NCIC CLINICAL TRIALS GROUP
SPRING MEETING OF PARTICIPANTS

DATA SAFETY MONITORING COMMITTEE
Friday, April 27, 2007

SUMMARY REPORT

NCI US-affiliated trials

Open to accrual

- **MA.17R**
  A double blind re-randomization to letrozole or placebo for women completing five years of adjuvant letrozole in the MA.17 study
  Activation Date: October 14, 2004

  There were no toxicity issues identified. Slow accrual was noted as a continuing problem. Target sample size is 1800 and accrual as of march 31 is 563 patients. The target accrual rate is approximately 39 patients per month; the actual accrual rate is 20 patients per month. However, Amendment #7 expands MA.17R eligibility to include women who have completed five years of adjuvant therapy including any aromatase inhibitor (i.e., letrozole, anastrozole or exemestane) regardless of prior MA.17 involvement or tamoxifen use.

  Recommendation: Continue to review accrual in light of the current amendment.

  Group Director's Response: Recommendation accepted

- **MA.27**
  A randomized phase III trial of exemestane versus anastrozole in postmenopausal women with receptor positive primary breast cancer
  Activation Date: June 2, 2003

  There were no toxicity or accrual issues with this trial.

  Recommendation: No new actions required.

  Group Director's Response: Recommendation accepted

- **MA.27B**
  The influence of five years of adjuvant anastrozole or exemestane on bone mineral density in postmenopausal women with primary breast cancer - a companion study to MA.27
  Activation Date: April 24, 2006

  There were no toxicity or accrual issues with this trial.

Recommendation: No new actions required.

Group Director's Response: Recommendation accepted

Closed to accrual

- **BR.19**
  A phase III prospective randomized double blind placebo controlled trial of the epidermal growth factor receptor antagonist ZD1839 (IRESSA) in completely resected Stage 1B, II, and IIIA non-small cell lung cancer
  Closing Date: April 22, 2005

  Patients were unblinded when the trial was closed. There were no toxicity issues.

  Recommendation: No new actions required.

  Group Director's Response: Recommendation accepted

- **HD.6**
  A phase III study of radiotherapy or ABVD plus radiotherapy versus ABVD alone in the treatment of early stage Hodgkin's disease
  Closing Date: April 05, 2002

  Recommendation: No new actions required.

  Group Director's Response: Recommendation accepted

- **PR.3**
  Intergroup (NCIC CTG, CUOG, SWOG, MRC-UK) phase III randomized trial comparing total androgen blockade versus total androgen blockade plus pelvic irradiation in clinical adenocarcinoma of the prostate
  Closing Date: August 31, 2005

  There were no toxicity or accrual issues with this trial.

  Recommendation: No new actions required.

  Group Director's Response: Recommendation accepted

- **PR.7**
  A phase III randomized trial comparing intermittent versus continuous androgen suppression for patients with Prostate-Specific-Antigen progression in the clinical absence of distant metastases following radiotherapy for prostate cancer
  Closed to accrual: November 30, 2005

  The committee noted that the experimental arm therapy(i.e., intermittent suppression) appears to be associated with fewer toxicities in comparison with the standard arm (i.e., continuous infusion). The DSMC noted that the first interim analysis is scheduled when the trial reaches 400 events, and final

analysis is scheduled for 800 events. The DSMC questioned whether the trial team should be reassessing the time of these analyses.

Dr. Chris O'Callaghan, Project Coordinator for this trial, reported briefly to Committee and indicated that this study was being conducted in an older population of men and so as the population ages, so too would the event rate increase, suggesting that it the time of the interim and final analyses may be sooner than current trends suggest. He also indicated that the trial team was aware of the toxicity profiles and did not consider an alteration of trial conduct to be necessary.

Recommendation: DSMC requests a comment from the trial team:

1. regarding the difference in toxicities between the two arms
2. requesting when the next analysis is to be conducted

Group Director's Response: Recommendation accepted. Based on the data reviewed by the DSMC, the Trial Committee will provide a report to the DSMC regarding toxicities observed.

Non NCI US-affiliated trials

Open to accrual

- **BL.11**
  A phase III study of Iressa® in combination with intravesical BCG versus intravesical BCG alone in high risk superficial transitional cell carcinoma of the bladder
  Activation Date: April 12, 2006

  There were no toxicity issues with this trial. Accrual is slower than expected.

  Recommendation: No new actions required at present but scheduled for review in the Fall.

  Group Director's Response: Recommendation accepted

- **BR.24**
  A phase II/III double blind randomized trial of AZD2171 versus placebo in patients receiving paclitaxel/carboplatin chemotherapy for the treatment of advanced or metastatic non-small cell lung cancer
  Activation Date: September 07, 2005
  AZD2171 is an oral antiangiogenic agent and was tested in the same combination with paclitaxel and carboplatin in a preceding phase I trial by NCIC CTG (IND.171).

  Following brief presentations from Drs. Ralph Meyer, Lesley Seymour and Glen Goss, the DSMC began its discussion by reviewing deaths that have occurred during the conduct of this trial, including deaths while on therapy. The DSMC concluded that no changes in the conduct of the trial are required at this time.

The DSMC considered what next steps should be taken, if any, to ensure the safety of this trial. It noted that following the March, 2007 conference call, the committee recommended the trial team review the consent to ensure the risks were adequately identified and conveyed. The team reported back that the consent had been reviewed and it was felt it adequately addressed the risks of the study. The DSMC also reviewed the consent form and agreed with the trial team.

Recommendation: The DSMC requests continuation of the existing process to review Grade 5 SAEs as each of these SAEs is reported. The Chair will then continue to determine whether further discussion of the DSMC is required.

Group Director's Response: Recommendation accepted. In addition, the Group Director and leaders of the Trial Committee, will work with the DSMC Chair to ensure that the DSMC is receiving any additional information that would assist in monitoring this trial.

- **BR.25**
  A phase II study of hypofractionated 3-dimensional conformal radiotherapy (3DCRT)for inoperable stage I/II non-small cell lung cancer (NSCLC)
  Activation Date: April 26, 2006

  There were no toxicity or accrual issues with this trial.

  Recommendation: No new actions required.

  Group Director's Response: Recommendation accepted

- **HN.4**
  A phase II study of cisplatin and gemcitabine in patients with locally advanced/ recurrent or metastatic malignant salivary gland tumours
  Activation Date: October 23, 2003

  There were no toxicity issues with this trial. Target accrual is ≤34 patients, current accrual is 29 patients. Actual accrual rate is < .4 patients per month.

  Recommendation: Request timelines for completion of accrual from study team.

  Group Director's Response: Recommendation accepted. The Trial Committee will respond to the DSMC Chair reading the rate of anticipated accrual.

- **HN.5**
  A phase I study of adjuvant OSI-774 (Tarceva) in patients following combined chemo-radiotherapy for locally advanced squamous cell carcinoma of the head and neck
  Activation Date: November 5, 2003

Accrual is an issue. Target accrual is ≤20 patients, current accrual is 14 patients. Projected accrual rate was 1-2 patients per month. Actual accrual rate is < .7 patients per month. It was noted that no higher grade toxicities were present and that toxicities are what was expected. There was an analysis of tolerability at the beginning at 100 mg and then moved up to a more standard dose of 150 mg.

Recommendation: Request timelines for completion of accrual from study team. There are no toxicity or safety issues identified. Review in the Fall.

Group Director's Response: Recommendation accepted. The Trial Committee will respond to the DSMC Chair reading the rate of anticipated accrual

- **LY.12**
  A phase III study of gemcitabine, dexamethasone, and cisplatin compared to dexamethasone, cytarabine, and cisplatin plus/minus rituximab as salvage chemotherapy for patients with relapsed or refractory aggressive histology non-hodgkin's lymphoma prior to autologous stem cell transplant and followed by maintenance rituximab versus observation
  Activation Date: August 7, 2003

  There were no toxicity issues identified. Accrual continues to be a problem. Target accrual is 630 patients and as of March 31, 306 patients have been entered. Projected accrual rate was 17.5 patients per month. Actual accrual rate is approximately 7 patients per month.

  Recommendation: Accrual is of concern. The trial is below 50% targeted accrual and the DSMC will consider specific actions in the Fall if there are no signs of improvement.

  Group Director's Response: Recommendation accepted. Based on a protocol-defined accrual target that has now been satisfied, an interim analysis is scheduled for the fall of 2007 and is anticipated to be available for the Fall Meeting of the DSMC. Changes to the conduct of this trial should be evaluated based on these results.

- **LY.13**
  A multi-centre phase II trial investigating the efficacy and tolerability of bortezomib added to cyclophosphamide, vincristine, prednisone and rituximab (BCVP-R) for patients with advanced stage follicular non-hodgkin's lymphoma requiring systemic first-line treatment
  Activation Date: December 14, 2006

  This trial has just opened and has to date no patients have been entered.

  Recommendation: No actions required; review in the Fall.

  Group Director's Response: Recommendation accepted

- **MA.22**
  A phase I/II study of increasing doses of epirubicin and docetaxel plus pegfilgrastim for locally advanced or inflammatory breast cancer
  Activation Date: February 25, 2003

  There were no toxicity or accrual issues were idetified.

  Recommendation: No new actions required; review in the Fall.

  Group Director's Response: Recommendation accepted

- **MAP.3**
  A phase III randomized study of exemestane versus placebo in postmenopausal women at increased risk of developing breast cancer
  Activation Date: February 11, 2004

  There were no toxicity issues identified, and accrual is slow but steady.

  Recommendation: No new actions required; review in the Fall.

  Group Director's Response: Recommendation accepted

- **MY.10**
  A randomized phase III study of thalidomide and prednisone as maintenance therapy following autologous stem cell transplant in patients with multiple myeloma
  Activation Date: September 16, 2002

  There were no toxicity issues identified, but it was noted that accrual was slow. Target accrual is 324 patients and as of March 31, 228 patients have been entered. Projected accrual rate was 7-8 patients per month. Actual accrual rate is approximately 4 patients per month.

  Recommendation: An interim analysis is expected in 9-12 months. Pending the results of this analysis the DSMC may recommend that trial team consider changing the primary outcome of the study from overall survival to progression-free survival and explore inclusion of these results in an individual patient meta-analysis. Review in the Fall.

  Group Director's Response: Recommendation accepted

- **MY.11**
  A randomized phase II dose finding study of lenalidomide and melphalan in patients with previously untreated multiple myeloma
  Activation Date: December 13, 2005

  Study was put on hold upon review of the toxicities until the doses were reevaluated. The trial was reopened less than a year ago. It is too early in the trial to gauge accrual. It was noted that the trial design is complex and the DSMC could not fully evaluate the conduct of the trial with the information

provided. Updated information regarding whether accrual to the run-in phases and /or the randomized phase is required.

Recommendation: From a safety perspective, no concerns. Review with more detail in the Fall. Request updated data regarding the status of the phases of the trial from study team.

Group Director's Response: Recommendation accepted. The Trial Committee will provide a report to the DSMC updating the status of the phases of this trial.

- **SC.20**
  A phase III international randomized trial of single versus multiple fractions for re-irradiation of painful bone metastases
  Activation Date: January 7, 2004

  Toxicity level is acceptable. Accrual issues were initially identified, but appear to have been addressed.

  Recommendation: No new actions required; review in the Fall.

  Group Director's Response: Recommendation accepted

- **SC.20U**
  A phase III study of the effect of re-irradiation for bone pain on urinary markers of osteoclast activity

  Companion study of SC.20. Not an intervention study.

  Recommendation: No new actions required; review in the Fall.

  Group Director's Response: Recommendation accepted

Closed to accrual

- **EN.5**
  A phase III randomized trial comparing TAH BSO versus TAH BSO plus adjuvant pelvic irradiation in intermediate risk, carcinoma of the endometrium
  Closing Date: March 31, 2005

  The primary analysis has been completed and an abstract submitted to ASCO 2007.

  Recommendation: No actions required.

  Group Director's Response: Recommendation accepted

- **MA.14**
  A randomized trial of antiestrogen therapy versus combined antiestrogen and octreotide LAR therapy in the adjuvant treatment of breast cancer in postmenopausal women

Final analysis is expected this summer.
Recommendation: No actions required.

Group Director's Response: Recommendation accepted

- **MA.20**
  A phase III study of regional radiation therapy in early breast cancer
  Closing Date: February 2, 2007

  Closed in February 2007 after reaching target accrual. No toxicity issues.

  Recommendation: No actions required

  Group Director's Response: Recommendation accepted

- **MA.21**
  A phase III adjuvant trial of sequenced EC + filgrastim + epoetin alfa followed by paclitaxel versus sequenced AC followed by paclitaxel versus CEF as therapy for premenopausal women and early postmenopausal women who have had potentially curative surgery for node positive or high risk node negative breast cancer
  Closing Date: April 29, 2005

  Presented in San Antonio December 2006. Only issue is whether there are any late toxicities the DSMC should be aware of.

  Recommendation: Request that trial team report late toxicities to DSMC in the Fall.

  Group Director's Response: Recommendation accepted

- **MAP.1**
  A randomized feasibility study of letrozole in postmenopausal women at increased risk for development of breast cancer as evidenced by high breast density
  Closing Date: June 9, 2006

  Slow accrual led to early closure of this trial. No issues identified.

  Recommendation: No actions required; the DSMC requests an update of the analysis plan.

  Group Director's Response: Recommendation accepted. The Trial Committee will provide an updated analysis plan.

- **MAP.2**
  A randomized study of the effect of exemestane (Aromasin) versus placebo on breast density in postmenopausal women at increased risk for development of breast cancer
  Closing Date: June 9, 2006

  Slow accrual led to early closure of this trial. No issues identified.

Recommendation: No actions required; the DSMC requests an update of the analysis plan.

Group Director's Response: Recommendation accepted. The Trial Committee will provide an updated analysis plan.

- **OV.16**
  A phase III study of cisplatin plus topotecan followed by paciltaxel plus carboplatin versus paclitaxel plus carboplatin as first line chemotherapy in women with newly diagnosed advanced epithelial ovarian cancer
  Closing Date: June 29, 2005

  Primary analysis is planned for summer, 2007. This trial was flagged to the DSMC due to febrile neutropenia and thromboembolic events.

  Recommendation: No actions required.

  Group Director's Response: Recommendation accepted

- **PRP.1**
  A double-blind, placebo-controlled, randomized study of combination vitamin E, selenium and soy protein product in subjects with high grade prostatic intraepithelial neoplasia
  Closing Date: July 23, 2004

  Closed to accrual in July 2004. Study followup continues.

  Recommendation: No actions required.

  Group Director's Response: Recommendation accepted

- **PRP.1B**
  An investigation of molecular and genetic risk factors associated with development of prostate cancer in subjects with high grade prostatic intraepithelial neoplasia treated with placebo or combination vitamin E, selenium and soy protein product
  Activation Date: July 29, 2005

  No issues identified.

  Recommendation: No actions required.

  Group Director's Response: Recommendation accepted