NCIC Clinical Trials Group
Data Safety Monitoring Committee Conference Call
Wednesday October 13, 2004
Summary of the Minutes

BR.20 Safety Analysis Report. This is a randomized Phase II study comparing ZD6474 to placebo in patients with small cell lung cancer who have had either a complete or partial response to initial chemotherapy, with or without radiation. The required sample size is 120 and the safety analysis is being done on the first approximately 45 patients.

There were no significant differences in toxicities between the 2 arms. Information was provided on ECG changes and the DSMC felt they needed cardiology expertise to interpret this data.

Recommendations:

1. **The DSMC felt the toxicity was as expected but needs to be followed closely, particularly the pulmonary toxicity.**
2. **W. Shelley will seek a cardiology opinion on the ECG data and report back to the committee**

OV.16 toxicity. This is a study of cisplatin and topotecan followed by paclitaxel and carboplatin compared to paclitaxel and carboplatin alone in patients with advanced ovarian carcinoma. It was activated in August 2002 with a planned sample size of 800. 640 have been accrued so far. At our last meeting, the DSMC expressed concern about the incidence of febrile neutropenia in the topotecan arm and asked that this be broken down by patient age and performance status and also by the cycle number in which it occurred. This has been done and there is no difference in the incidence of febrile neutropenia by age or performance status. However, there seems to be a higher likelihood in the first and second cycles of chemotherapy in the topotecan arm. There is an 18% incidence of febrile neutropenia with Grade 3 or 4 neutropenia versus a 6% incidence in the paclitaxel and carboplatin arm alone. There were no other significant differences in toxicity. Given the persistent high incidence of this toxicity, particularly in the early part of treatment, the DSMC recommends that prophylactic antibiotics be instituted in this arm of study. The Committee recognizes the lack of high quality evidence supporting the efficacy of prophylactic antibiotic coverage but the Committee members feel there has been a precedent for this in the pilot trial for the MA.5 study where the incidence of febrile neutropenia was also high. With the institution of prophylactic antibiotic coverage, this incidence dropped.

There was also concern about the reliability of reporting of febrile neutropenia. In the MA.21 study, this issue was raised by the physician coordinator and it may also be an issue in this study. The DSMC therefore recommends that accurate reporting be obtained to verify each incidence of febrile neutropenia.

Recommendations:

1. **The DSMC recommends that antibiotic coverage, as is given in the MA.21 study, be instituted in OV.16 on the topotecan arm.**
2. **The DSMC recommends that all the required information needed to confirm a febrile neutropenic episode, as defined in the common toxicity criteria, be obtained so we can be confident that these rates of febrile neutropenia are real.**

SEE NOTE AT END

MA.21. This is a study of adjuvant chemotherapy in early stage breast cancer patients and it compares CEF vs EC plus taxol vs AC plus taxol. Again, the major concern is a high incidence of

febrile neutropenia on CEF (24.3%) and EC-taxol(18.6%), compared to AC-taxol(5%). The physician coordinator has pointed out that the central office is not getting the details of the febrile neutropenic episodes it was getting in the past because a serious adverse event reporting form is no longer required. There is concern that not all of these reported episodes really fulfill the criteria for this toxicity and that the reported incidence rate may be higher than the real incidence. 4.3% of patients have stopped treatment due to toxicity and there has been 1 treatment-related death. The DSMC members were concerned about this high level of febrile neutropenia, particularly on the CEF arm, given that the incidence of febrile neutropenia on the MA.5 study, using the same regimen, was only approximately 8%.

Recommendations:

1. **The DSMC recommends that the central office staff obtain retrospectively the additional information they need on the reported febrile neutropenic cases to confirm that these events do fulfill the toxicity criteria for febrile neutropenia and that this information continues to be collected prospectively so we have an accurate reporting of this toxicity.**
2. **The DSMC requests that this information be forwarded to the Committee as soon as it is available.**
3. **If the incidence is confirmed to be as high as it is in the current report on the CEF arm, the DSMC recommends that interim blood counts be done in the same manner that was done on the MA.5 study and that appropriate dose modifications be made according to these interim counts, again in the same manner that was done on the MA.5 study.**

BR.15. This is a Phase III study in patients with locally advanced, inoperable, Stage III non small cell lung cancer who have been treated with cisplatin, etoposide and radiotherapy with consolidation docetaxel. They are then randomized to ZD1839 or placebo. This is an intergroup study that is being coordinated by SWOG and is being monitored by the SWOG DSMC. The planned sample size is 840 and, as of last April, 405 patients had been enrolled. The NCIC DSMC received reports on 2 deaths reported as being due to pneumonia/pneumonitis, both from the same Canadian centre. Both deaths occurred during the consolidation phase, prior to randomization to the study drug. Both were felt to be due either to their chemotherapy or progressive lung cancer. The NCIC Clinical Trials Group has reported the events to the investigators on this study and to Health Canada. This was also brought to the attention of the SWOG coordinating centre staff who have informed the NCIC Clinical Trials Group that they have not observed a similar trend in the whole study population. The toxicity will be reviewed by the SWOG DSMC at their meeting later in October.

Recommendation:

The NCIC-CTG DSMC members could not comment on this without knowledge of the whole data set. They were reassured that the information had been appropriately conveyed to the investigators, Health Canada, and SWOG and that the SWOG DSMC will be reviewing all of the toxicity data on this study later this month. The NCIC-CTG DSMC did not feel any further action is required

NCIC Celebrex studies-MA.27 and MAP.3. The NCIC Clinical Trials Group has 2 studies involving Celebrex. The first is MA.27 which is a 4-arm study in postmenopausal women with early stage breast cancer. It compares exemestane versus anastrozole for 5 years and Celebrex versus placebo for 3 years. The planned sample size is 6,830 and 1,094 patients have been enrolled thus far. The second study is MAP.3 which is a 3-arm randomized trial of exemestane alone, exemestane plus Celebrex, or placebo in women who are felt to be at increased risk of developing breast cancer. This is a prevention study that was activated in February 2004. It has a planned sample size of 5,100 and there have only been a few patients enrolled thus far.

The concern about these studies relates to the recent removal of Vioxx from the market, because of an observed increase in serious cardiovascular events in a randomized trial of Vioxx versus placebo as a preventative for the recurrence of colonic adenomatous polyps. The results have not yet been published but the information was made public when the drug was withdrawn. This study involves 2,600 patients and it was started in 2000. The difference in incidence of cardiovascular events did not become apparent until patients had been on the drug for 12-18 months.

Papers reporting the association of cardiovascular toxicity and Cox-2 inhibitors were distributed to the DSMC members by the NCIC Clinical Trials office prior to the call and they were reviewed.

The MA 27 toxicity data was reviewed. At this time, there is no difference in the incidence of cardiovascular toxicity between the Celebrex and placebo arms.

Based on all of this information, the DSMC members felt that both studies should continue. The Committee felt that the consent forms need to be modified to inform people about the results of the Vioxx study and to reassure them regarding the results we have about the lack of association of Celebrex with cardiovascular toxicity thus far. The consent form should state that the studies will be monitored very closely by the DSMC in terms of this toxicity, and that patients and investigators will be informed promptly if any significant difference is observed. The consent form should also state that other Celebrex studies are ongoing and are also being closely monitored. The Committee recommends that a letter giving the same information be forwarded to patients already enrolled on the studies. The Committee supports the idea of sharing toxicity data with other cooperative groups. The committee also recommends that patients with a prior history of cardiovascular disease be excluded from both studies and those who are already enrolled who had a prior history of cardiovascular disease should be taken off either the Celebrex or the placebo and informed of the reason why. The DSMC Committee members recognized there was no evidence suggesting that those with a history of cardiovascular disease would be at higher risk of subsequent events with Celebrex but, on one of the Vioxx studies, there did seem to be a higher event rate on those with a history. The DSMC therefore thought that, despite the fact that there was no evidence regarding Celebrex, it would be best to be overly cautious in this regard.

Recommendations:

1. **The MA.27 and MAP.3 studies should continue.**
2. **The consent form needs to be modified as stated above.**
3. **A letter to patients already enrolled on the study should be sent detailing the same information as is in the consent form.**
4. **Sharing of toxicity data with other groups conducting Celebrex studies should be encouraged.**
5. **Patients with a prior history of cardiovascular disease should be excluded from both studies and any patients already enrolled on the studies with a prior history of cardiovascular disease should be removed from the Celebrex/placebo part of the study with an explanation as to why this is being done.**
6. **The comparison of cardiovascular toxicity on the Celebrex versus placebo part of both studies should be a clear objective of these studies and the Trial Committee should ensure that they collect all of the baseline information they need regarding cardiovascular history, as well as ensuring prospectively that all information needed**

to document cardiovascular toxicity is also recorded. Some expertise from a cardiovascular expert might be appropriate.

7. **Subsequent to the meeting of the DSMC, NCI US issued a statement for investigators in trials involving celecoxib. This statement contained many of the recommendations made by the DSMC and outlined the steps that will be taken to review and monitor data on cardiovascular toxicity from ongoing trials. This letter was reviewed by the DSMC chair who agreed its distribution to MA27 and MAP3 investigators would meet the objectives of the recommendations above. Since the NCI statement did not suggest the exclusion of patients with cardiovascular disease from ongoing trials, it was also agreed that the decision whether to implement this exclusion should await the results of the reviews described in the NCI statement.**

Remaining Phase III Studies.

Study	Accrual	Toxicity
BR.19	Good	Acceptable
CL.2	Complete	Acceptable
EN.5	Acceptable	Acceptable
HD.6	Complete	Acceptable
HN.3	Acceptable	Acceptable
HN.4	Good	Acceptable
HN.5	Slow	Acceptable
LY.12	Acceptable	Acceptable
MA.12	Complete	Acceptable
MA.14	Complete	Acceptable
MA.20	Acceptable	Acceptable
MA.22	Acceptable	Acceptable
MAP.1	Acceptable	Acceptable
MAP.2	Acceptable	Acceptable
MY.10	Acceptable	Acceptable
PR.3	Acceptable	Acceptable
PR.7	Good	Acceptable
PRP.1	Good	Acceptable – no change to consent required
SC.20	Acceptable	Too early for data
CO.17	Good	Data forthcoming in near future

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W. Shelley, MD, FRCPC
Chair

NOTE – The NCIC CTG process is for recommendations of the DSMC to be reviewed by the Group Executive before implementation. In the case of OV16, the Executive decided that accurate data on the frequency of febrile neutropenia should be obtained prior to implementation of a protocol amendment requiring the use of prophylactic antibiotics.