financial interest is between \$0-\$50,000.

Description of the Particular Matter to Which the Waiver Applies:

Discussion of Biologics License Application (BLA) 125084, trade name Erbitux (cetuximab), sponsored by ImClone Systems, Inc., and BLA 125147, trade name Vectibix (panitumumab), sponsored by Amgen, Inc., regarding types of studies and data needed to establish K-ras mutational status as predictive of response to drug therapy or as prognostic biomarker in colon cancer.

Additional Facts:

Erbitux (cetuximab) is an Epidermal Growth Factor Receptor (EGFR) inhibitor approved for the treatment of patients who have colorectal cancer that has spread to other parts of the body (1) as a single agent for patients whose disease has progressed after receiving both irinotecan and oxaliplatin for patients who are unable to tolerate chemotherapy with irinotecan; and, (2) in combination with another chemotherapy drug, irinotecan, for patients whose disease has progressed after receiving chemotherapy with irinotecan.

Vectibix (panitumumab) is an EGFR antagonist approved as a single agent for the treatment of metastatic colorectal carcinoma with disease progression on or following

fluoropyrimidine (i.e., capecitabine, floxuridine, or fluorouracil), oxaliplatin (Eloxatin), and irinotecan (Camptosar) chemotherapy regimens.

Recent study data suggest that colorectal cancer patients whose tumors have mutated K-ras genes do not benefit from treatment with EGFR-inhibitors, such as Erbitux (cetuximab) and Vectibix (panitumumab).

Basis for Granting the Waiver:

First, it is important to consider that these ECOG and CALGB trials are federally funded, not industry sponsored. Even if the committee's recommendations and subsequent FDA action with respect to the matter at issue affect pharmaceutical firms that are developing or marketing colon cancer therapies, the funding for the National Cancer Institute (NCI)-sponsored trials likely would not be affected.

Second, it is highly unlikely that the outcome of the matter will directly and predictably affect the NCI-sponsored trials. It is difficult to predict that any action, short of a "clinical hold" determination, would cause NCI to suspend or terminate these studies. The administrative and funding instrument used for NCI's Clinical Trials Cooperative Group Program is the cooperative agreement, an assistance mechanism (rather than an acquisition mechanism). Under a cooperative agreement, NCI works jointly with the cooperative group in a partner role. NCI does not assume direction, primary responsibility or a dominant role in the research conducted. The "Terms and Conditions" of the cooperative agreement define the responsibilities, relationships, and governance of the research to be conducted, as well as the circumstances under which the terms of the cooperative agreement may be modified. Consequently, NCI cannot arbitrarily decide to terminate an agreement based on the outcome of the matter before the committee. Likewise, since the clinical trials cooperative group funding is not typically linked to any specific clinical trial, NCI cannot reduce or increase the funding for a specific study based on the outcome of the matter before the committee.

Third, although the trials involve affected products, the focus of the research is to evaluate the effects of different regimens of chemotherapy to determine the most effective combined therapy approaches in colon cancer treatment. Because colon cancer is usually treated using combined therapy, not a single agent, and no one therapy or treatment regimen is effective for all patients, any decision with respect to the approved products Erbitux (cetuximab) and Vectibix (panitumumab) and the types of studies and data needed to establish K-ras mutational status as predictive of response to therapy or as prognostic biomarker in colon cancer is not likely to affect the ECOG and CALGB trials currently underway.

Moreover, Dr. Grem herself has no personal financial interest in the matter. The fact that these financial interests impute to her from her employer should lessen conflict of interest concerns in light of the essential need for her expertise.

Further, according to the Office of Oncology Drug Products, Dr. Grem's participation is necessary to afford the committee essential expertise. Dr. Grem is a Professor of

Medicine at the University of Nebraska Medical Center (UNMC), Hematology and Oncology Section. She also serves as the Associate Director for Translational Research at the Eppley Cancer Center. Prior to joining the UNMC in 2003, Dr. Grem was the Head of the Gastrointestinal Malignancies Section, Cancer Therapeutics Branch at the National Cancer Institute (NCI) and a Senior Investigator at NCI. Dr. Grem is the Associate Team Leader for the Colorectal Disease Site Team for the American College of Surgeons Commission on Cancer and serves as a Panel Member for the Colon Cancer, Rectal Cancer and Anal Cancer within the National Comprehensive Cancer Network. Dr. Grem has published over 175 journal articles in such journals as *Cancer Research* and the *Journal of Clinical Oncology*.

As co-program leader in the cancer genes and molecular regulation program of the UNMC Eppley Cancer Center, and a co-director of the cancer center's recently-secured Gastrointestinal/Pancreatic Cancer Specialized Program of Research Excellence grant, Dr. Grem is known nationally as an expert in gastrointestinal malignancies. She is currently investigating several novel therapeutic approaches in both colon and pancreatic cancer at UNMC. She is investigating the treatment of cancer tumors at the molecular level and is developing clinical trials that will use a patient's molecular profile to determine the best drug therapy for a particular cancer.

Dr. Grem is one of two recognized experts in colorectal cancer available for participation on the Committee. Five individuals with similar expertise were invited to the meeting and two were recused because of conflicts of interest and two were unable to attend. Inclusion of at least two experts is necessary in order to avoid potential biases that may result in reliance on the advice of a single expert. In addition, she has extensive experience in the practical experience of clinical trial conduct and analysis of study results. Other members of the committee provide expertise in medical oncology, however few have Dr. Grem's extensive experience in the practice of medicine and clinical research.

The Office of Oncology Drug Products feels that it is imperative to have the participation of Dr. Grem for this very important meeting. Her expertise in colorectal cancer and her experience as serving as a consultant for the Oncologic Drugs Advisory Committee during previous meetings discussing the safety and efficacy of new drugs for the treatment of colorectal cancer is essential for committee discussion of the topic. Her knowledge of clinical trial design, as evidenced by more than 110 peer-reviewed articles on clinical trial results brings a wide range of practical knowledge and experience in the clinical practice of medical oncology and the specific expertise in clinical trial methodology. In addition, Dr. Grem brings unique expertise in the area of the treatment of colorectal cancer, as evidenced by her membership on the Gastrointestinal Tumor Committee of the NSABP (1996), in the National Comprehensive Cancer Network, Panel Member for Colon Cancer, Rectal Cancer, and Anal Cancer; (2004-2008), Member, ASCO Program Committee, Gastrointestinal Cancers (200, 2001, 2002, 2006, and 2007), an invitation to serve on the NCI Colorectal Cancer Progress Review Group Roundtable (2000) and her service as Associate Team Leader: Colorectal Disease Site Team for the American College of Surgeons Commission on Cancer (2002-2008).

Accordingly, I recommend that you grant a waiver under 18 U.S.C. § 208(b)(3) to Jean Grem, M.D., a member of the Oncologic Drugs Advisory Committee, from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

The individual may participate – The need for the Special Government Employee's services outweighs the potential for a conflict of interest.

Limitations on the Regular Government Employee or Special Government Employee's Ability to Act:

Non-voting

Other (specify):

Denied – The individual may not participate.

/S/
Randall W. Lutter, Ph.D.
Deputy Commissioner for Policy

11/25/2008
Date