Recommendations of the ECOG Data Monitoring Committee, April 18, 2006

The Data Monitoring Committee (DMC) of the Eastern Cooperative Oncology Group met by conference call on March 21, 2006 and April 18, 2006, and reviewed all ongoing phase III studies coordinated by ECOG. This report is being provided to ECOG investigators and to other participating groups for transmission to their local IRBs.

The DMC review included examination of aggregated adverse event data by treatment arm for each study, consideration of whether studies were making adequate progress towards completion, and, when appropriate, examination of interim outcome results. Results from other studies and other recent literature that might be relevant to the research were also considered. The complete ECOG DMC policy is available at http://www.ecog.org/general/monitoring.html. The adverse event data reviewed by the DMC is summarized in the interim reports contained in the agenda volume for the November 2005 ECOG Group Meeting. Local investigators should make copies of the relevant reports available to their local IRBs. ECOG members can obtain these reports from http://www.ecog.org/agenda. Copies are also provided to the operations offices of other participating groups. If an IRB requires additional information, please contact the ECOG Operations Office at (617) 632-3610.

The DMC accepted the reports on E1302, E1602, E1697, E2496, E2501, E2902, E4201, E4203, E5202, E5204 and E5597 without discussion, recommending that these studies continue without modification. The DMC was also notified that the rate of accrual to E2499 had been less than 20% of the planned rate during the 5th and 6th quarters since reactivating under the modified design, so this study was being closed, as required by the NCI policy on slowly accruing phase III studies. The DMC recommendations on the other studies are listed below.

E1900 - A Phase III Trial in Adult Acute Myeloid Leukemia: Daunorubicin Dose-Intensification and Gemtuzumab-Ozogamicin Consolidation Therapy Prior to Autologous Stem Cell Transplantation. *Study Chair: Dr. Hugo Fernandez. Statistician: Zhuoxin Sun.*

Recommendation: The first interim analysis of disease-free survival (DFS) was reviewed, as was information on toxicity by age. Criteria for early stopping were not met, and the DMC recommended that this study continue. It was noted that a substantial number of patients on arms C and D (the autologous transplant arms) were going off study before receiving transplant therapy, and that most of the patients on arm D (HDAC + Mylotarg + auto transplant) who had not received transplant were also not receiving Mylotarg. No allowance was made for early discontinuation of treatment in the study design, so the primary DFS comparison will be substantially underpowered. The DMC recommended that the Study Chair and the Leukemia Committee leadership be made aware of this issue and that they be required to submit a plan for addressing the problem to the DMC by no later than immediately following the ECOG Group Meeting in June.

E1Z01 - Study of Epoetin Alpha vs. Epoetin Alpha with Dexamethasone in Hormone Refractory Prostate Cancer Patients: Impact on anemia, fatigue, functional status and quality of life. *Study Chair: Dr. Victor Chang. Statistician: Judi Manola.*

Recommendation: This study has been open for more than 22 months and is accruing very slowly (10 entries total). Since this study is not making adequate progress towards completion, and the DMC recommended that it be closed.

E2603 - A Double-Blind, Randomized, Placebo-Controlled Phase III Trial of Carboplatin, Paclitaxel, and BAY 43-9006 versus Carboplatin, Paclitaxel and Placebo in Patients with Unresectable Locally Advanced or Stage IV Melanoma. Study *Chair: Dr. Keith Flaherty. Statistician: Sandra Lee.*

Recommendation: Since carboplatin + paclitaxel is not a standard treatment for melanoma, this protocol included early stopping rules requiring that responses be seen early in the study in both the combined cohort of patients and in the control arm. These stopping rules and the status of the data were reviewed. The responses required to continue with accrual had been confirmed, so the DMC recommended that this study continue as designed.

E3201 - Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-FU and Leucovorin vs Oxaliplatin, Leucovorin and 5-FU vs 5-FU and Leucovorin for Patients with Stage II or III Rectal Cancer. *Study Chair: Dr. Al Benson. Statistician: Paul Catalano***.**

Recommendation: This study was closed because of the need for major design changes with only 7% of its planned enrollment (accrual was also quite slow). In response to a request from ECOG, the DMC recommended that all results from this study be released to the investigators for possible presentation and publication.

E3598 - A Phase III Trial of Carboplatin, Paclitaxel and Thoracic Radiotherapy, with or without Thalidomide, in Patients with Stage III Non-Small Cell Lung Cancer. *Study Chair: Dr. Joan Schiller. Statistician: Sigui Li.*

Recommendation: This study was amended to include low dose aspirin for DVT prophylaxis on the thalidomide arm in January 2005. The DMC reviewed updated information on thrombosis / embolism toxicity broken down by time period. The DMC recommended that this study continue as currently designed. The DMC will review toxicity again at their next meeting.

E3999 - Phase III, Randomized, Placebo-Controlled, Double-Blind Trial of the MDR Modulator, LY335979, During Conventional Induction and Post-Remission Therapy in Patients Greater Than 60 Years of Age with Newly Diagnosed Acute Myeloid Leukemia, Refractory Anemia With Excess Blasts in Transformation or High-Risk Refractory Anemia with Excess Blasts. *Study Chair: Dr. Larry Cripe. Statistician: Haesook Kim.*

Recommendation: The second planned interim analysis of the primary outcome (survival) was discussed. Criteria for early stopping were met, and the DMC recommended that the results be released to the investigators for possible presentation and publication. Follow-up will continue, and an analysis will still be performed at the planned full information for this study.

E4402 - Randomized Phase III Trial Comparing Two Different Rituximab Dosing Regimens for Patients with Low Tumor Burden Indolent non-Hodgkin's Lymphoma. *Study Chair: Dr. Brad Kahl. Statistician: Shuli Li.*

Recommendation: The ECOG Lymphoma Committee proposed a modification to the design to make the primary comparison in the subset of patients with follicular histology, while continuing to enroll patients with other histologic types. This change will require an increase in the accrual goal to ensure a sufficient number of follicular patients to address the primary question. The DMC voted to approve the requested change to the design. The DMC also voted to approve a requested change to the quality of life evaluation.

E4697 - A Randomized Placebo-Controlled Phase III Trial of Yeast Derived GM-CSF vs. Peptide Vaccination vs. GM-CSF Plus Peptide Vaccination vs. Placebo in Patients with "No Evidence of Disease" after Complete Surgical Resection of "Locally Advanced" and/or Stage IV Melanoma. *Study Chair: Dr. David Lawson. Statistician: Sandra Lee.*

Recommendation: The results of the third interim analysis of outcome data were briefly discussed. The DMC recommended that this study continue as planned.

E4A03 - A Randomized Phase III Study of CC-5013 plus Dexamethasone versus CC-5013 plus Low Dose Dexamethasone in Multiple Myeloma with Thalidomide plus Dexamethasone Salvage Therapy for Non-Responders. *Study Chair: Dr. Vincent Rajkumar. Statistician: Susanna Jacobus.*

Recommendation: This study was suspended on September 14, 2005 because of the high rate of thrombosis / embolism toxicity on the high dose dexamethasone arm, and it was reopened on November 23 with an amendment requiring DVT prophylaxis. Updated data on thrombosis / embolism toxicity were reviewed. The DMC recommended that this study continue as currently designed. The DMC will review toxicity again at their next meeting.

E4Z02 – Phase III Randomized Placebo-Controlled Trial to Determine Efficacy of Levocarnitine for Fatigue in Patients with Cancer. *Study Chair: Dr. Ricardo Cruciani. Statistician: Judi Manola.*

Recommendation: This study is accruing extremely well, and the DMC reviewed a proposed expansion of the accrual goal. The DMC voted to approve the requested change to the design.

E6201 - A Phase III, Randomized Study of Gemcitabine (fixed-dose rate infusion) and Oxaliplatin versus Gemcitabine (fixed-dose rate infusion) versus Gemcitabine (30-minute infusion) in Pancreatic Cancer. *Study Chair: Dr. Elizabeth Poplin. Statistician: Donna Levy*

The third interim analysis of outcome data was discussed. The DMC recommended that unblinded interim data be released to the investigators for possible abstract submission.