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Cancer and Leukemia Group B

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“I’ve got cancer. What should I eat?”

Charles Fuchs, MD, Dana Farber Cancer Institute

- A. “It doesn’t matter—diet won’t affect cancer outcome.”**
- B. “Eat healthy foods like [x]. I read somewhere that it might help.”**
- C. “We have no idea. There hasn’t been an effective study of the role of diet among cancer patients.”**

The right answer: there is no right answer.

Lifestyle and diet choices have been examined extensively to discover what might cause or prevent cancer. But once a patient has cancer, we know much less about which dietary and lifestyle choices will help recovery, palliate symptoms, or interact with treatment regimens (positively or negatively). At this point, any answer a physician or health care provider gives to a cancer patient who asks about diet or lifestyle is likely to be unsatisfying.

And for patients who have been diagnosed with cancer and are desperately trying to figure out what they should start doing, the vacuum left by the dearth of scientific data is quickly filled by pro-

ponents of various alternative therapies. A significant percentage of cancer patients take unproven therapies during their illness. Alternative nutritional therapies, of which there is a wide variety, are the most common form of complementary therapy among cancer patients. In one study of breast cancer patients, 80% reported changing their diets after diagnosis,

most commonly to a low-fat-high fiber diet¹. In addition, 85% of patients started taking vitamins, averaging 4 to 5 per day. Moreover, twenty-five percent were taking some form of alternative medication including shark cartilage, herbs, and mistletoe, among others. Unfortunately, few studies have rigorously assessed the role of these approaches on patient outcome.

Dietary measures have been strongly linked to the risk of developing specific cancers. For colon cancer, epidemiologic and scientific research indicates that diet and other lifestyle factors have a significant influence on the risk of developing colon cancer. Consumption of red meat and alcohol, obesity, and cigarette smoking are associated with an increased risk of colon cancer, whereas intake of calci-

um, fiber, folic acid, and aspirin and regular physical activity are considered protective²⁻⁶.

However, no clear scientific evidence exists



The GI and Cancer Control Committees are collaborating to assess the role of diet and other lifestyle factors on the risk of cancer-recurrence among patients with stage III colon cancer.

MESSAGE FROM THE CHAIR

Priority on Institutional Compliance

Many of you are no doubt aware of recent actions taken by the NIH Office for Protection from Research Risks that resulted in the suspension of privileges for institutions to enroll patients in Federally-funded clinical research studies, including CALGB protocols. Since May of this year, two CALGB main member institutions have had their multiple project assurances suspended because of irregularities in IRB procedures or failure to appropriately obtain patient informed consent for participation in



Richard L. Schilsky, M.D.

research. In neither case were patients ever endangered or harmed and in both cases the institutions in question moved quickly to correct the problems that resulted in the OPRR action. Nevertheless, the reputations of the institutions involved suffered considerably in the research and medical communities; they may have lost funding for ongoing research or been prevented from applying for new research funding, and they clearly lost momentum and continuity in ongoing clinical research programs and were faced with explaining the OPRR sanctions to confused and concerned physicians, research staff and patients. The problems identified at these institutions stem primarily from overworked and understaffed institutional review boards and could happen at any CALGB institution. Adequate documentation of IRB actions is an area that requires particular attention at many institutions. OPRR regulations require that the minutes of IRB meetings be clear as to attendance at the meetings; what actions were taken; the number of members voting for, against or abstaining on each vote; and reasons for modifying or disapproving research projects and informed consent documents. IRB membership must be appropriately diverse as specified by OPRR guidelines; a quorum (including at least one community member) must be present for the IRB to convene and continue a meeting and members must disclose conflicts of interest with respect to review of specific research proposals. IRB members as well as investigators should receive adequate training with respect to regulations governing pro-

tection of human subjects and the ethical conduct of clinical research.

In 1998, the General Accounting Office reported to Congress that the national IRB system had serious problems due primarily to the large volume of clinical studies under review at many institutions and inadequate staff support provided to many IRBs. Certainly the recent actions of OPRR reflect the increased vigilance of Federal regulatory agencies with respect to these concerns and should capture the attention of each CALGB institution. Every institution is urged to undertake a systematic review of their IRB procedures to insure compliance with all applicable Federal regulations and to make any necessary adjustments. As you know, CALGB audits now report separate ratings for IRB, pharmacy and data quality. In June, 1999, the Board of Directors approved a policy that requires immediate suspension of registration privileges on CALGB protocols for any

institution that receives a rating of "Unacceptable" in the IRB category of the audit report. Registration privileges will be reinstated following acceptance of a written plan of corrective action by the Group Chair and a re-audit of the institution's IRB activities will occur within six months to insure that the corrective action plan has been implemented and is effective.

The clinical research enterprise at every institution is increasingly challenged by the need to be in compliance with the myriad Federal regulations that govern clinical research and reimbursement for clinical services provided to patients enrolled in research studies.

This year, the Office of the Inspector General (OIG) of the Department of Health and Human Services announced that part of its "Work plan" would include evaluation of whether institutions are inappropriately billing Medicare for clinical services provided to patients as part of research grants or clinical trials of investigational drugs. Actions have already been taken against some institutions for inappropriate billing practices. The key criterion for the Health Care Financing Administration (HCFA) in determining whether a procedure, device, drug or biological is eligible for reimbursement is its demonstrated safety and effectiveness. Therefore, to be reimbursable, an intervention must be generally accepted in the medical community or proven to be safe and effective based on authoritative evidence. Devices, drugs and services that meet these definitions are considered "reasonable and necessary." Items or services that are not reasonable or necessary for the diagnosis or treatment of illness or injury or to improve the function of a malformed body part are generally

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excluded from Medicare coverage. The most egregious example of inappropriately billing Medicare involves directly billing Medicare for the cost of items or services that are otherwise reimbursable to providers through Federal research grants or support from pharmaceutical company sponsors. Many more subtle examples of inappropriate billing practices exist and must be considered by every institution engaged in clinical research studies. Institutional compliance programs should have mechanisms in place to detect and correct any inappropriate practices. In many institutions, problems may arise because the staff and systems involved in billing patients for clinical services are completely separate from those involved in enrolling and monitoring patients in clinical research studies. Often, research staff are unaware of how billing systems work and billing staff are unaware that patients are involved in a sponsored research study that should be billed for research-related clinical services. Education of both billing and research staff regarding acceptable billing practices and research procedures is essential to minimize inappropriate billing practices.

The clinical research enterprise at every institution is increasingly challenged by the need to be in compliance with the myriad Federal regulations that govern clinical research and reimbursement for clinical services provided to patients enrolled in research studies. Issues to be addressed include development of procedures to identify research-related expenses that should be reimbursed by research sponsors; development of clinical trial budgets that provide appropriate compensation for research-related expenses; establishing training programs for research and billing staff; modifying hospital information systems to enable compatibility of billing systems and research databases; providing a centralized clearinghouse to provide investigators with current and definitive information on prevailing reimbursement policies; and developing audit procedures that monitor compliance with billing practices as well as clinical and ethical practices in conducting research. These complex issues cannot be addressed easily unless institutional leaders recognize the potential problems and devote institutional resources toward developing an appropriate infrastructure for support of clinical research. Penalties for non-compliance with Federal regulations regarding Medicare billing can be severe and include substantial fines and criminal prosecution. Perhaps more importantly, however, the penalty for non-compliance is the loss of the privilege to participate in clinical research studies and thereby to advance the state of our knowledge in the treatment and prevention of cancer and other diseases. I urge all CALGB institutions to review all Federal regulations governing the conduct and reimbursement of clinical research and to develop appropriate mechanisms to assure compliance so that we may all continue the work we have set out to do in improving the outcomes of patients with cancer.

MEDICAL OPINION

Drug Development of Non-Cytotoxic Agents: Some Further Thoughts

Walter M. Stadler, MD, University of Chicago

In the last issue of the CALGB Newsletter, [CAL•GAB 8(3): p. 6-7, Summer 1999] Dr. Elisabeth Eisenhauer makes cogent comments on the challenges and opportunities inherent in the development of non-cytotoxic (or "cytostatic") antineoplastic agents. These agents, usually developed against specific molecular targets, include anti-angiogenic agents, farnesyl-transferase inhibitors, matrix metalloproteinase inhibitors, and anti-growth factor or growth factor receptor agents. Theoretical considerations as well as animal studies suggest that many will be effective in preventing further tumor growth, but will not necessarily cause tumor shrinkage. As Dr. Eisenhauer points out, the difficulty in clinical development of these drugs is choosing the appropriate phase I and II trial end-points such that appropriate decisions as to further development can be made. One must recall that the vast majority of new agents, whether they be traditional cytotoxic agents or newer cytostatic agents, will prove to be ineffective in patients. Clearly, it is thus undesirable to take every new drug to a large phase III trial.

Dr. Ratain and I have also considered these issues in some detail and I offer several brief comments here.¹ Before proceeding, a brief review of phase I, II, and III trial objectives is in order. Ultimately, one desires to determine whether a drug has a beneficial effect for patients. Thus phase III trials must be randomized and must use an endpoint that clearly measures patient benefit, usually survival or quality of life. The statistical issues for such trials have been well described and the trials are usually quite large, on the order of several hundred patients. There should be no inherent difference in the conduct of phase III trials for cytostatic as opposed to cytotoxic agents. Phase II trials use small numbers of patients to determine whether a drug is likely to have patient benefit. Thus a

Further Thoughts *continued on next page*

The CAL•GAB is published quarterly by the Cancer and Leukemia Group B and is distributed free to the CALGB active membership. Suggestions for articles are encouraged.

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PLEASE NOTE:

While we make every effort to provide accurate dosing information in the CAL•GAB, you should always check the appropriate drug dosages before prescribing and/or administering any medication.

Further thoughts on phase I/phase II testing for new non-cytotoxic agents

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surrogate endpoint that correlates with ultimate patient benefit is used. For traditional cytotoxic drugs the most common surrogate endpoint is “objective response.” Although this measure correlates well with improvements in survival in phase III studies, it should be pointed out that the usual 50% decline in the sum of perpendicular diameters on a radiologic exam is a completely arbitrary number. Furthermore, improvements in overall response rate do not always translate into improvements in survival. Finally, phase I studies are dose-finding and toxicity studies used to define doses and schedules appropriate for further phase II testing.

For phase I studies, I argue that toxicity is still a valid end-point. During this early clinical phase of development the relationship between tumor growth inhibition and serum levels, or target inhibition in a specific tissue, is unlikely to have been established firmly. Furthermore, one would want to avoid the situation in which a phase II study conclusion is that a dose higher than tested during phase I evaluation should have been used. Dose escalation to maximum tolerated dose (MTD) during phase I testing does not preclude additional testing of potential surrogate endpoints, such as target inhibition.

For phase II evaluations I would suggest that studies be performed in two separate but overlapping stages. During phase IIA studies, the primary endpoint can be target inhibition. Thus a study could be designed such that x% of patients experience at least y% inhibition of the target in an easily accessible tissue (such as peripheral blood monocytes) or in the tumor (via biopsy or in patients receiving treatment before surgical resection). If target inhibition closely correlates with tumor growth inhibition in preclinical studies and if a small phase IIA study is unable to demonstrate sufficient target inhibition in patients at or close to MTD, one must seriously consider curtailing further development.

During phase IIB trials, one would then try to assess whether the new agent induces stable disease. I disagree with Dr. Eisenhauer that this could be performed by simply setting a minimal value for the number of patients who progress. Her suggestion implies that an appropriate null hypothesis for the number of patients who maintain at least stable disease (fail to progress) over a given interval can be made. Unlike objective response in which the

expected response rate in the absence of therapy is zero, the natural history of most solid tumors is so variable, and the patients in most phase II trials so highly selected, that no accurate hypothesis as to the rate of stable disease can be made. Instead, I argue that such phase IIB studies can only be performed if some type of randomization is performed. Although there is insufficient space to discuss all options, one that we have advocated is the randomized discontinuation design. With this approach all patients receive the drug of interest. After a specified time period patients with stable disease are randomized to continue the agent or to receive placebo. The primary endpoint is the rate of stable disease in the two groups following an additional specified time period. Of note, patients with objective responses at any point will continue therapy on the new agent, and patients who progress on placebo can have the opportunity to cross over to active therapy. Since patients with rapidly progressing disease or excess toxicity

will not be randomized, the randomized population is enriched for patients most likely to experience the endpoint. As a result the efficiency of the trial rises dramatically and an appropriate decision as to therapy efficacy can be made with rather modest patient numbers. We have recently proposed this design for evaluating the putative anti-angiogenic agent CAI in metastatic renal cancer. With 100 randomized patients in

this study design, we calculate that we will have sufficient statistical power (85%) to detect an effect of CAI that reduces average tumor growth rate 46% or less than in controls. Since the trial does not fully evaluate all patients, and since it does not use survival, time to progression, or quality of life as a primary endpoint it can not be considered a phase III trial.

Clearly this is not the only possible phase IIB design. I also recognize that the randomized discontinuation design is still open to certain criticisms. Nevertheless, this and some of the other approaches that Dr. Eisenhauer suggests need to be prospectively evaluated. As she notes, a large number of potentially cytostatic antineoplastic agents are entering clinical trials. There is little doubt that novel approaches are needed to evaluate them in the most efficient manner possible such that ineffective ones are quickly shelved and the most promising ones are quickly moved into definitive phase III trials.

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A phase IIA study could be designed such that x% of patients experience at least y% inhibition of the target in an easily accessible tissue (such as peripheral blood monocytes) or in the tumor...

...phase IIB studies, using a randomized discontinuation design, could assess how well a new agent induces stable disease.

BREAST COMMITTEE

Innovative Breast Cancer Trial Designed to Speed Identification of Effective Cytostatic Agents

CALGB 49806, currently in development, proposes testing new agents using a new phase II endpoint—rate of disease progression—in a novel setting: metastatic breast cancer patients on “drug holiday” after effective palliation by induction chemotherapy. IL-12 will be the first new agent tested.

The search for new anti-cancer agents is increasingly focused on cytostatic drugs—those more likely to inhibit the growth and spreading of cancer cells rather than shrink tumors. The challenge facing researchers is that traditional phase II testing of these agents, requiring measures of objective response in tumor size, can fail to identify agents that could have a positive impact on overall survival, symptom palliation, or time to disease progression.

In metastatic breast cancer, the classic phase II trial design poses additional obstacles: almost half of potentially eligible patients don't have measurable disease. Accrual is slow when testing experimental agents in patients with untreated metastatic disease—physicians and patients are reluctant to delay the opportunity for immediate palliation with a proven agent. And phase II testing in the refractory setting, where the disease is already highly resistant to therapy, can generate falsely low estimates of drug efficacy. The classic phase II design deems new agents “active” if they generate objective response in 20% of tested patients. That measure can be of dubious clinical utility, in that experimental agents deemed active may be substantially less effective than proven agents.

CALGB 49806 proposes phase II testing of new cytostatic agents in metastatic breast cancer in a more opportune setting: patients who have achieved palliation with a standard induction chemotherapy regimen and are eligible for a drug holiday. Earlier clinical trials have established that there is no adverse effect on survival for patients who are given a “drug holiday” after chemotherapy achieves palliation, compared to patients who remain on continuous therapy. Higher QOL measures for the intermittent regimen underscore patient and physician preference for drug holidays if palliation (i.e. complete or partial remission) has been achieved.

The proposed endpoint for this trial is rate of disease progression after six months. Eligible patients will be randomized to treatment with the investigational agent or to a “drug holiday” (observation) for six months. If the experimental agent's success rate—the percentage of patients who have not progressed after 6 months—exceeds the success rate for observation arm patients by a statistically significant amount, the agent can be considered “active.”

Patients on the observation arm can cross over to receive the experimental agent after 6 months or after disease progression, but will be followed only for toxicity.

The first investigational agent to be tested in this trial is IL-12. It meets study criteria for selection: *in vitro* tests show that IL-12 inhibits growth rates of several solid tumor cell lines; phase I toxicity trials are completed, with an established recommended phase II dosage schedule; and IL-12 is available through the NCI for phase II trials.

The study design calls for 46 patients per arm. This will give sufficient statistical power to differentiate between a hypothetical success rate of 60% for the investigational agent and 30% for the observation arm. If the trial design is successful, up to six investigational agents can be tested simultaneously, each with 46 patients per arm (patients would be randomized in a balanced fashion to each agent currently active and the observation arm).

Summary

The novel design of 49806 has the following advantages over the classic phase II design:

- Accrual should be simple and fast: measurable disease is not required and patients must only have evidence of metastatic breast cancer which has been palliated with chemotherapy.
- Cross-over allows all patients access to the investigational agent (either at randomization for treatment or after progression while on observation).
- All patients get standard treatment first, with no unwanted delay for proven treatments.
- Will identify cytostatic as well as cytolytic (tumor-shrinking) agents.
- Tests for new agents before patients have refractory disease.
- Will identify agents with bona-fide clinical utility. A reduction in the rate of progression without chemotherapy side effects can be useful in an up-front metastatic setting and can also predict utility in the adjuvant setting.
- Should be more cost efficient: disease evaluation is performed 3 times at most (at entry, at 3 months, and at 6 months; or earlier if the patient shows signs of disease progression).

The protocol for CALGB 49806 is currently undergoing final stages of review, and is expected to open later this year. Comments should be addressed to study chair Dan Hayes at hayesdf@gunet.georgetown.edu.

Diet and lifestyle factors to be assessed for impact on cancer-recurrence include: intake of red meat, calcium, vitamin D, alcohol, fiber, vitamin E, other anti-oxidants, methionine, and folic acid. We will also look at the influence of body mass index, physical activity, smoking, aspirin and nonsteroidal anti-inflammatory drug use.

Diet & Cancer *continued from page 1*

that dietary manipulation is a successful primary or adjunctive therapy for established colon cancer. Nonetheless, patients often seek to understand what, if any, diet and lifestyle changes will reduce their mortality from colon cancer as well as the potential toxicities associated with therapy.

In a proposed amendment to a GI Committee phase III treatment study of 1260 patients with stage III colon cancer (CALGB 89803) all enrolled patients will be given a food-frequency questionnaire midway through their adjuvant therapy (four months following surgical resection) and then at six months after the completion of adjuvant therapy (14 months following surgical resection). The questionnaire has been extensively validated among large populations and provides comprehensive data on 131 food items and over 100 micro-nutrients⁷. Patients will complete the questionnaire at home on their own and return it at their outpatient visit. Included are questions about leisure-time physical activity, cigarette smoking, height and weight, as well as supplement use and alternative medicine use.

CALGB 89803 is an intergroup trial assessing whether the addition of CPT-11 will enhance the survival advantage associated with fluorouracil-based adjuvant therapy.

The proposed amendment will assess the influence of various dietary factors on the rate of cancer recurrence, and on the toxicities of adjuvant therapy. Factors to be examined include: intake of red meat, calcium, vitamin D, alcohol, fiber, vitamin E, other anti-oxidants, methionine, and folic acid. We will also look at the influence of body mass index, physical activity, smoking, aspirin and nonsteroidal anti-inflammatory drug use on patient outcomes.

The possible mechanisms by which dietary constituents may affect patient outcome are numerous. Nutrients can interact with chemotherapeutic agents, thereby influencing their efficacy. Recent studies suggest that vitamin E may enhance the cytotoxicity of 5-fluorouracil on colon cancer

cells. Chinery et al observed that the antioxidants pyrrolidinedithiocarbamate and vitamin E induced apoptosis in colorectal cancer cells⁸. This effect was mediated by induction of p21WAF1/CIP1, an inhibitor of the cell cycle, through a mechanism involving C/EBPbeta (a member of the CCAAT/enhancer binding protein family of transcription factors), independent of p53. Antioxidants significantly enhanced colorectal cancer tumor growth inhibition by 5-fluorouracil in vitro and in vivo. However, to date, no prospec-

tive studies have assessed this relationship in the adjuvant setting.

In addition, dietary constituents may influence the activity of enzymes responsible for the biotransformation and metabolism of chemotherapeutic agents. Enzymes such as glutathione S-transferase, UDP-glucuronosyl transferase, and cytochrome P450 1A1 can be induced by a variety of dietary factors. Moreover, these enzymes are critically involved in the activation and degradation of several anticancer drugs. By influencing the activity of these enzymes, dietary constituents can influence either the efficacy or the toxicity of a chemotherapeutic agent.

To date few studies have assessed diet among cancer patients. In a small study of colon cancer patients, Slattery observed an improved survival with



increasing consumption of calories, fat, and protein⁹. By contrast, the highest level of fiber intake was associated with a decreased survival when compared with the lowest level of intake.

Another study by Holmes and colleagues assessed diet among breast cancer patients¹⁰. They observed no apparent association between fat intake and mortality. However, an increased survival was noted among women eating more protein. The relative risk of mortality comparing the highest with the lowest quintile of protein intake was 0.65 (95% CI, 0.47-0.88).

Based on these preliminary studies, more extensive

Diet & Cancer *continued on next page*

CALGB GROUP NEWS

CALGB solicits international collaborations on clinical trials

CALGB study accrual could be accelerated by opening more protocols to international groups, under an initiative by the CALGB to encourage committee chairs and study chairs to actively consider international collaborations.

CALGB 9581, a GI Committee study, was recently opened by the Cancer Research Campaign—Clinical Trials Unit in the United Kingdom. 9581 has also been opened through the NCIC in Canada, and discussions are ongoing to make the protocol available to other European countries through the EORTC.

All foreign groups that participate in NCI-sponsored clinical trials must comply with U.S. regulations which include:

- An approved international cooperative project assurance from the Office for Protection from Research Risks
- All investigators who register patients must have a 1572 form on file with the Investigational Drug Branch if investigational drugs are supplied by the IDB.
- Audits must be conducted and reported according to the Clinical Trials Monitoring Branch audit guidelines.

The CALGB Data Management Center will work out procedures for patient registration, data submission and special circumstances that may dictate new CALGB procedures. The NCIC was allowed to use patient initials and hospital ID numbers to identify enrolled patients on CALGB 9581, because social security numbers aren't available in Canada and the NCIC doesn't collect patient names.

Committee and study chairs interested in developing international collaborations should contact their commit-

tee's Executive Officer or Karen Sartell at the CALGB Central Office.

New CALGB Staff:

Sarah Duggan is the newest Protocol Editor at the Central Office. Duggan, a Chicago native, has a B.A. from Connecticut College and a Certificate in Maternal and Child Health from the Boston University School of Public Health. She was most recently the Senior Clinical Research Assistant at the Behavioral Psychopharmacology Research Laboratory at McLean Hospital. The lab studied the effects of drugs and alcohol in different clinical populations.

Jennifer Zelazny joined the Central Office Information Systems staff in June as User Support Specialist. Jennifer Z. comes from Penn State University where she received her B.A. and worked in the computing services department. At the CALGB CO, she is responsible for handling day-to-day computer support, user training, and documentation. She will also maintain the CO File Server.

Jennifer Margeson is new to CALGB IS staff at the Data Management Center in Durham as Help Desk Manager/Trainer. Jennifer M. will establish the CALGB call center to support the Data Management Center as well as support issues related to the integrated IS applications. In addition Jennifer M. will be responsible for developing and conducting IS specific training sessions for both internal and external uses.

Leigh Hutchens is joining the IS team in Durham as a documentation specialist. Leigh will be responsible for all technical documentation for both internal and external consumption. Leigh will also assist Jennifer Margeson in the areas of training and development.

Diet & Cancer *continued from page 6*

efforts are needed. The proposed amendment represents an attempt to rigorously examine the affect of nutrition and lifestyle on the outcome of patients with stage III colon cancer. In the future, opportunities to explore the role of diet in other malignancies should be considered.

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CANCER CONTROL COMMITTEE

CALGB 9872: Is There a Correlation Between APC Resistance and Tamoxifen-Associated Thrombosis?

Judy Garber, M.D., Dana Farber Cancer Institute

Risk of thrombosis or pulmonary embolism from tamoxifen therapy may be reduced by screening for Factor V Leiden: a genetic mutation mediating APC resistance.

Evidence from breast cancer clinical trials shows that women taking tamoxifen are 3 to 4 times more likely to suffer thromboembolic complications—deep vein thrombosis, blood clots, or pulmonary embolism—than women taking placebos or alternative agents. The increased risk of a potentially fatal thromboembolic event is likely to be the most serious adverse effect associated with tamoxifen use.

Factor V Leiden mutation and APC resistance

Activated Protein C (APC) resistance is a described inherited hypercoagulable state found in 20-60% of patients with venous thrombosis. APC resistance is mediated by a single mutation in factor V (G1691A), termed Factor V Leiden, which destroys the site for factor V cleavage by protein C, resulting in slower inactivation¹. Heterozygotes for the Factor V Leiden mutation have a 7-fold increase in the risk of deep venous thrombosis; the risk among homozygotes is increased 80-fold².

Women with Factor V Leiden mutations have increased blood coagulability in the presence of heightened estrogen levels due to pregnancy or oral contraceptives. In a large study evaluating this relationship, the relative risk of DVT was 4 for oral contraceptive (OCP) users, 8 among Factor V Leiden heterozygotes, and 34.7 in women with both risk factors³. In a study of women with thrombosis during pregnancy, a state of high hormone levels, 60% had Factor V Leiden⁴.

These observations led investigators to ask whether Factor V Leiden might be an identifiable risk factor for the development of blood clots in women taking tamoxifen, if the enhanced coagulability associated with tamoxifen is related to its estrogenic activity. The literature contains one report of 3 women with blood clots on tamoxifen, all of whom had a Factor V Leiden mutation⁵. This is quite suggestive, given that Factor V Leiden is present in 3-10% of the general Caucasian population and 2-15% of minority cohorts.

Tamoxifen is associated with an increased risk of vascular events

In a large ECOG study of chemo-hormonal adjuvant therapy for breast cancer, the incidence of thromboembolic complications was 5.4% among patients receiving adjuvant therapy, and 1.6% among patients on the observation arm ($p=0.0002$)⁶; the difference was almost entirely restricted to patients receiving tamoxifen. In NSABP-B14, the rate of thrombosis among women taking adjuvant tamoxifen without chemotherapy was increased approximately 4-fold

compared to placebo (1.5% vs. 0.4%)⁷.

Most compelling, perhaps, are the data demonstrating an excess of thrombotic events in women taking tamoxifen for breast cancer prevention in NSABP P-1⁸. In this trial, an elevated risk ratio could be demonstrated for both deep vein thrombosis (RR 1.60, 95% CI 0.91-2.86) and for pulmonary embolism (RR 3.01, 95% CI 1.15-9.27). Three women in the tamoxifen arm suffered fatal pulmonary emboli. A non-significant RR of 1.59 was also observed for stroke, which were mixed hemorrhagic, occlusive and unknown type. The same magnitude of effect has been observed for the first of the SERM agents, raloxifene, but to date no fatal complications have been reported⁹.

Clinical implications of an association between Factor V Leiden and thrombosis on tamoxifen

Testing for Factor V Leiden prior to initiation of tamoxifen therapy could have a significant impact on the safety of preventive and adjuvant therapies. The relationship may extend to the next generation of tamoxifen-related compounds, the SERMS. Raloxifene, another synthetic estrogen/antiestrogen has also been associated with thrombotic complications.

Clinical testing for Factor V Leiden has been recommended for women considering pregnancy who have a family history of thrombosis or thromboembolism during pregnancy¹⁰. Such testing could be clinically useful for women with similar family histories who are considering tamoxifen for breast cancer prevention or therapy. The assay for Activated Protein-C Resistance is already widely available. Factor V Leiden determination is a simple and inexpensive molecular test that is increasingly available. If most clots on tamoxifen are attributable to identifiable predisposing factors, the majority of women for whom its benefits are potentially important can be less fearful of tamoxifen-induced clot. Women with Factor V Leiden may be able to take tamoxifen or related compounds along with prophylactic anticoagulants to lessen their risk of thrombotic events.

Protocol 9872

The most efficient way of addressing the role of APC resistance (Factor V Leiden) in the risk of thrombosis for women receiving adjuvant tamoxifen therapy is a case-control study. In the CALGB study, cases are women who experienced a venous or arterial thromboembolic event while taking adjuvant tamoxifen, with or without chemotherapy. They will be compared to control women who did not develop a clot while taking tamoxifen in similar circumstances. To enhance accrual, adjuvant tamoxifen may have been administered on or off CALGB treatment protocols. Other factors contributing to clots will be evaluated in the analysis. Susan Halabi, the project statistician, estimates that 120 sets of a case plus 2 controls per case

will provide sufficient power to answer the question.

Fortunately, since blood clots on tamoxifen are relatively uncommon (risk of DVT or PE in women on tamoxifen from the BCPT is 3 per 1000 per yr), this study does not rely on women who are taking tamoxifen at the time a blood sample is taken. The Factor V Leiden analysis is a genetic test so it can be done at any time, including while the patient is taking coumadin. Women may be taking coumadin when they give their blood sample, but could not have been using coumadin at the time of the blood clot or during the time they are considered controls.

To date, a few sites have provided the majority of subjects, particularly Wake Forest, Wayne County and the University of Iowa.

The Cancer Control committee wants to complete this study quickly to get an answer to this important question as soon as possible. The PI, Judy Garber, will help you and your site in any way she can. Please contact her with questions or comments at judy_garber@dfci.harvard.edu.

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What is involved in participation?

What the patient has to do:

- Read and sign informed consent
- Provide a blood sample.
- Complete a survey about family history and other risk factors for clots (the On-Study form).

What the physician/site has to do:

- Put the protocol through your IRB.
- Notify the study chair (Judy Garber at judy_garber@dfci.harvard.edu) that you have eligible case(s) and control(s). She will send you collection kits containing the blood tubes and mailers, and pre-addressed FEDEX slips for pre-paid shipment.
- Contact the patients, consent them, and register them with the CALGB. Controls may be registered up to three months after the case.
- Obtain participant blood specimens and complete their On-study survey forms.
- Send the specimen to Lynn Dressler's lab (address on the FEDEX form) and fax the On-study form to the Data Management Center at Duke.
- Submit documentation of the clot to the DMC within 1 week of registration, or ASAP.
- Collect Cancer Control Credits (0.3 credits per case/control set).

What about results?

In order to expedite approval of the protocol by the NCI and IRBs, the specimen bank will be anonymized. Therefore, results of the Factor V Leiden and any future studies will not be available to individual patients or their physicians. However, all participating physicians will be contacted with the overall study results, so that they can make a decision regarding the appropriateness of testing individual patients for Factor V Leiden or Activated Protein C resistance.

PSYCHO-ONCOLOGY COMMITTEE

Measuring the Psychological Impact of Cancer

Gary Rodin, M.D., Toronto Hospital, Toronto

Understanding the psychiatric health of cancer patients means untangling overlapping symptoms stemming from situational, pre-existing and treatment-related causes. New diagnostic tools and use of qualitative approaches can give us a clearer picture of cancer patients' psyches, which can ultimately improve the effectiveness of cancer treatment in the presence of psychiatric disorders, as well as trigger timely and appropriate mental health care interventions.

A diagnosis of cancer is often a personal tragedy for individuals who are affected and for their families. Patients may feel overwhelmed by what they perceive as a catastrophic event. Psychiatric disorders, particularly depression, are common in such patients, but much less frequent than are problems in coping and adjustment. In this regard, of the 2,500 referrals in 1999 to the Psychosocial Oncology Program at the Princess Margaret Hospital in Toronto, requests for assistance with coping were six times more common than referrals for a suspected psychiatric disorder.

An important goal of psychosocial research in cancer should be to develop methods which capture more fully the experience of illness and the sources of psychological morbidity. Considerable suffering in cancer patients may not be revealed by the current diagnostic assessments for psychiatric morbidity. Further, psychological screening tests which are symptom-based do not necessarily detect psychological disturbances related to the disease or treatment, even when these disturbances are profound.

Self-esteem and self-concept are specific aspects of experience that are not adequately assessed by the usual measures of distress or psychiatric morbidity. In that regard, many studies have failed to demonstrate an expected fall in self esteem after the onset of cancer¹. Such negative findings may reflect the resilience and adaptability of many individuals to the stress of cancer or may be due to the limitations of the measurement tools used. In particular, the impact of cancer on specific dimensions of self-esteem, such as body self esteem and social self esteem, may not be demonstrated by traditional measures, such as the *Rosenberg Self Esteem Scale*, which provides only global scores. New multidimensional measures of self-esteem are being employed in current studies to assess the impact of cancer on multiple domains of self-esteem^{2,3}.

Cancer patients may find that they lose touch with their self identity after the illness begins and that they "become" the cancer or its treatment. The *Modified Engulfment Scale*⁴ was developed to assess the degree to which self-concept is defined by chronic illness. When used in patients with major psychiatric disorders, elevated scores were associated with hopelessness and low self-esteem, poorer adjustment and more severe illness. This "engulfment" of the self by the experience of illness may be an important determinant

of adjustment and quality of life in cancer patients.

Particularly when the disease is in remission, engulfment of the self may indicate the need for psychosocial intervention. Research is now in progress⁵ to determine the utility of this measure in cancer patients and the extent to which engulfment of the self predicts quality of life.

These and other qualitative dimensions are not captured by the traditional diagnostic screening. Qualitative approaches are needed to help identify important psychological disturbances in cancer patients. However, tools to gather qualitative data may be time-consuming and complex to develop, administer and interpret. Measures which assess subjective experience but which also have a quantitative dimension may be more feasible to employ in many clinical and research settings. One recently developed tool is the *Explanatory Model Interview Catalogue* (EMIC)⁶, a semistructured interview used to obtain both qualitative and quantitative data about patients' understanding of their illness. It serves to elicit information about patterns of distress, the perceived causes of the illness, preferences for health care and treatment, general illness beliefs and the extent to which stigma is perceived to be associated with the condition. It has been of value with both medical and psychosomatic disorders to help caregivers provide treatment which takes into account the explanatory model of their patients. Salmon et al developed a *Life Evaluation Questionnaire* with 5 dimensions: freedom versus restriction, appreciation of life, contentment, resentment and social integration. They found that this scale added significantly to the clinical evaluation and identified concerns that were largely not tapped by symptom-based measures.

These approaches, when combined with other screening tools and diagnostic instruments, help to bridge the gap between clinical judgment and empirical observations. Such methodology may help to increase the relevance of psychosocial research in cancer and to develop interventions to improve quality of life and to reduce unnecessary health care utilization.

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Surgical Resection of Pulmonary Metastases

Julie Schuetz, MS, RN, Greenebaum Cancer Center,
University of Maryland Medical Center, Baltimore, MD

Although distant spread of cancer is considered an ominous sign, and often relegates a patient to palliative care options, there is evidence that pulmonary metastases deserve a closer look. There are a number of retrospective studies that have shown survival benefits for patients treated with surgical resection of their pulmonary metastases. While potentially promising, this is an aggressive approach and careful patient selection is of paramount importance.

Pulmonary metastases occur in a number of different cancers, including melanoma, colon, renal, germ cell tumors and sarcoma. In a number of cancers, when lung metastases are the only remaining site of disease, surgical resection, known as pulmonary metastatectomy, can provide a survival advantage and cure. The degree of benefit differs by primary tumor type, with osteogenic sarcoma, renal cell carcinoma, head and neck cancers and germ cell tumors having the most favorable results (48-59% long-term survival). Soft tissue sarcoma and colon cancers have cure rates in the range of 30% following resection of isolated pulmonary metastases. Metastatic melanoma has the least favorable results, although carefully selected patients may enjoy long term survival after resection.

Furthermore, up to 50% of patients may require repeated metastatectomies, as additional lesions become apparent. Multi-institution data supports this aggressive approach. In fact, retrospective reviews have shown that patients with repeated episodes of lung metastasis benefit from repeated surgical resection, provided they have adequate pulmonary function to tolerate such procedures.

Traditionally, these pulmonary metastatectomy resections have been performed via sternotomy or thoracotomy. Surgeons have preferred these open approaches that allow them to palpate the entire lung field for tumors. More recently, modern CT scanning (in particular, spiral CT) allows the detection of very small (<3 mm) tumors. Tumors this small are unlikely to be palpable during an open procedure.

CALGB surgeons have been at the forefront of prospectively studying video-assisted thoracic surgery (VATS). Through a number of clinical trials (there are 6 currently open), they have demonstrated the safety, efficacy and feasibility of VATS. VATS allows direct visualization of the chest and its structures. Patients prefer VATS because their incisions are smaller, their hospitalizations and recovery times are typically shorter and their pain is usually less. Most patients are able to return to work in 2 weeks or less, rather than the 6 weeks expected following traditional open procedures.

Although traditional surgical teaching has dictated open resection with manual palpation of the lung as the proper method of resection for pulmonary metastases, many surgeons now believe VATS can achieve similar survival bene-

fits with less morbidity and pain to the patient. In particular, for patients who will require repeated procedures for recurrent pulmonary metastases, VATS may offer even greater benefit.

CALGB 39804: A Phase III Randomized Prospective Trial of Open versus Minimally Invasive, Video-assisted Resection of Pulmonary Metastases was activated February 15, 1999. It is an intergroup study. Patients who are considered for the study must (1) have their primary tumors controlled, (2) have no more than 4 lesions, all amenable to VATS, (3) have no other site of distant metastasis and (4) have adequate predicted postoperative pulmonary reserve. Following spiral chest CT, patients will be randomized to receive either open resection or minimally invasive VATS.

The primary objective of CALGB 39804 is to compare the overall survival between a minimally invasive and open approach in the treatment of isolated pulmonary metastases. Secondary objectives are:

- to compare the failure-free survival between a minimally-invasive and open approach;
- to compare patterns of recurrence with minimally invasive and open approaches, and to determine what factors are predictive of recurrence
- to test for differences in patients' reported quality of life between the two methods and
- to measure the difference in cost between the open approach and VATS.

The CALGB Surgery Committee predicts that this prospective randomized trial will definitively affirm video-assisted thoracic surgery to be a safe, practical and cost-effective alternative to open procedures in the management of patients with isolated pulmonary metastases, with less pain and disruption to the lives of the patients.

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CRA NEWS

Mentoring for New CRAs

Laurie Smith, CRA, University of Missouri, Ellis Fischel Cancer Center

The CRA Committee has launched a new pilot mentoring program for attendees of the 1999 Beginner's Workshop held in Durham this past August. Over the last few years, members of the CRA Committee have discussed ways to increase the level of support that is offered to CRAs at CALGB institutions. Some CRAs working on CALGB studies are working in very cohesive environments, alongside other staff members knowledgeable about CALGB data requirements, policies and resources that are in place within the Group. Other CRAs are working as single staff members in affiliate institutions, or in specialties within an institution, and may be more isolated from the hub of CALGB activity. Consequently, accessibility to changes within CALGB is highly variable within the Group.

Training new CRAs can also place a strain on institutions that are stretched for resources, and synthesizing the most current information available through CALGB can be quite challenging. The Central Office and the Data Management Center are both affected by transitions within institutions that affect data management on particular studies, and a high turnover rate of entry level CRAs can ultimately have an effect on the overall quality of data collected. For all of these reasons; for the individual CRAs, for member institutions, and for the administrative units of the Group, the CRA Committee decided to implement a mechanism of support for CRAs in the field by establishing a mentor program. A mentoring program offers the opportunity to address individual questions and concerns, and may provide insight regarding general issues within the Group.

Mentoring programs have been implemented in a variety of professional settings, both in the corporate and academic environments. This unique professional relationship has the potential to improve individual job satisfaction, promote interaction and communication, and ultimately to improve the quality of data collection. The individual approach to mentoring programs allows both mentor and participant to adapt the level of exchange to the experience of participants. Many individuals attending the Beginner's Workshop are quite new to research, while others are experienced health professionals who are simply new to CALGB. Consequently, the expectations and needs will vary greatly across the Group.

Implementation of a pilot test of the mentoring program started with attendees at the CRA Beginner's Workshop this

summer in Durham, NC.

The pilot program is structured to include sequential assessments for a period of 12 months. Each member of the CRA committee will contact approximately nine CRA participants who attended the August workshop. The initial introductory phone call will provide an opportunity to discuss the program, answer any questions that arose from the Beginner's Workshop and address any current issues. CRA mentors will encourage participants to contact them at any time throughout the year for any concerns related to CALGB activities. Subsequent contacts will be scheduled at three month intervals, from the third through the twelfth months following the workshop. During these scheduled assessments, CRA mentors will inquire about overall job satisfaction, particular problems or concerns, and frequency of contact with the CALGB Data Management Center and Central Office. Any unscheduled contacts will be documented by the CRA mentors to allow the committee to

assess any patterns of concerns or problems across the Group. All conversations between the mentor and participant will be kept confidential.

The CRA Committee is hopeful that the mentoring program will benefit the Group in several ways. By providing an opportunity for CRAs to communicate directly

Mentors may be in a unique position to hold out the big picture and help to clarify how the day-to-day details of CALGB data management fit into our common vision of better care for patients

with others in the field, mentors may be able to clarify issues and disseminate information that will encourage more effective utilization of the new resources available in CALGB, such as the website and database. Each of us has a commitment to high quality data collection and a common goal of better treatment for patients. Efforts through CALGB to consistently improve policies and enhance our technological capabilities can sometimes appear confusing to a CRA new to Group practice. A high volume of new information combined with expectations for scientific rigor and careful attention to myriad details can be overwhelming to new CRAs. Support for research is typically lean in medical centers across the country, and people are frequently being asked to do more with less. Mentors may be in a unique position to hold out the big picture and help to clarify how the day to day details of CALGB data management fit into our common vision of better care for patients.

The CRA committee would like to thank all CRAs who are participating in this exciting initiative. If you have any questions about the Mentoring pilot program, please contact Jean Roark at (314) 996-5569.

PROTOCOL NEWS

NEW STUDIES

August 15, 1999

CANCER CONTROL COMMITTEE

79804—Issues of survivorship among breast cancer survivors: follow-up of disease-free survivors of CALGB 8541., *Study chair: Electra D. Paskett, Ph.D.*

September 15, 1999

RESPIRATORY COMMITTEE

39809—Phase II trial of gemcitabine/vinorelbine, gemcitabine/taxotere and gemcitabine/CPT-11 in stage IIIB/IV non-small cell lung cancer
Study chair: Caio Max S. Rocha Lima, M.D.

CLOSED STUDIES

August 1, 1999

RESPIRATORY COMMITTEE

9495—Induction chemoradiotherapy followed by surgical resection for non-small cell lung cancer involving the superior sulcus (Pancoast tumors): a phase II trial. *Study chair: Frank C. Detterbeck, M.D.*

August 31, 1999

LYMPHOMA COMMITTEE

9550—AMC 003: Low-dose interleukin-2 in AIDS lymphoma: a pilot study
Study chair: Michael A. Caligiuri, M.D.

September 1, 1999

SOLID TUMOR CORRELATIVE SCIENCES COMMITTEE

8861—Monitoring CA 15-3 antigen in patients during and after adjuvant therapy for stage II, node positive carcinoma of the breast: companion to 8541, 8782, and replacement studies. *Study chair: Daniel F. Hayes, M.D.*

9484—Linkage of molecular and epidemiological breast cancer investigations with treatment data: a specialized registry companion to 9082, 9342, 9343 and 9344. *Study chair: O Ross McIntyre, M.D.*

Protocol Distribution Mainly on CALGB Web Site

Thanks to the successful implementation of protocol publication on the CALGB web site, August 1999 was the last month that CALGB protocols were sent via "snail-mail" to CALGB main member institutions and CCOP institutions. Some protocol information that is not available in its entirety on the CALGB web site, including certain amendments or protocol documents from intergroup studies, will continue to be mailed.

The monthly "protocol mailing" to CALGB main members and CCOPs is now conducted via an e-mail broadcast to members notifying them of new protocol documents available for downloading from the CALGB web site (www-calgb.uchicago.edu).

A PIN number is required to access the protocols on the web. Lead CRAs at each main member and CCOP have been provided with a list of PIN #s for their members. If you are unable to obtain your PIN # from your lead CRA, please contact Gabrielle Dye at the CALGB Central Office (gdye@midway.uchicago.edu, 773-834-2545). If you experience difficulties in accessing and downloading documents, please contact Jennifer Zelazny (jjzelazny@uchicago.edu, 773-834-4014). Questions regarding the content of protocols and protocol updates should continue to be directed to the responsible protocol editor.

CALGB STUDY FUNDING

Support is available to qualifying institutions for participation in these studies. Payments are made through the main member institution. For more information, visit the CALGB website or contact Mary A. Sherrell, Financial Officer at (773) 702-9856.

9270 – Colorectal Adenoma Prevention Trial Using Aspirin. Phase III Study.

9473 – Omega-3 Fatty Acids for Cancer Cachexia. Phase I/II Trial.

9481 – Hepatic Artery Floxuridine, Leucovorin, and Dexamethasone vs Systemic 5-FU and Leucovorin as Treatment for Hepatic Metastases from Colorectal Cancer. Phase III Study.

9490 – Does an Oral Analgesic Protocol Improve Pain Control for Patients with Cancer? (ECOG E4293)

9499 – Chemoprevention Trial to Prevent Second Primary Tumors with Low-Dose 13-CIS Retinoic Acid in Head and Neck Cancer. (MDACC DM90-094)

9581 – Adjuvant Immunotherapy with Monoclonal Antibody 17-1A after Resection for Stage B2 Colon Cancer. Phase III Randomized Study.

9594 – Intermittent Androgen Deprivation in Patients with Stage D2 Prostate Cancer. Phase III Study. (SWOG 9346)

9596 – Vincristine, Doxorubicin, and Dexamethasone with or w/o PSC-833 in Patients with Relapsing or Refractory Multiple Myeloma. Phase III Study. (ECOG E1A95)

9682 – Prognostic Significance of Endorectal MRI in Predicting Outcome After Combined Radiation and Androgen Suppression for Prostate Cancer. Prospective Phase II Study.

9730 – Taxol vs. Taxol + carboplatin for advanced NSCLC. Randomized Phase III Study.

9770 – High-Dose vs Conventional Dose Octreotide Acetate vs Loperamide in the Treatment of Chemotherapy-related Diarrhea in Patients with Colorectal Cancer. Randomized Trial. (ECOG E1295)

9782 – Phase II trial of potency-sparing hormonal therapy in patients with elevated serum PSA after radiation therapy or radical prostatectomy for prostate cancer.

9870 – Quality of life and cost analysis of a prospective randomized phase III trial comparing trimodality therapy to surgery alone for esophageal cancer.

9872 – Activated protein C resistance and tamoxifen-associated thrombosis

19801 – A Phase II Study of 506U78 in Patients with Refractory or Relapsed T-Lineage Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL)

19803 – Randomized phase II trial of oral topotecan given twice a day for 5 days vs. 1x/day for 10 days to patients with myelodysplastic syndromes

39802 – Video-assisted lobectomy for peripheral (3 cm or less) N0, non-small cell lung cancer – a phase II feasibility study

39804 – Phase III randomized prospective trial of open versus minimally invasive, video-assisted resection of pulmonary metastases

39803 – Pre-resectional minimally invasive surgical restaging of stage III (mediastinal node positive) non-small cell lung cancer (NSCLC)

49805 – Phase III randomized double blind study of letrozole versus placebo in women with primary breast cancer completing five or more years of adjuvant tamoxifen

89804 – Randomized phase III trial of 3 different regimens of CPT-11 plus 5-FU and leucovorin compared to 5-FU and leucovorin in patients with measurable advanced adenocarcinoma of the colon and rectum.

79802 – Randomized controlled trial to evaluate the impact of easy-to-read informed consent statements

509801 – Phase III Study of Adjuvant Ganglioside Vaccination GM2-KLH/QS-21 Therapy vs High-Dose Interferon Alfa-2b (IntronA) for High Risk Melanoma (T4 > 4 mm Primary or Regional Lymph Node Metastasis).

CALGB FALL MEETING SPECIAL SECTION

CALGB Fall 1999 Group Meeting: Miami Beach, Florida, November 11-14



The Fontainebleau Hilton, a favorite among celebrities and the site of famous film shots, hosts CALGB's 1999 Fall Group Meeting. Located on 20 acres of beachfront, this four-star, four-diamond resort offers guests first-class recreational, dining and night life enjoyment. The Hilton is conveniently located near area attractions, the renowned Bal Harbour Shops and the exciting Art Deco District or "South Beach."

Miami's South Beach brings a stylish era back to life with a number of art museums and galleries calling this home. South Beach is definitely a neighborhood on the move. European-type outdoor cafes, international specialty restaurants and shops as well as entertainment abound along the Atlantic coastline community of South Beach, accessible from most areas by water-taxi. Additionally, nearby Bayside Marketplace is an exceptional shopping establishment with great dining right on the water.

GROUP MEETING HIGHLIGHTS:

Plenary Session

Saturday, Nov. 13, 2 – 4 p.m.

- **Group Chair Remarks**
Richard L. Schilsky, M.D.
University of Chicago
- **“Current status and new directions in the management of bladder cancer”**
Dean F. Bajorin, M.D.
Memorial Sloan Kettering Cancer Center
- **“New imaging technology for detection and treatment of cancer”**
Bruce J. Hillman, M.D.
University of Virginia Health System

Study Chair Workshop

Friday, Nov. 12, 8 a.m.– Noon

CALGB requires that all first-time study chairs attend the Study Chair Workshop. The Workshop is designed to provide new study chairs with the necessary skills and information to be an effective study chair during protocol development and after study activation. If the first-time study chair does not attend this Workshop, he/she will not be permitted to continue with the study. In addition, study chairs are required to attend the Study Chair Workshop every four years. Therefore, current study chairs who last attended a workshop in 1995 will be required to attend this November. The next Study Chair Workshop will be held at the Combined Core/Group meeting in November of 2000. Advance registration is required—please see the registration form on page 17.

Audit Preparation Workshop

Friday, Nov. 12, 3–5 p.m.

The Audit Prep Workshop is designed to assist the CRA and physician in preparing for federally mandated audits by CALGB. Attendees at past Audit Prep Workshops have given consistently high ratings, assessing that the workshop “meets their needs to a great extent.”

Coordinated by Barbara Barrett, MS, CCRA, University of Missouri Ellis Fischel Cancer Center. Advance registration is required—please see the registration form on page 17.

CALGB Database Hands-On Training: On-Line Patient Registration

*Saturday, Nov. 13,
8– 8:45 a.m.; 9– 9:45 a.m.; 10– 10:45 a.m.;
11– 11:45 a.m.; 4:30– 5:15 p.m.; 5:30– 6:15 p.m.*

On-line patient registration hands-on training sessions will be conducted at the Fall 1999 Group meeting. These sessions will allow you to become familiar with the software that you will be using to register patients. Any institution that has registration privileges and that has been given an account on the Statistical Center computer system and has downloaded the CALGB IS software should plan on having at least two representatives attend a session. Session open to CRAs from main member institutions, CCOP administrative offices, and affiliates that accrue over 30 patients per year.

The on-line system is now in use for some trials. Space is limited—you must register in advance. See the registration form on page 17.

An open invitation from the Radiation Oncology Committee

Friday, Nov. 12, 2– 8 p.m.

*Andrew T. Turrisi, M.D., chair, Radiation Oncology
Committee*

Radiation Oncology has become a frequent partner in many disease sites. Many studies have critical or incidental aspects requiring radiotherapy. The Radiation Oncology Committee aims to work with disease committees to provide expert information on the use of radiotherapy in investigative and standard treatment regimens.

We welcome participation of new people from CALGB main member institutions, affiliates, at-large members, and CCOPs. The Radiation Oncology committee meets at all group and core meetings, and welcomes new people, even one-time or first-time participants. All meetings are open, and all CALGB members are invited to attend.

In order to link CALGB radiation oncologists or their facilities through e-mail, we are creating a roster of radiation oncologists and physicians that provide radiation oncology at CALGB institutions. This roster, with physician specialty information, is intended to foster communication about radiation oncology and resolve problems at the earliest time. We also hope to offer open radiation oncology conference call sessions to facilitate protocol development and review between meetings. Please submit names, e-mail addresses, contact information and disease specialties to Dr. Turrisi at the address listed below.

For further information, questions or comments, please contact Dr. Turrisi, Medical University of South Carolina; fax: (843)792-5498; e-mail turrisi@radonc.musc.edu.

Reception and Dinner

Saturday, Nov. 13, 6:30 – 9:30 p.m.

CALGB registrants are invited to experience a Caribbean-themed reception to be held on the hotel's grounds' outdoor lawn area, adjacent to the pool and overlooking the ocean. Feast on an assortment of eclectic foods while mingling with your colleagues and taking in the ocean breezes while enjoying light entertainment.

MEETING REGISTRATION

Group Meetings are open to the membership of the CALGB, as well as to invited guests.

Funding: The purpose of the committee budgets in the Central Office grant is to support Core Meetings, not Group Meetings. Committee Chairs may, however, request that these budgets be used to support the travel and lecture fees of non-CALGB speakers at their Group Meeting Committee meetings.

Deadline and Fees: \$40 (for registrations postmarked by Nov. 1); \$65 for registrations postmarked after Nov. 1 or on-site registration. Registration fees are nonrefundable.

Substitutions: If you are unable to attend the meeting, substitutions are permissible, providing, however, you inform the Central Office in writing by Nov. 1. After this date, we will be unable to accept substitutions.

To Register: Fill out the Registration Form on page 17; and mail or fax to the CALGB Central Office by Nov. 1.

Continuing Medical Education Credits

M.D., Ph.D., D.O., and P.A.s

The University of Chicago has approved co-sponsorship of CALGB's Fall Group Program. The University of Chicago is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. Approval of approximately 18.0 credit hours in Category I of the Physician's Recognition Award of the American Medical Association has been granted.

R.N., O.C.N., and A.R.N.P.s

The Illinois Nurses Association has approved Continuing Education Credit (approximately 22.0 contact hours) for nurses.

C.C.R.A.s

An application for approval of continuing education credit has been submitted to the Society of Clinical Research Associates.

CME and CEU forms and instructions will be available at the Information Table at the Group meeting located at CALGB Registration.

CALGB Fall Group Meeting Schedule

November 11–14, 1999 • Fontainebleau Hilton • Miami Beach, Florida

THURSDAY, NOV. 11

7 am – 6 pm	Registration
8 am – Noon	Extended Executive Committee*
8 am – Noon	Patient Advocate Training
Noon – 4 pm	Cytogenetics Workshop
1 – 3 pm	Transplant Core Committee*
1 – 3 pm	GI – Solid Tumor Correlative Sciences Committee*
1 – 7 pm	Prostate Core Committee*
3 – 9 pm	GI Core Committee*
3 – 9 pm	Leukemia Core Committee*
3 – 9 pm	Respiratory Core Committee*
6 – 8 pm	Core Dinner Buffet*
7 – 9 pm	Prostate – Solid Tumor Correlative Sciences Committee*

FRIDAY, NOV. 12

6:30 am – 6 pm	Registration
7 – 9 am	Core Continental Breakfast Buffet*
8 – 10 am	Quality of Life Sub-Committee*
8 am – Noon	Study Chair Workshop†
8 am – Noon	CRA Core Committee*
8 am – Noon	Patient Issues Core Committee*
8 am – Noon	Oncology Nursing Core Committee*
8 am – 2 pm	Lymphoma Core Committee*
10 am – Noon	Breast-Solid Tumor Correlative Sciences*
10 am – Noon	Pharmacy Core Committee*
10 am – Noon	Clinical Economics Sub-Committee*
10 am – Noon	Prevention Sub-Committee*
Noon – 1 pm	Conflict of Interest Committee*
Noon – 2 pm	Symptom Control Sub-Committee*
Noon – 2 pm	Core Luncheon Buffet *
Noon – 3 pm	CRA Committee
Noon – 5 pm	Data & Safety Monitoring Board*
Noon – 6 pm	Pathology Core Committee*
1 – 2 pm	Membership Committee*
2 – 8 pm	Radiation Oncology Committee
2 – 8 pm	PET Core Committee*
2 – 8 pm	Breast Core Committee*
2 – 8 pm	Corr Sciences Leukemia/Lymphoma Core*
3 – 5 pm	Audit Preparation Workshop†
5 – 8 pm	Oncology Nursing/Pharmacy Committees
5 – 8 pm	Melanoma Working Group Core*
6 – 8 pm	Core Dinner Buffet*
8 – 10 pm	Data Audit Committee*

SATURDAY, NOV. 13

6:30 am – 5 pm	Registration
7:30 – 9:30 am	Surgery Committee
8 – 9 am	Constitution Committee*
8 – 10 am	Prostate Committee
8 – 10 am	Pathology Committee
8 – 11:45 am	CALGB Database Hands-On Training**
8 am – Noon	Leukemia & Leukemia Corr Sci Cmte
9:30 – 11:30 am	Thoracic Surgery Sub-Committee
10 – 10:30 am	BREAK
10 – 11 am	Institution Performance Evaluation Cmte*
10:30 am–12:30 pm	Cancer Control & Health Outcomes Committee
10:30 am–12:30 pm	Melanoma Working Group
10:30 am–12:30 pm	GI Surgery Sub-Committee
10:30 am–12:30 pm	Respiratory Committee
Noon – 1 pm	Membership Committee*
2 – 4 pm	Plenary Session
4 – 4:30 pm	BREAK
4:30 – 5:30 pm	Surgical Quality Assurance Review Committee*
4:30 – 6:15 pm	CALGB Database Hands-On Training**
4:30 – 6:30 pm	PET Committee
4:30 – 6:30 pm	Transplant Committee
4:30 – 6:30 pm	Lymphoma & Lymphoma Corr Sci Cmte
4:30 – 6:30 pm	Cancer in the Elderly Working Group
4:30 – 6:30 pm	Breast Surgery Sub-Committee
4:30 – 6:30 pm	Solid Tumor Correlative Sciences Committee
6:30 – 9:30 pm	Reception

SUNDAY, NOV. 14

7 – 11:30 am	Registration
7:30 – 10:30 am	Board of Directors*
8 – 10 am	Patient Issues Committee
10:30 am–12:30 pm	Breast Committee
10:30 am–12:30 pm	GI Committee
10:30 am–12:30 pm	CCOP Committee
10:30 am–12:30 pm	Respiratory-Solid Tumor Correlative Sciences*

* Closed meeting

** 45-minute training sessions: advance registration required, schedule assignments made by Central Office

† Advance registration required

ATTENDEE INFORMATION

NAME & TITLE _____ SOCIAL SECURITY # _____
 INSTITUTION _____ PHONE # _____
 ADDRESS _____ FAX # _____
 _____ E-MAIL _____
 CITY _____ STATE _____ ZIP _____

REGISTRATION

ADVANCE REGISTRATION DEADLINE IS Nov. 1, 1999 – *Forms must be postmarked by deadline to receive discount.*
 Please check off your selections, enter the appropriate fees, and fill in your total below.

GROUP MEETING
(Fee includes Agenda Book)

COST
\$40 advance/
\$65 after Nov. 1

AGENDA BOOK ONLY
(Order by Nov. 1 to guarantee availability)

\$30

DONATION TO CALGB FOUNDATION *(Optional)*
 I wish to make a tax-deductible donation in the following amount:
You will receive an acknowledgment from the Foundation by mail.

REGISTRATION DATE:	
PAYMENT AMOUNT	CHECK #
\$ _____	# _____
\$ _____	# _____
\$ _____	# _____
TOTAL DUE	
\$ _____	# _____

CENTRAL OFFICE USE ONLY

WORKSHOP REGISTRATION

Advance registration is required for the following workshops. Check your selections and **circle your preferred dates and times*** where applicable. There are no extra fees for workshop attendance. If you are submitting your registration via mail, you may fax this form separately to the CALGB Meetings Manager, 312-345-0117, to reserve your spot(s).

Study Chair Workshop
Fri. Nov. 12 8 am – Noon

Audit Preparation Workshop
Fri. Nov. 12 3 – 5 pm

CALGB Database Hands-on Training*
Sat. Nov. 13 8 – 8:45 am 9 – 9:45 am 10 – 10:45 am 11 – 11:45 am
 4:30 – 5:15 pm 5:30 – 6:15 pm

*Space will be assigned on a first-come basis. Depending on availability, we will attempt to assign registrants to one of their preferred sessions. Registrants will receive their assigned schedule in the mail.

PAYMENT

- PAYING BY CHECK:** You may pay for all items with one check. Make check(s) payable to University of Chicago/CALGB
- PAYING BY CREDIT CARD:** You may use Visa or MasterCard

CARDHOLDER'S NAME _____ Visa MasterCard
 CARD NUMBER _____ EXP. DATE _____
 CARDHOLDER'S SIGNATURE _____

IMPORTANT

CANCELLATIONS AND SUBSTITUTIONS

Regretfully, we are unable to issue refunds for meeting cancellations. If your registration has been processed and you cannot attend the meeting, you may send a substitute provided we receive your request in writing by Nov. 1, 1999.

AGENDA BOOKS

The registration fee includes the Agenda Book. However, Agenda Books may not be available if you register after Nov. 1.

REGISTER BY FAX OR MAIL

For credit card payment, you may fax this form to CALGB Central Office, fax # 312-345-0117. You may also mail this form with your payment to: CALGB Registration, 208 S. LaSalle, Suite 2000, Chicago, IL 60604-1104.

MEETING INFORMATION *continued from page 15*

HOTEL RESERVATIONS

Fontainebleau Hilton

4441 Collins Avenue

Miami Beach, FL 33140

800-548-8886

RATES:

\$ 99 Single; \$149 Double

Room rates are subject to 12.5% city and state occupancy taxes

DEPOSITS:

All reservations must be accompanied by a first-night's NON-REFUNDABLE DEPOSIT.

CHECK-IN/CHECK-OUT TIMES:

Check-in is 3 pm; Check-out is 11 am.

Note: Should you check-out earlier than your scheduled departure you will be assessed a \$50 early check-out fee.

RESERVATIONS DEADLINE:

All reservations must be received by the hotel no later than October 21, 1999. Room reservations will be available on a first-come, first-served basis until CALGB's hotel block is filled. Rooms reserved after the cutoff date are subject to hotel availability and prevailing hotel rates.

RESERVATIONS PROCEDURES:

You may make reservations by phone, fax, or mail utilizing one of the following methods:

Phone Reservations: Call the Fontainebleau at 1-800-548-8886. Be sure to identify yourself as a Cancer and Leukemia Group B (CALGB) attendee in order to receive the special convention rate and have credit card information available at the time of your call.

Fax Reservations: 1-305-673-5351. Fax the completed copy of the Hotel Reservation Form from this newsletter directly to the hotel. Be sure to include your credit card information on the form along with expiration date for the first night's non-refundable deposit.

Reservations by Mail: Send the completed Hotel Reservation Form from this newsletter directly to the Fontainebleau Hilton, Reservations Department, 4441 Collins Avenue, Miami Beach, FL 33140.

If using the mail-in method, be aware of your mailing date. Reservations should be received at the hotel by October 21, 1999 to ensure availability and special convention rates.

TRAVELING TO MIAMI

AIR TRANSPORTATION

CALGB has contracted with US Airways for a 5–10% discount for travelers attending the CALGB Group Meeting. In order to receive the discount, you MUST contact Navigant Travel at 1-800-200-6338, CALGB's official travel management company. Be sure to indicate to the Navigant travel representative that you are attending CALGB's Group Meeting in order to receive the discount.

GROUND TRANSPORTATION

It is recommended that you utilize "Supershuttle". Upon arrival at the Miami International Airport, just outside the baggage claim area, Supershuttle representatives are available to assist you for transportation to the hotel. Regular fares from the airport to the hotel are \$11 each way. For return reservations to the airport, stop by or phone the Supershuttle desk located in the hotel lobby. (Normal one-way taxi fares are about \$25-\$30.) Driving time from airport to hotel is approximately 20 minutes.

ACKNOWLEDGEMENTS

Thank you to organizations supporting the CALGB in 1999:

Alza Pharmaceuticals

Amgen, Inc.

Arrow International

Berlex Laboratories

Breast Cancer Research Foundation

Bristol-Myers Squibb Oncology

Cytogen

Glaxo Wellcome Oncology

Genentech BioOncology / IDEC Pharmaceuticals

Immunex Corporation

Impact Communications

LeukoSite Inc.

Lilly Oncology

Novartis Oncology

Ortho Biotech Inc. and the Janssen Research Foundation

Pharmacia & Upjohn

Pfizer, Inc.

Prime Group Realty Trust

Rhône-Poulenc Rorer Pharmaceuticals

Sanofi Lilly Oncology

Schering Corporation

SmithKline Beecham

T.J. Martell Foundation for Leukemia, Cancer and AIDS Research

Warner-Lambert (Parke-Davis)

CALGB 1999 Fall Group Meeting
Nov. 11 - 14, 1999

Hotel Reservation Form

Miami Beach, FL
Fontainebleau Hilton

ROOM RESERVATION DEADLINE: October 21, 1999. Please print or type.

NAME _____ PHONE # _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

NO. OF PERSONS IN ROOM: _____ ARRIVAL: _____ DEPARTURE: _____
(Date/Time—check-in time is 3:00 p.m.) * (Date/Time—check-out time is 11 am)

Non-Smoking Room Handicapped-accessible room. (Please describe handicap: _____)

RATES:

Single Occupancy

\$99

Double Occupancy

\$149

Room rates are in effect for the entire duration of your stay, based on availability.

Rates do not include state and local tax of 12.5%. Room reservations will be available on a first-come, first-served basis until CALGB's hotel block is filled. Rooms reserved after the cut-off date are subject to hotel availability and prevailing hotel rates.

**A \$50 early check-out fee will be charged if you leave before your scheduled departure date.*

ALL RESERVATIONS MUST BE ACCOMPANIED BY FIRST NIGHT'S NON-REFUNDABLE DEPOSIT.

Please provide credit card information below to guarantee your reservation.

I understand my credit card will be immediately charged for my first night's deposit.

Room deposits are non-refundable.

VISA MASTERCARD AMERICAN EXPRESS DISCOVER

CARDHOLDER'S NAME (Please print): _____

CARD NUMBER _____ EXP. DATE _____

CARDHOLDER'S SIGNATURE _____

Mail or Fax Reservation Form to: Fontainebleau Hilton, Reservations Office, 4441 Collins Ave., Miami Beach, FL 33140;
Fax: 305-673-5351; Phone: 1-800-548-8886



The **CAL•GAB** is CALGB's quarterly newsletter. Copies are mailed free of charge to CALGB members. Interested non-members may also request complimentary subscriptions.

The **CALGB 40th Anniversary Book** is now shipping! Limited copies are still available. This two-volume commemorative edition features selected published studies from the Breast, Lymphoma, Respiratory, GI, Prostate and Leukemia Committees. The compiled articles offer a retrospective view of the Group's accomplishments and invaluable contributions to cancer research since 1956.

Cancel

Please **Start/Update my Cal•Gab Subscription.**

Please send me:

____ **40th Anniversary Book(s) (\$45 each)**

NAME _____ PHONE # _____

INSTITUTION _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

My check enclosed, payable to **CALGB Foundation**, in the amount of \$_____.

Mail to: CALGB Foundation
Mary A. Sherrell, M.A., Treasurer
208 S. LaSalle St., Suite 2080
Chicago, IL 60604-1104

FAX to: (312) 345-0117

CALGB CALENDAR

Fall 1999 Group Meeting <i>Registration Deadline:</i>	Nov. 11–14, 1999 Nov. 1, 1999	Miami Beach, Florida— <i>Fontainebleu Hilton Resort & Towers</i>
Spring 2000 Core Meeting	Mar. 3–5, 2000	Chicago, IL— <i>Fairmont Hotel</i>
Summer 2000 Group Meeting	June 9–11, 2000	New Orleans, LA— <i>Fairmont Hotel</i>
Fall 2000 Group Meeting	TBD	TBD

ABSTRACT DEADLINES

Abstracts reporting on CALGB studies must be submitted to the Central Office for review at least two weeks prior to the submission deadline.

	ABSTRACTS DUE AT CENTRAL OFFICE	SUBMISSION DEADLINE	MEETING DATE	LOCATION
AACR American Association for Cancer Research	Oct. 16, 1999	Nov. 1, 1999	April 1–5, 2000	San Francisco, CA
ASCO American Society of Clinical Oncology	<i>Paper Submissions:</i> Nov. 8, 1999 <i>Electronic Submissions:</i> Nov. 19, 1999	Nov. 22, 1999 Dec. 3, 1999	May 19–23, 2000	New Orleans, LA



Cancer and Leukemia Group B
Central Office of the Chair
208 S. LaSalle St., Suite 2000
Chicago, IL 60604-1104

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