Recommendations of the ECOG Data Monitoring Committee, March 26 and May 2, 2007

The Data Monitoring Committee (DMC) of the Eastern Cooperative Oncology Group met by conference call on March 26, 2007 to discuss E4A03 and again on May 2, 2007, to review all other 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 E1602, E1697, E2496, E2501, E2603, E2805, E2902, E3805, E4201, E4203, E5202, E5597 and TAILORx (PACCT-1) without discussion, recommending that these studies continue without modification. The DMC recommendations on the other studies are listed below.

E1302 - Phase III randomized, placebo controlled, trial of docetaxel versus docetaxel+ZD1839 in PS2 patients or previously-treated patients with recurrent or metastatic head and neck cancer. *Study Chair: Athanassios Argiris. Statistician: Musie Ghebremichael.*

Recommendation: The second planned interim analysis of survival was presented. Criteria for early stopping were not met, and the DMC recommended that this study continue with accrual and blinded follow up.

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 planned interim analysis of induction response was presented. Criteria for stopping were not met, and the DMC did not recommend action

on the basis of the interim results. (8/0/0) There was also further review of the treatment compliance problems in the maintenance randomization and possible design changes. Because of the compliance issues, the primary DFS endpoint cannot be achieved. The DMC did not find the proposed alternative designs acceptable, and they proposed that this study should therefore be closed. The DMC thought that if the Group/Committee wished to continue with this study, the appropriate course would be for the Group Chair to pursue discussion of possible alternative designs with NCI under the appeal process in the DMC policy.

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: Suzanne Szwarc.

Recommendation: The third planned interim analysis of overall survival, the primary outcome, was reviewed. The results were not promising, and the DMC recommended that this study should be stopped and that the results should be released to the study team for public presentation. The DMC also recommended that thalidomide treatment should be stopped for patients currently continuing on protocol treatment.

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 study team requested that information on induction response and some baseline data be released for analysis of treatment pharmacokinetics. The DMC was concerned that an analysis of the pharmacokinetics on the current data would not be in accordance with the protocol design, and essentially would be an unplanned interim analysis of the pharmacokinetic data. They requested that additional information on the rationale for performing the analysis at this time be provided, and that a statistical adjustment for multiple analyses over time be considered.

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 fourth interim analysis of outcome data were briefly discussed. The DMC recommended that this study continue as planned. The study team requested access to information on the total number of events, distribution of some baseline characteristics, and information on frequency of disease evaluations during long-term follow-up. The DMC recommended releasing this information.

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 discussed only on the March 26 call. Results of the first planned interim analysis were reviewed. The DMC recommended that results of the primary response analysis not be released, since the protocol criteria for this endpoint had not been met. However, it was noted that survival was much better than expected on the low dose dexamethasone arm and appeared to be significantly better than on the standard dose dexamethasone arm. Because of this difference, the DMC recommended that accrual to the DVT prophylaxis substudy should be stopped as soon as possible, that patients currently in the prophylaxis substudy should be notified of the survival differences with the recommendation that there treatment be switched to low dose (or at least that high dose not be continued), and that information on the survival data should be made public as rapidly as possible.

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: The first planned interim analysis of outcome was reviewed. Criteria for early stopping were not met, and the DMC recommended that this study remain blinded until the data are ready for the next planned analysis.

E5204 – Intergroup Randomized Phase III Study of Postoperative Oxaliplatin, 5-Fluorouracil and Leucovorin vs Oxaliplatin, 5-Fluorouracil, Leucovorin and Bevacizumab for Patients with Stage II or III Rectal Cancer Receiving Preoperative Chemoradiation. *Study Chair: Dr. Al Benson. Statistician: Paul Catalano.*

Recommendation: The DMC reviewed the status of this study. Accrual has been much slower than planned. The activities currently under way to promote this study and modify the protocol to try to boost accrual were discussed. The DMC did not recommend any additional action at this time.