NCIC CLINICAL TRIALS GROUP
FALL MEETING OF COMMITTEES

DATA SAFETY MONITORING COMMITTEE
Saturday, October 20, 2007

SUMMARY REPORT

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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 with this trial but slow accrual continues to be a problem.
  Recommendation: Request more detailed information from the study team regarding local activation of centres and how/if Amendment #7 has affected accrual.

  Director's Response: Recommendation accepted; the Trial Committee will report on current accrual / centre activation status.

- **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 concerns.

  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 concerns.

  Director's Response: Recommendation accepted

PR.11

A phase III study of active surveillance therapy against radical treatment in patients diagnosed with favourable risk prostate cancer (START)
Activation Date: June 15, 2007
There was no data available for this trial since it was recently activated.

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
  There were no toxicity issues.
  Recommendation: No concerns.

  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
  There were no toxicity issues with this trial.
  Recommendation: No concerns.

  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 issues with this trial.
  Recommendation: Based on the toxicity concerns related to PR7, the DSMC suggests that consents be reviewed for all trials employing androgen deprivation therapy to ensure patients are adequately informed of the risks.

  Director's Response: Recommendation accepted

- **PR.7 (Scott)**

  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
  Closing Date: November 30, 2005
  There has been recognition that disparity exists in toxicities between the experimental arm (i.e., intermittent suppression) and the standard arm (i.e., continuous suppression). However, cardiovascular toxicities are known to be related to continuous androgen suppression and that they are fewer among patients whose treatment involves intermittent androgen suppression. In fact, the purpose of the trial is to determine whether the intermittent suppression is

as effective as continuous suppression while keeping the cardiovascular toxicity lower.
Recommendation: DSMC will request that the trial team send a letter to investigators stating that all patients, regardless of which treatment arm they have been assigned, need to be informed of "emerging toxicity information, including cardiovascular events, from androgen deprivation therapy".

Director's Response: Recommendation accepted. The Trial Committee will provide a letter to investigators indicating that patients and Research Ethics Boards be informed of emerging cardiovascular adverse event data. In addition, the Trial Committee will review the current protocol-defined parameters for performing an interim analysis. The DSMC will be informed of the results of this review, and if the review concludes that the statistical plan for conducting interim analyses should be revised, the DSMC will be asked to review and approve this plan.

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: Accrual continues to be a concern.

  Director's Response: Recommendation accepted. The Trial Committee will provide a report to the DSMC for its next meeting that address accrual status.

- **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
  There were no toxicity or accrual issues with this trial.
  Recommendation: Continue to monitor. An event-specified planned interim analysis is expected prior to the 2008 Spring Meeting and will be reviewed by the DSMC when available.

  Director's Response: Recommendation accepted

- **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 concerns.

  Director's Response: Recommendation accepted

- **CE.6**
  A randomized phase III study of temozolomide and short-course radiation versus short-course radiation alone in the treatment of newly diagnosed glioblastoma multiforme in elderly patients
  Activation Date: May 1, 2007
  There was no data available for this trial since it was recently activated.

- **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 although accrual continues to be a problem.
  Recommendation: Allow trial to continue until Spring Meeting.

  Director's Response: Recommendation accepted

- **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.
  Recommendation: Allow trial to continue until Spring Meeting.

  Director's Response: Recommendation accepted

- **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 with this trial although accrual continues to be a problem.
  Recommendation: Accrual remains an issue. The DSMC awaits the interim analysis expected to be available in January 2008.

  Director's Response: Recommendation accepted

- **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
  There are no toxicity concerns, but accrual appears to be getting off to a slow start, which could be related to the rate at which centres are getting locally activated.

Recommendation: No concerns.

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 with this trial.
  Recommendation: No concerns.

  Director's Response: Recommendation accepted

- **MA.29**
  A feasibility study of pre-operative sunitinib (SU11248) with multiple pharmacodynamic endpoints in patients with T1c-T3 operable carcinoma of the breast
  Activation Date: February 25, 2003
  There was no data available for this trial since it was recently activated.

  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 with this trial, and accrual is slow but steady.
  Recommendation: No concerns.

  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 with this trial, but it was noted that accrual was slow.
  Recommendation: Wait for interim analysis which should be available by Spring Meeting.

  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
  No concerns regarding toxicity, but accrual continues to be slow.
  Recommendation: Review in the Spring.

  Director's Response: Recommendation accepted

- **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 and accrual is okay.
  Recommendation: No concerns. Interim analysis should be available at Spring Meeting.

  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 concerns.

  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 DSMC is no longer required to review this trial.

  - **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
    Closing Date: July 21, 2000
    Final analysis is expected this summer.
    Recommendation: No concerns.

    Director's Response: Recommendation accepted

  - **MA.20**
    A phase III study of regional radiation therapy in early breast cancer
    Closing Date: February 2, 2007
    No toxicity concerns.
    Recommendation: No concerns

    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
  Recommendation: No concerns.

  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
  The DSMC is no longer required to review this trial.

  Director's Response: Recommendation accepted

- **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
  The DSMC is no longer required to review this trial.

  Director's Response: Recommendation accepted

- **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
  Recommendation: No concerns.

  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
  A recent publication brought to the attention of Central Office has indicated that selenium supplementation did not seem to prevent type 2 diabetes, and may increase risk for the disease. The trial team notified investigators by way a "Dear Dr." letter in August 2007 instructing them to notify their patients of this and to provide this information to their local REB. In addition, a formal amendment to the protocol related to a follow-up and evaluation process of these patients will be issued shortly.
  Recommendation: DSMC Chair to follow-up with Director.

Director's Response: Recommendation accepted; this trial has completed its protocol–defined follow-up and a final analysis is in preparation. All investigators have received instructions to notify their Research Ethics Boards and their patients about the findings that associate selenium with type 2 diabetes mellitus. The PRP.1 Trial Committee is assessing the feasibility of evaluating glucose levels and / or clinical reports of diabetes mellitus in patients enrolled onto PRP.1; as many patients have completed protocol defined follow-up, the feasibility of these further assessments is under review.

- **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
  Companion study to PRP.1.
  Recommendation: No issues.

  Director's Response: Recommendation accepted