Investigator Training Program
March 9, 2010

Can I do this study? Considerations for Conducting Studies at Upstate
Why are we at Upstate?

Goals of an Academic Medical Center

- Patient Care
  - Tertiary care
  - Care for patients without concern for insurance

- Teaching
  - Stimulating environment

- Research
  - Basic research versus clinical research
Clinical Research

- Can we further the field and contribute to generalizable knowledge (research)?
- Can we contribute to the practice of evidence-based medicine?
YES!!
Improved Survival in Stage III Non-Small-Cell Lung Cancer: Seven-Year Follow-up of Cancer and Leukemia Group B (CALGB) 8433 Trial

Robert O. Dillman, James Herndon, Stephen L. Seagren, Walter L. Eaton, Jr., Mark R. Green*
Single-Agent Versus Combination Chemotherapy in Advanced Non–Small-Cell Lung Cancer: The Cancer and Leukemia Group B (study 9730)

What are the Strengths of Upstate Medical University?

- Only medical school in a large geographic area
- Active clinical staff (excellent clinicians/teachers)
- Multidisciplinary capabilities
  - Examples: Joslin Diabetes Center, Thoracic Oncology Program
- Excellent Departments
What are our Weaknesses?

- We are a smaller university
- Clinicians are very busy
  - Lack of protected time to conduct research
  - Emphasis on “productivity”
  - Lack of mentors
- Difficult to balance the basic versus the clinical missions
- Budget constraints
Where to Start?
Institutional Resources

- Clinical Trials Office (CTO)
- Contracts (Research Foundation)
- Institutional Review Board (IRB)
- Quality Assurance and Improvement Program (QAIP)
- Pharmacy
- Clinical Research Associates (CRAs)
Where to Start?
Ingredients for Clinical Research

- **Time**
  - Set goals and be protective of that protected time

- **Mentors**
  - Where to start?
  - Use that experience
  - Get trainees involved (Fellows, students)

- **Clinical Research Associates**
  - Key expertise
Where to Start?
Ingredients for Clinical Research

- Do I have the patients?
- Is it an important question?
- Do I have the time?
- Is the budget adequate?
- Are my colleagues on board?
- Do I have the support necessary?
CLINICAL RESEARCH ASSOCIATES (CRA)

- IRB submissions, Regulatory
- Assist in placing patients on-study - assure eligibility requirements, pre-study testing
- Maintain protocols-availability, accurate, updates
- Abstract information from charts to flow sheets, send data to data management center
- Communicate with affiliates
- Prepare for audits, Administrative functions
TYPES OF CLINICAL TRIALS

- Cooperative Group Studies (CALGB, SWOG, ECOG, COG, GOG)
- Drug company studies - investigator or company initiated
- In-house studies - investigator initiated or consortiums of institutions
- Promising institutional studies can lead to cooperative group studies (pilot studies)
- Rare diseases
What is the right mix of studies?

- **NIH/NCI sponsored trials**
  - Tend to ask paradigm questions, that define standard of care
  - Don’t pay as well

- **Pharmaceutical Trials**
  - Goal may be to position a drug or device for market
  - Many excellent studies available, but be critical
  - Meet with Scientific Liaisons
  - May pay more, but....
CANCER AND LEUKEMIA GROUP B (CALGB)

- one of three adult oncology multidisciplinary cooperative treatment groups funded by the National Cancer Institute
- others are Southwest Oncology Group (SWOG) and Eastern Cooperative Oncology Group (ECOG)
CALGB ORGANIZATION

- Central Office of the Chairman-University of Chicago, Dr. Richard Schilsky, Chairman
- Statistical Center-Duke University
- Data Management Center-Duke University
- Forty-six Institutions and Their Affiliates (>200)
- SUNY-Upstate Medical University
CALGB COMMITTEES

- GI
- GU
- BREAST
- MELANOMA
- LEUKEMIA
- LYMPHOMA
- RESPIRATORY
CALGB MODALITY COMMITTEES

- Cancer Control
- Correlative Sciences-Leuk/Lymphoma and Solid Tumor
- Data Management
- Oncology Nursing
- Pathology
- Pharmacy and Experimental Therapeutics (PET)
- Psycho-Oncology
- Radiation Oncology
- Surgery
- Transplant
MAIN MEMBER: SUNY UPSTATE MEDICAL UNIVERSITY

- Coordinating Center
- Data Management
- IRB Issues
- Quality Assurance
- Network-Affiliates (Faxton, VA)
INSTITUTIONAL GOALS

- Maintain High Accrual Rate (>100 Patients Per Year)
- Timely Submission Of Accurate, High Quality Data
- Contribute To Group Science And Leadership
- Increase Participation By Surgeons-become Truly Multi-disciplinary
HOW ARE WE FUNDED?

- Infrastructure Support from CALGB for Lead CRA, PI Salary Support and travel
- Per case accrual ($2,000/treatment accrual)
  - pays for data management (CRA salaries)
  - Office (Mailing, Computer Support)
- CALGB Foundation (Pharmaceutical Funds)
- CCOP Program (Community Clinical Oncology Program)
- VA/NCI Initiative, CTSU
  - $2,000 per patient placed on a treatment trial
WHAT IS A CANCER CLINICAL TRIAL?

- a study conducted with cancer patients, usually to evaluate a new treatment
- each study is designed to answer a scientific question
WHY ARE CLINICAL TRIALS IMPORTANT?

- help us to steadily improve treatment, discard ineffective treatment
- find less toxic treatments
- new treatments must prove to be safe and effective before they become widely available
- today’s standard treatment were research studies in the past
WHY WOULD A PATIENT BE INTERESTED IN A CLINICAL TRIAL?

- hope for best treatment for themselves
- hope for a longer time to live, a cure, a way to feel better
- contribute to research that may help others
- participating patients may be among the first to receive a new therapy before it is widely available
TYPES OF CLINICAL TRIALS

- PHASE I
- PHASE II
- PHASE III
PHASE I TRIAL

GOALS

- to determine the relation between toxicity and dose-schedule of treatment
- to determine the maximum-tolerated dose of therapy
- to define toxicity is the primary objective, efficacy is of secondary importance
- small cohorts, escalating doses of drugs to define dose-limiting toxicity
PHASE II STUDY

GOALS

- identify tumor types for which the treatment appears promising
- to define effectiveness
- often done in 2 stages
- usually 35-40 patients to define response rate
PHASE III STUDY

GOALS

- to determine the effects of a treatment relative to the natural history of the disease
- to determine whether a new treatment is more effective than a standard therapy
- to determine whether a new treatment is as effective as a standard therapy but is associated with less morbidity
- large numbers of patients required
CALGB GOALS

- Multi-institutional cooperative research group dedicated to the systematic planning, conduct, analysis, and reporting of research as applied to the therapy of patients with malignancy.

- Translate the most recent advances and therapies to large groups of patients in Central New York.
Selected Landmark Studies

- Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast cancer
- Intensive post remission chemotherapy in adults with acute myeloid leukemia
- Sequential Chemotherapy followed by Radiotherapy for unresectable stage III non-small cell lung cancer
- Role of cytogenetics in predicting outcome in acute myelogenous leukemia
Problems and Challenges

- Only 2-3% of adult cancer patients are enrolled on Clinical Trials
- Funding - NCI versus Pharmaceutical
- Insurance Coverage
  - Medicare, VA
  - Costs of Clinical Trials versus standard care
- Pressures on Institutional Review Boards
  - Duke, Johns Hopkins
- Pressure on Academic Physicians
- New Privacy Laws
Despite significant barriers, more than 80% of oncologists participate in clinical trials!!

Large reservoir of positive feelings toward cooperative group trials

Cost factors direct increased participation in industry supported trials

Insurers and Medicare pay for the clinical care costs of clinical trials

Clinical research is a “labor of love”
Clinical Trials and the Public Trust

- Virtually all of the advances in cancer therapy during the last 40-50 years have come from the randomized clinical trial.
- Most have been conducted by US Cancer Cooperative Groups.
- FDA requires evidence from well-conducted clinical trials for licensing of new agents.
CLINICAL RESEARCH IS GOOD CLINICAL CARE
“Just stay in the cab, Vern ... maybe that bear's hurt and maybe he ain't.”
## Treatment of Non-small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment of Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Surgery</td>
</tr>
<tr>
<td>II</td>
<td>Surgery</td>
</tr>
<tr>
<td>IIIA</td>
<td>Surgery for T3 lesions</td>
</tr>
<tr>
<td></td>
<td>Surgery/RT + chemotherapy</td>
</tr>
<tr>
<td>IIIB</td>
<td>RT + chemotherapy</td>
</tr>
<tr>
<td>IV</td>
<td>Palliative chemotherapy, RT or supportive care</td>
</tr>
</tbody>
</table>
Vinorelbine plus Cisplatin vs. Observation in Resected Non-Small-Cell Lung Cancer

Timothy Winton, M.D., Robert Livingston, M.D., David Johnson, M.D., James Rigas, M.D., Michael Johnston, M.D., Charles Butts, M.D., Yvon Cormier, M.D., Glenwood Goss, M.D., Richard Inculet, M.D., Eric Vallieres, M.D., Willard Fry, M.D., Drew Bethune, M.D., Joseph Ayoub, M.D., Keyue Ding, Ph.D., Lesley Seymour, M.D., Ph.D., Barbara Graham, R.N., Ming-Sound Tsao, M.D., David Gandara, M.D., Kenneth Kesler, M.D., Todd Demmy, M.D., and Frances Shepherd, M.D., for the National Cancer Institute of Canada Clinical Trials Group and the National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators
Kaplan-Meier Estimates of Survival among Patients Who Received Adjuvant Vinorelbine plus Cisplatin and Those Who Underwent Observation Alone

A Recurrence-free Survival, All Patients

B Overall Survival, All Patients

C Overall Survival, Patients with Stage IB Non–Small-Cell Lung Cancer

D Overall Survival, Patients with Stage II Non–Small-Cell Lung Cancer

Adjuvant Paclitaxel Plus Carboplatin Compared With Observation in Stage IB Non–Small-Cell Lung Cancer: CALGB 9633 With the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups

CALGB 9633
RCT OF ADJUVANT CHEMOTHERAPY IN STAGE IB NSCLC

T2N0MO
stage IB NSCLC

COMPLETE SURGICAL RESECTION
randomization within 4-8 wks of resection

STRATIFIED
squamous vs. other
poorly differentiated vs. other
mediastinoscopy: yes vs. no

ADJUVANT CHEMOTHERAPY
Paclitaxel, 200 mg/m²
Carboplatin, AUC=6 mg/ml x min
4 cycles over 12 weeks

OBSERVATION
Survival: Patients with Tumor $\geq 4.0$ cm

HR=0.66; 90% CI: 0.45-0.97; p=0.04

N=97

N=99
<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment of Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>Surgery</td>
</tr>
<tr>
<td>Stage IB</td>
<td>Surgery + <strong>Chemotherapy</strong></td>
</tr>
<tr>
<td>Stage II</td>
<td>Surgery + <strong>Chemotherapy</strong></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Surgery for T3 lesions + <strong>Chemo</strong></td>
</tr>
<tr>
<td></td>
<td>RT/Surgery + chemotherapy</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>RT +/- chemotherapy</td>
</tr>
<tr>
<td>Stage IV</td>
<td><strong>Palliative chemotherapy</strong>, RT or supportive care</td>
</tr>
</tbody>
</table>
Can We Ask Paradigm Questions?

Examples in Lung Cancer:
- CALGB 8433
- CALGB 9663
- CALGB 9795 (JBR.10)
- CALGB 9730
- Interest Trial
- ATLAS Trial
- Docetaxel vs Pemetrexed
Potential Therapeutic Targets

1. Growth factors and growth-factor receptors (e.g., EGFR family, VEGF-R)

2. Signal transduction pathways (e.g., RAS, raf, MAPK, MEK, ERK, PI3K, protein kinase C)

3. Vaccine Tumor-associated antigens or markers (e.g., gangliosides)

4. Proteasome

5. Cell survival pathways (e.g., mTOR, cyclin-dependent kinases, p53, Bcl-2)

6. Extracellular matrix / Angiogenic pathways (e.g., MMP, VEGF, integrins)

Current Clinical Trials for NSCLC

- Stage IA-B (Surgical) CALGB 30506: Phase III trial of CT vs Obs for early stage NSCLC
- Stage IB-IIIA – E1505: CT +/- bevacizumab
- Stage IIIA/IIIB unresectable
  - RTOG 0617: CT/RT +/- cetuximab to 6000 cGy vs 7400 cGy
  - CALGB 30605: PS 2 or PS 0-1 with ≥10% weight loss, CT → RT + cetuximab
- Stage IV
  - CALGB 30607: maintenance sunitinib/placebo p 4 cycles of CT
  - Boehringer-Ingelheim, For EGFR Mutation +: BI2292 vs chemotherapy
  - 2nd line- CALGB 30704: pemetrexed vs sunitinib vs both
  - 2nd line-Pfizer trial of PF for ALK+ patients
  - Merck: Phase III study of docetaxel +/- ASA404 for second-line treatment of NSCLC” (Gajra)
Clinical Trials for SCLC

- **Limited Stage SCLC**
  - CALGB 30610: Intergroup trial of 3 radiation therapy schedules (Dr. Bogart)

- **Extensive stage SCLC**
  - CALGB 30504: Platinum/etoposide +/- sunitinib maintenance
  - Celgene: Amrubicin versus topotecan for 2nd line therapy (Dr. Shah)
## Treatment of Non-small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment of Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>Surgery</td>
</tr>
<tr>
<td>Stage IB</td>
<td>Surgery + <strong>Chemotherapy</strong></td>
</tr>
<tr>
<td>Stage II</td>
<td>Surgery + <strong>Chemotherapy</strong></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Surgery for T3 lesions + <strong>Chemo</strong></td>
</tr>
<tr>
<td></td>
<td>RT/Surgery + chemotherapy</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>RT +/- chemotherapy</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Palliative chemotherapy, RT or supportive care</td>
</tr>
</tbody>
</table>
How to Be Effective

- Be Passionate!
- Decide on mix of studies, priorities
- Know the study (attend the investigator meeting)
- Watch the budgets (personnel may be on “soft” monies)
- Talk to Scientific Liaisons from Industry
- Talk to colleagues at other institutions
  - Consortiums can be effective (examples: Roswell Park, Duke, Rhode Island)
How to Be Effective

- Communicate within your Division/Section
  - Regular Conferences to discuss study details
  - Eligibility Criteria, Treatment specifics, Problems
  - Physicians, NP’s, Nurses
- Meet with CRA’s on a regular basis
- Communicate with Pharmacy
- Communicate with IRB, QAIP
CLINICAL RESEARCH IS GOOD CLINICAL CARE