



A PUBLICATION FOR MEMBERS OF THE NORTH CENTRAL CANCER TREATMENT GROUP

Group Chair Message



Jan C. Buckner, M.D.

I want to thank all those throughout the North Central Cancer Treatment Group (NCCTG) who played a role in the recent grant renewal efforts. Thank you to all personnel at the research base and those leaders from the NCCTG member sites who assisted in the preparation of the grant application and site visits.

Both the NCCTG Statistics and Data Center site visit and NCCTG site visit went well. The group received better review scores than those for the previous grant renewals three and six years ago, respectively. The review committee recommended funding for six more years. This achievement reflects the extensive efforts put forward by all involved to present NCCTG's current activities and future initiatives.

These accomplishments serve as encouragement to continue our efforts in developing and conducting high-quality clinical trials to improve cancer treatment. As we move forward, we want to reach new goals in our research, which include:

- Reduce the time for protocol development so that new trials can be initiated more quickly
- Establish an imaging initiative within NCCTG to incorporate imaging into current and upcoming clinical trials
- Develop enhanced informatics support for the NCCTG Biospecimen Resource

NCCTG member site participation will be essential to attain these goals. As software for both the imaging initiative and the management of biospecimens is made available, it is important for each member site to learn about the new programs, train personnel how to use the software and then implement these systems as part of routine activities with clinical trials. Personnel at Mayo Clinic in Rochester, Minn., the NCCTG research base, are ready to assist member sites in implementing each step of these new programs. By adapting these changes, we will improve the efficiency of clinical trials administration and the quality of our research.

As always, the efforts of our member sites in recruiting and enrolling patients in clinical trials are crucial for our continued success in finding new treatments for cancer. At our recent site visit in Washington, D.C., NCCTG was complimented on the way that community physicians are integrated into every facet of our organization. We value this partnership and appreciate your continued efforts.

Jan C. Buckner, M.D.
NCCTG Group Chair

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American Society of Clinical Oncology (ASCO) meeting highlights

The following section highlights several North Central Cancer Treatment Group (NCCTG) studies presented at the 2006 ASCO meeting. These studies illustrate the diverse research activities within the NCCTG disease programs. A complete list of NCCTG abstracts from the 2006 ASCO meeting begins on page 12.

Study evaluates effectiveness of testosterone cream in female cancer survivors with decreased libido



Debra L. Barton, Ph.D.

NCCTG researchers developed clinical trial N02C3, a randomized, placebo-controlled, crossover design trial, to evaluate the effectiveness of testosterone cream in enhancing sexual desire in women with a history of cancer who were bothered by a decrease in their libido.

The study randomized women to four weeks of testosterone cream versus a placebo cream and then crossed participants over to the opposite treatment for four weeks.

Study objectives included:

- Evaluate the efficacy of transdermal testosterone therapy for decreased libido in female cancer survivors and examine the toxicity associated with this therapy
- Examine the effects of the testosterone on serum concentrations of estrogen, testosterone and liver function
- Measure the effect of testosterone on mood, energy, and overall sexual health

Participants receiving both therapies reported an improvement in libido during both study periods. However, there were no statistically significant differences between the placebo and testosterone treatment during either period or in the crossover analysis.

Study results differed from previous placebo-controlled trials. "These results were different due to the fact that the women who participated in N02C3 were estrogen depleted and, to date, all previous studies were done with women who had

normal estrogen levels and were premenopausal or who had received supplemented estrogen," says Debra L. Barton, Ph.D., a researcher at Mayo Clinic in Rochester, Minn., and lead investigator on the study. "In looking at the clinical significance of the positive studies, the effects were mild at best. It appears that androgens, in and of themselves, are not enough to significantly impact libido."

Researchers believe a testosterone patch for women may be approved in the near future, and therefore, it was important to test this intervention method in cancer survivors. "Future studies evaluating interventions for sexual health, particularly for women, need to be tested specifically in populations of women who are estrogen deficient, as the ability to effect positive change may well be affected by the general hormonal milieu," says Dr. Barton.

NCCTG researchers plan to examine alternative treatments in future studies. In particular, methods involving nonhormonal pathways such as dopamine, melanocortin and nitric oxide for sexual health will be evaluated.

Results good for HER-2 positive breast cancer patients using trastuzumab with post-chemotherapy radiation



Michele Halyard, M.D.

NCCTG researchers have shown that patients who receive trastuzumab at the same time as post-chemotherapy radiation treatments for HER-2 positive breast cancer have no more risk for major side effects or complications than those who do not receive the drug.

The study resulted from NCCTG clinical trial N9831, from which breakthrough treatment findings were presented at the 2005 ASCO meeting. "The original N9831 study showed that trastuzumab reduced the recurrence of HER-2 positive breast cancer about 50 percent," says Michele Halyard, M.D., a radiation oncologist at Mayo Clinic Arizona and lead author



of the study. “We hoped also to show that trastuzumab did not add complications to radiation treatment, and the current study has certainly proven that, providing good news for many women.”

About 25 to 30 percent of breast cancers produce an overabundance of a growth-promoting protein called human epidermal growth factor receptor (HER-2). These tumors tend to grow faster and are generally more likely to recur than tumors that do not overproduce HER-2. Trastuzumab is the first identified monoclonal antibody designed specifically to attack this over-expressed protein, and is used as a follow-on treatment to chemotherapy.

Dr. Halyard’s study looked at the side effects related to adding trastuzumab to radiation therapy. In the 1,460 patients who received radiation in the original N9831 group, there was no significant difference in the incidence of skin reactions, pneumonitis, dyspnea, cough, esophageal dysphagia or neutropenia between those who received trastuzumab and those who did not. In addition, researchers found that within the group of 1,286 patients who received trastuzumab, those who had radiation were no more likely to have cardiac complications than those who did not.

Genetic testing helps researchers identify reasons for high recurrence rate among breast cancer patients



Matthew Goetz, M.D.

At the 2006 ASCO meeting, NCCTG researchers presented findings from a retrospective analysis of NCCTG 89-30-52, a tamoxifen adjuvant trial for early stage, estrogen-positive breast cancer. Patients with impaired CYP2D6 metabolism — either as a result of genetic variation or co-administration of CYP2D6 inhibitors (e.g., paroxetine and fluoxetine)

had a nearly threefold higher risk of recurrence compared to patients with genetically normal metabolism who were not taking CYP2D6 inhibitors. For CYP2D6 poor metabolizers, the two-year risk of relapse or death was greater than 30 percent

compared to 2 percent for extensive CYP2D6 metabolizers who were not administered a CYP2D6 inhibitor.

“Previous studies have demonstrated that tamoxifen treated women, who have genetically decreased levels of CYP2D6 or who are co-prescribed a CYP2D6 inhibitor, have significantly lower plasma levels of the most active tamoxifen metabolite, endoxifen,” says Matthew Goetz, M.D., a medical oncologist at Mayo Clinic in Rochester, Minn., and principal investigator for the study. “The results from our study are the first to demonstrate that tamoxifen may be less effective in patients with impaired CYP2D6 metabolism.”

“Based on this information, the NCCTG breast group, in collaboration with the Pharmacogenomics Research Network (PGRN), has proposed a phase III trial to determine whether sequential hormonal therapy (tamoxifen followed by anastrozole) is superior to anastrozole monotherapy in CYP2D6 extensive and ultrarapid metabolizers.”

This research resulted from collaboration between NCCTG researchers, the laboratories of Matthew Ames, Ph.D., and Richard Weinshilboum, M.D., at Mayo Clinic in Rochester, Minn.; David Flockart, M.D., Ph.D., at Indiana University, and James Rae, Ph.D., at the University of Michigan.

For more information on this clinical trial, see the article on NCCTG pharmacogenomics research on page 7.

Research illustrates difficulty in evaluating adverse events in cancer treatment trials



Shauna Hillman

NCCTG researchers have found that physician assessment of adverse events regarding their relationship to cancer treatment is significantly flawed. When reviewing over 1,000 adverse event attributions in patients taking a placebo, the researchers found that almost half were incorrectly attributed.

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“Determining whether an adverse event is related to a drug or some other condition takes considerable time and effort,” says Shauna Hillman, a cancer researcher at Mayo Clinic in Rochester, Minn., and lead author of the study. “This data is routinely collected, yet our experience suggests it might not be reliable, so we decided to scientifically review the process.”

The Common Toxicity Criteria (CTC) Version 2.0 was implemented in March 1998 by the National Cancer Institute (NCI) and requires collection and reporting of adverse events within a treatment study, and assigning them a relationship to the treatment or some other factor. NCI defines adverse events as unexpected medical problems that occur during drug treatment or other therapies. These events do not have to be caused by the drug or therapy, and can be mild, moderate or severe.

Hillman and her fellow researchers looked at patients in the placebo arm of a phase III clinical trial (NCCTG 97-24-51), which was comparing an experimental treatment — carboxyamido-triazole (CAI) — versus a placebo for stage III or IV non-small cell lung cancer. The placebo arm was examined because all adverse events are truly “unrelated” to treatment.

For the 84 patients in the placebo arm, more than 1,000 adverse events were reported. Not only were nearly half of the attributions incorrect, but the researchers also found that when patients experienced the same event more than once, 36 percent of the time the attribution category changed one or more times.

Because of the significant number of misattributions and inconsistency in attribution reporting, the researchers report limited confidence in the value or reliability of this type of data, and recommend revising the CTC requirements.

Research shows that chromosome translocation is predictor for low-grade oligodendroglioma



Jan C. Buckner, M.D.

this same relationship exists within low-grade oligodendroglioma patients.

Chromosome analysis is often used to help researchers understand the cause of cancerous tumors. In patients with high-grade oligodendroglioma, those patients with the chromosome 1;19 translocation have better survival. NCCTG researchers conducted a retrospective analysis on clinical trial 94-72-53 and found that

Investigators were able to grow tumor cells and conduct chromosome analysis that revealed the nature of this translocation. “We found that chromosomes 1p and 19q were not missing, but in fact attached to each other,” says Jan Buckner, M.D., a medical oncologist at Mayo Clinic in Rochester, Minn., NCCTG group chair and co-investigator for the study. “These findings are significant because they provide prognostic information that can be used right now. Patients with this translocation respond better to treatment.”



Robert Jenkins, M.D., Ph.D.

“In addition, these findings will contribute to our future understanding of why these tumors occur,” says Dr. Buckner. “It is likely that the translocation plays a role in the tumor development. Upcoming research studies will focus on why this chromosome translocation occurs. Our hope is that this research will lead to improved therapies for patients.”

Robert Jenkins, M.D., Ph.D., a researcher at Mayo Clinic, also served as the principal laboratory investigator on the study.



Fall Symposium focuses on pharmacoeconomics issues



Axel Grothey, M.D.

“Pharmacoeconomics in the Era of Targeted Therapies” will be the topic for the symposium session at the fall North Central Cancer Treatment Group (NCCTG) meeting in Rochester, Minn., on Sept. 28, 2006. “A critical problem in the treatment of cancer is that while we have developed therapies for advanced and localized cancers, the cost of these options are becoming increasingly expensive,” says Axel Grothey, M.D., symposium organizer and a medical oncologist at Mayo Clinic in Rochester. “This symposium will offer three different perspectives on the issue of pharmacoeconomics in cancer treatment — the viewpoints of the physicians treating cancer patients, the insurance companies providing reimbursement for these therapies, and the pharmaceutical company developing the medications to treat cancer.”



Neal Meropol, M.D.

Neal Meropol, M.D., a medical oncologist and director of the Gastrointestinal Cancer Program at Fox Chase Cancer Center in Philadelphia, Pa., will offer the view of the medical oncologist who must balance the availability of cancer treatment and treatment costs. Dr. Meropol has spoken extensively on pharmacoeconomics issues in cancer treatment.

A representative from Blue Cross and Blue Shield will present an insurance company perspective and a representative from Genentech will offer a pharmaceutical company viewpoint. Each will speak for 30 minutes, followed by a panel discussion with audience participation.

For more information on the symposium and the NCCTG fall meeting, visit the NCCTG Web site at <http://ncctg.mayo.edu/member.html>.

Spring Meeting Highlights



Daniel Haller, M.D., a faculty member at the University of Pennsylvania School of Medicine in Philadelphia, presented the 12th annual Charles G. Moertel lecture at the spring meeting symposium. Charles G. Moertel, M.D., was a founding member of NCCTG and served as its group chair from 1983 to 1993. Pictured above (from left to right) are Jan C. Buckner, M.D., NCCTG group chair, Dr. Haller and Axel Grothey, M.D., NCCTG cancer treatment program director and symposium organizer.



Bunny Richards, a member of the NCCTG Patient Advocacy Committee, at left, and Dr. Buckner, NCCTG group chair, at right, visit with two patients at the Oncology on Canvas booth. Oncology on Canvas is an art competition and exhibition sponsored by Lilly Oncology.



New North Central Cancer Treatment Group (NCCTG) Clinical Trials

New study to investigate role of whole brain radiation and radiosurgery in patients with cerebral metastases

Approximately 1.2 million Americans will be diagnosed with cancer this year. An estimated 15 percent to 30 percent of these individuals will develop cerebral metastases, making metastatic disease the most common malignancy affecting the brain. The management of cerebral metastases is evolving, particularly with the use of stereotactic radiosurgery and other focal treatment options which have been found to improve local control and overall survival.

Although whole brain radiation therapy (WBRT) has been found to improve survival and delay neurologic progression in the treatment of patients with cerebral metastases, conflicting data exists regarding the overall benefit of routine WBRT delivered after stereotactic radiosurgery (adjuvant WBRT). The addition of WBRT has been thought to add benefit by providing better control of brain metastases. But it is unclear whether this benefit results in a survival advantage or decreased risk of neurologic death. In addition, there are no prospective data about the influence of adjuvant WBRT on quality of life or neurocognition.

To address the role of WBRT with radiosurgery, NCCTG, in partnership with other cooperative groups through the Clinical Trials Support Unit (CTSU), will soon be opening N0574. This study is a phase III, randomized trial of the role of whole brain radiation therapy in addition to radiosurgery in the management of patients with one to three cerebral metastases. The primary objective is to ascertain if one treatment, compared to the other, is associated with better overall survival. Secondary objectives will compare time to local failure, quality of life, duration of functional independence, long-term neurocognitive status, and post-treatment toxicity. The accrual goal for N0574 is 458 patients.



Paul Brown, M.D.

“This clinical trial is designed to determine the benefit of adding WBRT to radiosurgery,” says Paul Brown, M.D., principal investigator for the study and a radiation oncologist at Mayo Clinic in Rochester, Minn. “Based on data from a small phase III trial, it is clear adjuvant

WBRT improves control of brain metastases. However, this small study did not answer whether WBRT provides a survival benefit, and adjuvant WBRT’s impact on long-term cognitive function and quality of life is unknown. N0574 is designed to answer these very important questions.”

Upcoming gastrointestinal clinical trials will focus on the evaluation of targeted agents and combined modality efforts



Axel Grothey, M.D.

Future research of the Gastrointestinal (GI) Cancer Program within NCCTG will involve two areas — the evaluation of targeted agents and the use of combined modality treatments. “The new frontier in cancer research is the use of targeted agents. Oncology is moving away from the use of chemotherapy,” says Axel Grothey, M.D., cancer treatment program director for NCCTG and a medical oncologist at Mayo Clinic in Rochester, Minn. “Our challenge will be to move from using chemotherapy plus one targeted agent to the use of only targeted agents that are selected based on a patient’s genetic makeup and their response to therapies.”

Two new studies evaluating the effectiveness of targeted agents are in development. N054C is a phase II study of Sorafenib/Bevacizumab as a second-line therapy in patients with metastatic colorectal cancer. N0548 is a randomized, phase II trial of Cetuximab/Bevacizumab (CB) as a palliative first-line therapy in patients with advanced colorectal cancer followed by FOLFOX+CB versus FOLFOX+B. Dr. Grothey is the study chair for both trials.



Robert Cima, M.D.

Combined modality treatments are also an area of emphasis in the NCCTG GI Cancer Program. Currently in development, N044L is a phase II trial which will evaluate the effectiveness of chemotherapy combined with surgery for patients with abdominal carcinomatosis from metastatic colon cancer. Patients will initially undergo chemotherapy, and those patients whose tumor does not progress will also undergo surgery to remove the tumor and affected area of the peritoneum. Surgery will then be followed by additional chemotherapy. Robert Cima, M.D., is the principal investigator for this trial.



The future is now — Using genetic information to improve cancer therapies An update on the North Central Cancer Treatment Group's pharmacogenomics research efforts

Pharmacogenomics research strives to identify genetic factors that influence an individual's response to medications, allowing physicians to individualize therapy. For more than three decades, Mayo Clinic, which serves as the research base for the North Central Cancer Treatment Group (NCCTG), has been engaged in pharmacogenomics research. NCCTG has benefited from Mayo Clinic's research efforts and has increasingly incorporated pharmacogenomics into clinical trials research. This article provides an update on NCCTG's efforts in this area.

The role of pharmacogenomics research



Richard Weinshilboum, M.D.

"In this post-genomic era, the race to complete the Genome Project, which identified the human genetic profile, was a race to the starting line, not the finish line," says Richard Weinshilboum, M.D., a researcher at Mayo Clinic in Rochester, Minn. "The starting line being to use that genetic information to help us truly individualize medicine — both in terms of diagnosis and in tailoring the therapy to the genetic ability of the patient to respond."

Because of the efforts involved in completing the Genome Project, a great deal of technology exists to enhance the researcher's ability to test hypotheses about the influence of genetic factors. In addition, a revolution has taken place in drug development, leading to the discovery of therapies that dramatically improve the outcomes for patients. However, these powerful drugs often have a narrow therapeutic index, which results in a small difference between the dosage that will help and the dosage that results in toxicity.

"Our challenge will be to translate this scientific research into clinical practice so that patients benefit," says Dr. Weinshilboum. "The goal of pharmacogenomics research is to maximize the therapeutic effect of medical therapies while avoiding adverse responses. We want to treat the right patient with the right medication, using the right dose every time."

Collaboration in pharmacogenomics research



Matthew Ames, Ph.D.

NCCTG is part of a collaborative effort in pharmacogenomics research. Many of NCCTG's current research activities involve collaboration with other medical centers, networks and research funding efforts. Over the past seven years, the NCCTG has benefited from collaboration with the lab of Matthew Ames, Ph.D. at Mayo Clinic to implement pharmacogenetics into early phase drug studies, many of which are brought forward into NCCTG clinical trials. Dr. Ames' laboratory has also been principally responsible for conducting pharmacogenetic studies in multiple phase II and phase III NCCTG clinical trials.

In addition, Mayo Clinic has been a member of the Pharmacogenomics Research Network (PGRN) since 2000. The National Institutes of Health (NIH) established this network, which currently includes 10 research centers across the country. The network conducts multidisciplinary, integrated research in pharmacogenomics. Dr. Weinshilboum is a founding member of the network and is principal investigator for the Mayo Clinic site.

Many of the lab facilities and researchers involved in the PGRN also work on NCCTG research initiatives, including James Ingle, M.D., Alex Adjei, M.D., Ph.D., and Matthew Goetz, M.D., medical oncologists at Mayo Clinic.

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In addition, several NCCTG researchers receive funding from other sources to conduct pharmacogenomic research. Mayo Clinic Cancer Center has recently received several Specialized Programs of Research Excellence (SPORE) grants from the National Cancer Institute. Dr. Ingle serves as the principal investigator for a breast cancer SPORE grant which funds several core studies closely tied with either completed or ongoing NCCTG clinical trials.

Using genetic testing to target breast cancer therapies



Matthew Goetz, M.D.

The drug tamoxifen is one of the most widely used agents to treat breast cancer in the world. Recently, new information has demonstrated that tamoxifen undergoes activation by the Cytochrome P4502D6 (CYP2D6) enzyme to the highly potent tamoxifen metabolite, endoxifen. Because this activation step is under genetic control,

NCCTG researchers hypothesized that common genetic variation in this enzyme might influence the risk of breast cancer recurrence. Using tissue samples and patient records from the NCCTG clinical trial 89-30-52, researchers extracted DNA from stored tissue samples to identify genetic factors that influence the response to tamoxifen. DNA results also were confirmed by obtaining current blood samples from surviving patients from the original trial.

“Our results, originally published in the *Journal of Clinical Oncology* and updated at the American Society of Clinical Oncology (ASCO) meeting in June, indicate that the status of CYP2D6 appears to be crucial in predicting response to tamoxifen,” says Dr. Goetz, principal investigator for the study. “Patients with decreased levels of CYP2D6 — either as a result of genetic variation or the co-administration of CYP2D6 inhibitors — had a nearly threefold higher risk of recurrence compared to patients with genetically normal metabolism who were not taking CYP2D6 inhibitors. For CYP2D6 poor metabolizers, the two-year risk of relapse or

death was greater than 30 percent compared to 2 percent for extensive CYP2D6 metabolizers who were not administered a CYP2D6 inhibitor.”

Approximately 10 percent of Caucasian women are CYP2D6 poor metabolizers and more than 30 percent of tamoxifen treated breast cancer patients are co-prescribed antidepressants (many of which inhibit CYP2D6) for the treatment of hot flashes or depression.

“Based on the results of this study, the Food and Drug Administration (FDA) is holding a public advisory committee meeting on Oct. 18, 2006, to consider incorporating the CYP2D6 genetic information into the tamoxifen label,” says Dr. Goetz. “In addition, we have received approval from the Breast Cancer Intergroup of North America to develop a prospective adjuvant clinical trial using CYP2D6 genotyping as an initial screening test to identify women who can be effectively treated with sequential hormonal therapy (tamoxifen followed by an aromatase inhibitor). If fully approved, this would represent a paradigm shift in the way clinical trials are conducted.”

The tamoxifen studies are an excellent example of the ongoing collaboration between NCCTG, Mayo Clinic and the PGRN as these studies were conducted in the laboratories of Dr. Ames and Dr. Weinshilboum of Mayo Clinic, David Flockart, M.D., Ph.D., from Indiana University and James Rae, Ph.D., from the University of Michigan.

Genotyping guides treatment selection for gastrointestinal cancers

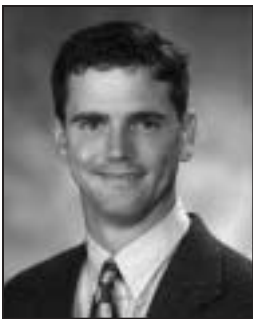
As in the treatment of breast cancer, genetic testing has also been used to identify the best treatment for colon cancer patients. A prospective, phase I dose-escalation trial conducted at Mayo Clinic demonstrated that patients with genetically decreased levels of the enzyme UGT1A1 tolerate significantly lower doses of a three drug combination of irinotecan, oxaliplatin and capecitabine.

UGT1A1 is a liver enzyme responsible for the inactivation of SN-38, a potent irinotecan metabolite responsible for the life-threatening side effects of neutropenia and diarrhea. “Although



the FDA previously changed the irinotecan label to reflect the importance of genetic variation in UGT1A1, our study is the first to determine that UGT1A1 genotype determines the dose of chemotherapy that should be delivered," says Dr. Goetz, the principal investigator for the study.

In this trial, a DNA sample was collected and analyzed in the laboratory of Dr. Ames, and the results of genotyping were used to escalate (or de-escalate) the dose of chemotherapy for each patient. The results demonstrated that patients homozygous for the UGT1A1 *28 polymorphism require substantially lower doses of irinotecan yet achieve similar or higher plasma drug levels of the most important metabolite, SN38, compared to patients with normal levels of the enzyme receiving twice the dose of irinotecan.



Robert McWilliams, M.D.

Based on these findings, a new phase II clinical trial, N0543, for patients with small bowel cancer will utilize UGT1A1 genetic testing prior to treatment to select the dose of chemotherapy that each patient should receive. Robert McWilliams, M.D., an oncologist at Mayo Clinic in Rochester, Minn., is the principal investigator for this trial which will open in late 2006.

"Small bowel cancer has proven difficult to treat in the advanced setting. Genotype-based dosing will hopefully allow treatment with a triple-combination regimen of irinotecan, oxaliplatin, and capecitabine while minimizing the risk of toxicity," according to Dr. McWilliams. "The rapid turnaround of genotyping in Dr. Ames' lab allows prospective treatment assignment based on UGT1A1 genotype. We are very excited about this new paradigm of therapeutic planning."

NCCTG clinical trial N9741 was one of the first clinical trials to incorporate pharmacogenomics analysis. N9741 led to the adoption of oxaliplatin in the treatment of patients with advanced colon cancer. Richard Goldberg, M.D., an oncologist formerly with Mayo Clinic and now at the University of North Carolina, was the principal

investigator and Howard McCleod, M.D., also at the University of North Carolina, conducted the pharmacogenomics analysis. As part of the study, researchers looked for genetic factors that could predict drug response or toxicity. Results indicated that the level of UGT1A1 did predict for neutropenia (low blood counts).

Several follow-up studies involving pharmacogenomics have resulted from the initial data collected in N9741. Genetic factors influencing quality of life were evaluated and presented at ASCO in 2004. (See below for study results.) In addition, NCCTG clinical trial N0548 results, presented at ASCO in 2005, indicated that patients with a variation in their coding for an enzyme called glutathione-S-transferase P1 (GSTP1) suffered early onset neurotoxicity when treated with oxaliplatin.



Axel Grothey, M.D.

"This was a retrospective analysis," says Axel Grothey, M.D., an oncologist at Mayo Clinic and NCCTG cancer treatment program director, who presented the data at ASCO. "We are now evaluating these genetic predictors in a trial done through NCCTG's cancer control program. Most NCCTG trials now have a

pharmacogenomics component and more trials are using this analysis in prospective studies."

At the 2006 ASCO meeting, Dr. Goldberg presented a follow-up study to N9741 in which he examined the effect of ethnicity on toxicity and efficacy of treatment. Study results indicated that African-American and non-Asian patients experienced a lower rate of side effects such as diarrhea but also experienced a lower response rate to treatment.

How genetic factors influence quality of life

Can a patient's genetic makeup influence his or her quality of life (QOL), specifically at the time of a cancer diagnosis and during treatment? This was the question asked by NCCTG researchers and initially tested in NCCTG clinical trial N9741, which involved the treatment of patients with advanced colon cancer. In the past, a patient's QOL seemed to

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be determined by life experiences and social and psychological state at the time of treatment. After analyzing the data provided by more than 700 patients, NCCTG researchers found evidence that people with specific genetic factors were more prone to fatigue. People with other genetic factors seemed to have diminished QOL.



Jeff Sloan, Ph.D.

“The exciting part of this research is that we entered the project with a skeptical eye — yet the data showed that there clearly was a relationship between genetic factors and QOL,” says Jeff Sloan, Ph.D., chair of the NCCTG quality of life committee. “As we did this trial, we will continue to evaluate QOL as we do all other scientific endpoints — it must be precise, consistent, measurable and interpretable.”

NCCTG researchers have continued to evaluate genetic factors that influence QOL in clinical trials involving breast cancer, lung cancer and neuro-oncology. “Our goal is to find genetic variables that tell us, even upon diagnosis, how a patient will do in terms of cancer experience and translate this information into improved treatment outcomes and survival benefits,” says Dr. Sloan. “If we can identify, based on genetic factors, those patients who are more likely to experience a side effect affecting QOL, such as fatigue, then we can implement prophylactic measures to intervene with these patients before we begin treatment.”

NCCTG members play a key role as investigators move forward in this new area of QOL research. “NCCTG has established a very good track record in assessing QOL, largely due to our members’ efforts,” says Dr. Sloan. “Because of our members’ acceptance of this research and their efforts to collect quality QOL data, we are able to accurately evaluate QOL. In addition, many members have provided important feedback on our QOL assessment tools, helping us to refine our research efforts.”

How NCCTG members help advance pharmacogenomics research

NCCTG members play a critical role in the group’s pharmacogenomics research. Each time a member site submits blood samples for a clinical trial participant, it is helping researchers to better evaluate the effectiveness of cancer treatments.



Wilma Lingle, Ph.D.

“Just having one blood sample from clinical trial participants is beneficial for future research,” says Wilma Lingle, Ph.D., co-director of the NCCTG Biospecimen Resource. “During the past five years, 27,491 biospecimens were submitted for 40 studies. We encourage members to continue to participate in

the translational research activities for every NCCTG clinical trial.”

“The role of NCCTG members is very important,” says Richard Weinsilboum, M.D., a researcher at Mayo Clinic. “Physicians and nurses at member sites are able to answer clinical trial participants’ questions and also explain how submitting blood samples enable researchers to extract DNA and analyze genetic factors that influence each participant’s response to medications.”

The procedure for collecting biospecimens and extracting DNA for pharmacogenetics is becoming standardized for all NCCTG studies. Member sites are asked to submit whole blood samples and/or tissue specimens for all participants in NCCTG clinical trials. All biospecimens received for NCCTG clinical trials are processed in the NCCTG Research Base Biospecimen Accessioning and Processing (BAP) Laboratory at Mayo Clinic and will be tracked in the new Research Accessioning Tracking System (RATS). As new systems are implemented, it is important that NCCTG members utilize these new procedures. These efforts will assist researchers in efficiently processing, tracking, and storing high-quality specimens that can be used in pharmacogenomics research.



North Central Cancer Treatment Group's Imaging Initiative — applying imaging technology to further clinical research

Incorporating imaging into clinical research



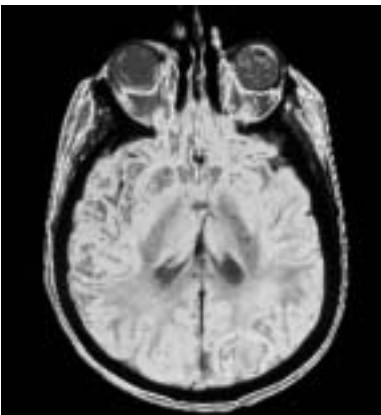
Jan C. Buckner, M.D.

"Incorporating imaging research into North Central Cancer Treatment Group (NCCTG) clinical trials represents an opportunity to improve and expand NCCTG research efforts," says Jan Buckner, M.D., NCCTG group chair and medical oncologist at Mayo Clinic in Rochester, Minn. "Imaging is a powerful method of assessing malignant disease, and advances in imaging techniques continually strengthen its role in medicine. The rapid advance of functional and molecular imaging methods has sparked interest in using these tools in clinical research."

Specifically, imaging can be used to more effectively target populations for clinical trials, to limit exposure to agents with toxicities to the minimum necessary duration, and to continue treatment only in those patients who show an early response.

Specifically, imaging can be used to more effectively target populations for clinical trials, to limit exposure to agents with toxicities to the minimum necessary duration, and to continue treatment only in those patients who show an early response.

Imaging initiative goals



NCCTG will establish an imaging program to collect, archive, distribute and assess images for multisite clinical trials and implement this procedure within NCCTG member institutions. The objectives of the imaging program will be:

- To develop standardized processes for image acquisition, electronic transfer and storage
- To develop standardized image measurement methods and tools
- To foster hypothesis-driven image research in NCCTG



Bradley Erickson, M.D., Ph.D.

"We believe that these efforts will enhance both the NCCTG and national clinical trials efforts," says Bradley Erickson, M.D., Ph.D., and the coordinator of the NCCTG imaging initiative. "We will build an infrastructure that will allow the next generation of imaging technologies to be incorporated into clinical trials more effectively."

Dr. Erickson brings extensive experience in imaging research to his role as program coordinator. He is a board-certified neuro-radiologist at Mayo Clinic in Rochester, Minn. and has a Ph.D. in biomedical imaging. He has led the development and implementation of the system of electronic image capture and display utilized throughout Mayo Clinic.

New Mayo Clinic system will enhance NCCTG efforts

Mayo Clinic recently committed capital funds to design a new Clinical Research Management System (CRMS). The CRMS is being created in accordance with the cancer Biomedical Informatics Grid (caBIG), a National Cancer Institute (NCI) guideline. NCCTG will utilize this system to create a similar program to be used in NCCTG clinical research. Imaging could be incorporated into this system by developing protocols that prompt the researcher to consider adding imaging assessments that can be performed in the community setting. This system also will provide an infrastructure for managing images across the cooperative group. NCCTG is aware of similar initiatives in other cooperative groups and will plan its activities to complement that research.





Listing of NCCTG Abstracts for ASCO 2006

Neuro-oncology

*94-72-53 — A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q in human oligodendrogliomas
Presenter: Robert B. Jenkins, M.D., Ph.D.

*94-72-53 — Diagnostic and prognostic significance of a t(1;19)(q10;p10) in patients (pts) with low-grade oligodendroglioma and astrocytoma
Presenter: Robert B. Jenkins, M.D., Ph.D.

*R9802 — Initial Report of Radiation Therapy Oncology Group (RTOG) 9802: Prospective Studies in Adult Low-Grade Glioma
Presenter: Edward Shaw, M.D.

**94-94-52 — Analysis of paired glioma tissues from initial diagnosis and recurrence in patients enrolled on NCCTG clinical trials: de-differentiation and association with survival
Presenter: Kurt A. Jaeckle, M.D.

**96-94-53 — Clinical Variables Associated with Overall Survival (OS), Progression-Free Survival (PFS), 6 month Progression-Free Survival (PFS6), Immediate Progression (ImmProg), and Response in Patients (pts) Enrolled in Recurrent Glioma Clinical Trials
Presenter: Jan C. Buckner, M.D.

***N997D — Phase II trial of irinotecan (CPT-11) and radiation followed by irinotecan and BCNU in glioblastoma patients (pts)
Presenter: Karla V. Ballman, Ph.D.

Breast Cancer

*89-30-52 — Cytochrome P450 2D6 status predicts breast cancer relapse in women receiving adjuvant tamoxifen (Tam)
Presenter: Stacey K. Knox, M.D.

*C9344 — HER2 Predicts Benefit from Adjuvant Paclitaxel After AC in Node-Positive Breast Cancer: CALGB 9344
Presenter: Daniel F. Hayes, M.D.

*N9831 — Adjuvant radiotherapy (RT) and trastuzumab in Stage I-I-IIA breast cancer: toxicity data from North Central Cancer Treatment Group Phase III trial N9831
Presenter: Michele Y. Halyard, M.D.

*S0012 — SWOG 0012, a randomized phase III comparison of standard doxorubicin and cyclophosphamide followed by weekly paclitaxel versus weekly doxorubicin and daily oral cyclophosphamide plus G-CSF followed by weekly paclitaxel as neoadjuvant therapy for inflammatory and locally advanced breast cancer
Presenter: Georgiana K. Ellis, M.D.

**MA.17 — Clinical Outcomes of Ethnic Minority Women in the NCIC CTG MA.17 Trial
Presenter: Beverly Moy, M.D.

**N0336 — Phase II Trial of RAF Kinase Inhibitor Bay 43-9006 As Single Oral Agent in Patients With Metastatic Breast Cancer Previously Exposed to Anthracycline and/or Taxane
Presenter: Alvaro Moreno Aspitia, M.D.



**N9831 — Cost-Effectiveness Analysis of Trastuzumab in the Adjuvant Setting for the Treatment of HER2+ Breast Cancer

Presenter: Louis P. Garrison Jr., M.D.

***MA.17 — Updated Analysis of NCIC CTC MA.17 (letrozole vs. placebo to letrozole vs. placebo) post unblinding

Presenter: Nicholas J. Robert, M.D.

***MA.17 — NCIC CTG MA.17: Intent to Treat Analysis (ITT) of Randomized Patients After a Median Follow-Up of 54 Months

Presenter: James N. Ingle, M.D.

Cancer Control

*N00CA — Phase III double-blind study of depot Octreotide versus placebo in the prevention of acute diarrhea during pelvic radiation therapy: Results of North Central Cancer Treatment Group protocol N00CA

Presenter: James A. Martenson Jr., M.D.

*N02C3 — Evaluation of Transdermal Testosterone Cream in Female Cancer Survivors with Decreased Libido

Presenter: Debra L. Barton, Ph.D.

*N03C5 — Phase III Randomized Trial to Evaluate the use of Gabapentin Alone vs with Continuing an Antidepressant in Women Failing an Antidepressant for the Treatment of Hot Flashes: North Central Cancer Treatment Group Study

Presenter: Charles L. Loprinzi, M.D.

**N00C1 — A Placebo-Controlled Trial of Etanercept, a Tumor Necrosis Factor (TNF) Inhibitor, in Patients with the Cancer Anorexia/Weight Loss Syndrome. A North Central Cancer Treatment Group (NCCTG) Trial (N00C1)

Presenter: Aminah Jatoi, M.D.

**N01C3 — The Efficacy of Lamotrigine in the Management of Chemotherapy-Induced Peripheral Neuropathy: A Phase III Randomized, Double Blind, Placebo-Controlled NCCTG Trial, N01C3

Presenter: Samar R. Renno, M.D.

GI Malignancies

*C9781 — *Trimodality Therapy is Superior to Surgery Alone in Esophageal Cancer: Results of CAIGB 9781*

Presenter: Mark Krasna, M.D.

*E3201 — ECOG E3201: Intergroup randomized Phase III study of postoperative irinotecan, 5-Fluorouracil (FU), leucovorin (LV) vs oxaliplatin, FU/LV vs FU/LV for patients (pts) with stage II/III rectal cancer receiving either pre or postoperative radiation (RT)/FU

Presenter: Al B. Benson III, M.D.

*N9741 — African-Americans (AA) with metastatic colorectal cancer (MCRC) had different polymorphisms, less toxicity, and a lower response rate than Caucasians (C) when treated with IFL, FOLFOX, or IROX in Intergroup N9741

Presenter: Richard Goldberg, M.D.

*R9811 — A phase III randomized study of 5-FU, mitomycin, and radiotherapy versus 5-FU, cisplatin and radiotherapy in carcinoma of the anal canal

Presenter: Jaffer A. Ajani, M.D.



**N9741 — Direct cost-survival analysis of therapies for metastatic colorectal cancer
Presenter: Yu-Ning Wong, M.D.

**N9741 — UGT1A1*28, toxicity and outcome in advanced colorectal cancer: Results from Trial N9741
Presenter: Howard McLeod, M.D.

**N9741 — A pooled safety and efficacy analysis of the FOLFOX4 regimen (bi-monthly oxaliplatin plus fluorouracil/leucovorin) in elderly compared to younger patients with colorectal cancer
Presenter: Daniel Sargent, Ph.D.

**N9741 — Response rate using conventional criteria is a poor surrogate for clinical benefit in metastatic colorectal cancer (M-CRC): A comparative analysis of N9741 and AVF2107
Presenter: Axel Grothey, M.D.

**N9945 — Systemic Capecitabine and Oxaliplatin Administered with Hepatic Arterial infusion (HAI) of Floxuridine (FUdR) Following Complete Resection of Colorectal Metastases (M-CRC) Confined to the Liver: A North Central Cancer Treatment Group (NCCTG) Phase II Intergroup Trial
Presenter: Steven R. Alberts, M.D.

**N994C — Alterations in cell proliferation and apoptosis in human colon cancers with microsatellite instability
Presenter: Frank A. Sinicrope, M.D.

**N994C — Microsatellite instability but not thymidylate synthase is a prognostic variable in primary colon cancers from patients treated in 5-FU-based adjuvant studies
Presenter: Frank A. Sinicrope, M.D.

***N034A — Combination of Gemcitabine and Oxaliplatin as a Highly Active Regimen in Pancreatic Cancer
Presenter: George P. Kim, M.D.

****N0442 — Epidermal growth factor receptor expression correlates with histologic grade but not microsatellite instability in primary colon carcinomas
Author: Rafaela Rego, M.D.

Lung Cancer

*97-24-51 — Should attribution be considered when interpreting event data: A North Central Cancer Treatment Group (NCCTG) evaluation of a phase III placebo controlled trial
Presenter: Shauna L. Hillman

***97-24-51 — Evaluation of platinum-based chemotherapy, glutathione metabolic genes, and survival in advanced non-small cell lung cancer: A NCCTG 97-24-51 based study
Author: Ping Yang, M.D., Ph.D.



Novel Therapies

**N0186 — Anti-tumor activity of mTOR inhibitor temsirolimus for relapsed mantle cell lymphoma: A Phase II trial in the North Central Cancer Group (AACR)

Presenter: *Stephen M. Ansell, M.D., Ph.D.*

***N0377 — NCCTG phase II trial of the mTOR inhibitor Everolimus (RAD-001) in metastatic melanoma

Presenter: *Ravi D. Rao, M.B.B.S.*

***N9981 — Salvage chemotherapy with rituximab DHAP (RDHAP) for relapsed non-Hodgkin lymphoma (NHL): A phase II trial in the North Central Cancer Treatment Group

Presenter: *Thomas E. Witzig, M.D.*

****N0189 — Phase II study of rituximab and cladribine (2-CDA) in newly diagnosed mantle cell lymphoma (MCL) (N0189)

Presenter: *David J. Inwards, M.D.*

Quality of Life

**What role do cancer patients want to play in treatment decision making: A pooled-analysis

Presenter: *Jeff A. Sloan, Ph.D.*

**Comparison of baseline quality of life between minority and non-minority patients participating in oncology clinical trials

Presenter: *Angelina D. Tan*

***N0074, 98-72-51, 98-72-52 — Validation of single item Linear Analogue Scale Assessments (LASAs) for assessing quality of life (QOL) in patients with newly diagnosed high-grade gliomas

Presenter: *Paul A. Decker*

***What is the value of added patient reported outcomes relative to physician rated symptom assessments?

Presenter: *Sumithra J. Mandrekar, Ph.D.*

***A population-based study on the quality of life for cancer patients as reported in a tumor registry follow-up

Presenter: *Paul J. Novotny*

***The relationship between cancer patient treatment decision-making roles and quality of life (QOL)

Presenter: *Pamela J. Atherton*

***How much missing data is too much? A single study exploration

Presenter: *Amylou C. Dueck, Ph.D.*

Key:

*Oral Presentation

**Poster Discussion

***Poster

****Publication



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Future Meeting Dates

April 16–19, 2007
Sept. 24–27, 2007

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