Report of the ECOG Data Monitoring Committee Meetings, September 19 and October 17, 2005

The Data Monitoring Committee (DMC) of the Eastern Cooperative Oncology Group (ECOG) met by conference call on September 19 and October 17, 2005, 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 June 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 studies reviewed at this meeting were E1199, E1302, E1602, E1697, E1900, E1D96, E1Z01, E2496, E2499, E2501, E2603, E2902, E3201, E3598, E3999, E4201, E4203, E4402, E4697, E4A03, E5202, E5597, and E6201. Interim analyses of outcome data were conducted on E1199, E2496, E4697, and E6201.

The DMC accepted the reports on E1302, E1602, E2499, E2501, E2603, E2902, E3201, E3999, E4203, E4402, E5202, and E5597 without discussion, recommending that these studies continue without modification. The DMC recommendations on the other studies are listed below.

E1199 – A Phase III Study of Doxorubicin-Cyclophosphamide Therapy Followed by Paclitaxel or Docetaxel Given Weekly or Every 3 Weeks in Patients with Axillary Node-Positive or High Risk Node-Negative Breast Cancer. *Study Chair: Dr. Joseph Sparano. Statistician: Molin Wang.*

Recommendation: The DMC reviewed the results of the 4th planned interim analysis of disease-free survival. The DMC recommended that the results be released to the investigators for possible presentation and publication.

E1697 - A Randomized Study of Four Weeks of High Dose IFN Alpha2b in Stage T3-T4 or N1 (microscopic) Melanoma. *Study Chair: Dr. Sanjiv Agarwala. Statistician: Sandra Lee.*

Recommendation: The DMC reviewed that status of accrual to this study and the progress toward adding EORTC as a participating group. Accrual remains above the level of 160 patients per year set as the minimum for continuing at the last DMC meeting. Progress continues to be made with EORTC, although it is still not clear when they will be able to activate this study. The possibility of a future design change, reflecting changes in the study population due to EORTC participation, was also briefly discussed. The DMC agreed with the plan to wait for data on accrual from EORTC before making any changes in the design, and recommended that this study continue.

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: Toxicities on the autologous transplant arms of this study were reviewed. The DMC recommended that this study continue. The DMC also recommended that the data center review the toxicity data by age (focusing on the 55-60 age group) and report findings at the next DMC meeting.

E1D96 - Phase III Study of Paclitaxel Versus Liposomal Doxorubicin for the Treatment of Advanced AIDS-Associated Kaposi's Sarcoma. *Study Chair: Dr. Jamie Von Roenn. Statistician: Sandra Lee.*

Recommendation: This study closed early due to slow accrual in May 2002 with a total of 89 patients entered. The status of the data was reviewed. The DMC recommended that the data be released to the study committee members for use at their discretion.

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: Victor Chang. Statistician: Sara Eapen.*

Recommendation: This study has been open since June 2004 and accrual has been very slow, with only 8 patients entered as of the DMC meeting. The DMC thought that the amendment simplifying and expanding the eligibility criteria, which was about to activate, might not do much to boost accrual. The DMC recommended that the chairs of both Symptom Management and GU Committees write a letters of commitment indicating their continued support and provide a plan to improve accrual to this study. The letters and plan need to be received within 6 weeks. At that time the DMC will review the plan and vote on whether to continue accrual to this study. The study will continue as planned until that time.

E2496 - Randomized Phase III Trial of ABVD vs. Stanford V +/- Radiation Therapy in Locally Extensive and Advanced Stage Hodgkin's Disease. *Study Chair: Dr. Sandra Horning. Statistician: Shuli Li.*

Recommendation: The results of the first planned interim analysis of outcome were reviewed. The DMC recommended that the interim results not be released and that this study continue as planned.

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: Donna Levy.*

Recommendation: The DMC reviewed thrombosis/embolism toxicity on this study. The DMC recommended that this study continue as planned. The DMC requested that updated information on thrombosis/embolism toxicity be provided to them in 3 months. At that time the DMC will evaluate whether the addition of low dose aspirin (in amendment 6) has adequately reduced the rate of thrombosis/embolism toxicity.

E4201 - A Randomized Phase III Study of Gemcitabine in Combination with Radiation Therapy versus Gemcitabine Alone in Patients with Localized, Unresectable Pancreatic Cancer. *Study Chair: Dr. Patrick Loehrer. Statistician: Donna Levy.*

Recommendation: This study opened in April 2003 and only 71 patients had been entered through the end of September 2005. The accrual rate has shown no improvement since the last DMC meeting, and it remains at about 3 patients / month. The DMC recommended that this study be closed, since it does not appear to be feasible to complete it in a timely manner.

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 second interim analysis of outcome data were briefly discussed. The DMC recommended that this study continue as planned. The DMC also recommended releasing updated analyses on correlative markers to the investigators. These analyses do not involve data on primary outcomes.

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: Emily Blood.*

Recommendation: Accrual to this study was suspended on September 14, 2005 because of concerns about the rate of thrombosis/embolism toxicity. On the September 19 call, the DMC recommended that the protocol be amended to mandate aspirin use, as had been

recommended by the study chair, and that full anticoagulation could also be used at the discretion of the treating physician. The DMC also recommended that accrual should remain suspended until the amended protocol is approved for reactivation. On the October 17 call, the DMC was updated on the thrombosis/embolism toxicity and on the status of the amendment (which was pending review by the Central IRB). The DMC approved a request from the study chair to release information on the rate of thrombosis/embolism in this study for possible presentation (e.g. in a letter to the editor). The DMC noted with concern that a grade 5 event previously listed as grade 5 thrombosis/embolism had had the grade 5 changed to a different toxicity category and that the grade of thrombosis/embolism had been reduced. The DMC recommended that this case, all other grade 5 events and the cases with reported thrombosis/embolism toxicity should be carefully reviewed to ensure proper and complete reporting of the thrombosis/embolism events. For the next DMC meeting, the DMC wants to see a review of thrombosis/embolism events separately by whether patients were receiving aspirin following the amendment requiring aspirin use.

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.*

Recommendation: The results of the second planned interim analysis of survival were reviewed. The DMC recommended that the interim results not be released and that this study continue as planned. The DMC agreed to allow submission of a late breaking abstract for the ASCO 2006 meeting. The DMC also approved the confidential release of the interim results to select members of NCCTG, ECOG and the Intergroup for planning purposes.