Abstract
At the 25th Annual General Thoracic Surgical Club meeting in March 2012 the major cooperative
groups presented updates on clinical trials at the Robert Ginsberg Clinical Trials meeting. There
were approximately 57 in attendance. Representatives from Radiation Treatment Oncology
Group (RTOG), American College of Surgery Oncology Group (ACOSOG), Cancer and
Leukemia Group B (CALGB) and Eastern Cooperative Oncology Group (ECOG) presented an
overview of the trials that are current ongoing. These include oncologic trials that thoracic
surgeons are currently accruing patients to in North America. The purpose of this review is to
centralize the information to assist surgeons enrolling patients onto oncologic clinical trials in
thoracic surgery.
Introduction
The General Thoracic Surgery Club met for its 25th annual meeting in San Diego, California from March 3-5, 2012. The Clinical Trials portion of the meeting, dedicated in memory to its founder, Dr. Robert J. Ginsberg, was held for the 25th time. The meeting represents one of the largest collections of academic general thoracic surgeons to occur on a regular basis. The following is a summary of all active (currently enrolling), NCI funded, cooperative group clinical trials that relate to general thoracic surgery. All of the trials are presented with the format:

1. Cooperative group initials with trial number
2. Title of trial
3. Study chair(s) name(s) with e-mail address(es)
4. Primary objective
5. Secondary objective
6. Schema figure
7. Date opened
8. Accrual goal
9. Current accrual
10. Summary to date/ Problems/ Issues
11. Web address of the trial

An updated version of each trial's information can be found at the General Thoracic Surgical Club’s web site www.GTSC.org.

ACOSOG Z4099/ RTOG 1021
A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-small Cell Lung Cancer (NSCLC)

ACOSOG Study Chair: Hiran Fernando, MD (hiran.fernando@bmc.org)
RTOG Study Co-Chair: Robert Timmerman, MD (robert.timmerman@utsouthwestern.edu)

Primary Objective
To ascertain whether patients treated by SBRT have a 3-year overall survival (OS) rate that is no more than 10% less than patients treated with Sublobar Resection (SR).

Secondary Objectives
To compare loco-regional, recurrence-free survival between the study arms; compare disease-free survival between study arms; compare grade 3 or higher specific adverse event (AE) profiles between study arms, specific comparisons will include AEs at 1, 3, 6 and 12 months post therapy; compare pulmonary function between patients treated with SBRT and patients treated with SR; compare the adverse events and PFTs in each arm for patients with low or high Charlson comorbidity index scores, including a test interaction between Charlson comorbidity index scores (low vs. high) and treatment arm.

Schema for ACOSOG Z4099/ RTOG 1021: Figure 1
Date opened: May 2, 2011  
Accrual goal: 420 patients  
Current accrual: 5

Summary to date/Problems/Issues: Accrual to date has been challenging given the randomization between a surgical versus non-surgical study arm. Some screened patients have expressed reluctance to undergo a tissue biopsy prior to randomization. Recent updates to the protocol have removed the requirement of a tissue biopsy prior to SBRT treatment, and have increased the size of allowable lesions up to 4cm.

Web address of trial: https://www.acosog.org/studies/thoracic-cancer-studies-lung-esophagus

**RTOG 0839**  
Randomized Phase II Study of Pre-Operative Chemoradiotherapy +/- Panitumumab (IND #110152) Followed By Consolidation Chemotherapy in Potentially Operable Locally Advanced (Stage IIIA, N2+) Non-Small Cell Lung Cancer

Principal Investigator: Martin J. Edelman (medelman@umm.edu)  
Thoracic Surgery Co-Chair: Jessica Donington, MD (jessica.donington@nyumc.org)

**Primary Objective:** Mediastinal nodal clearance following completion of induction chemoradiation +/- panitumumab  
**Secondary Objective:** Overall survival; Patterns of first failure; Acute and late adverse events; Surgical morbidities among resectable patients at reassessment; Correlation between biomarkers (including at least EGFR and ras mutation status) in pre- and post-therapy and outcomes (mediastinal nodal clearance and overall survival); Evaluation of the prognostic value of plasma osteopontin and microRNA for overall survival; Assess the ability of PET/CT can re-staging to predict outcome; Estimate response rate.

Schema for RTOG 0839: Figure 2

Date opened: 7/6/2011  
Accrual goal: 97  
Current Accrual: 28

Summary to date/Problems/Issues: There have been 19 patients that have completed therapy and are in follow-up. The trial’s accrual was on hold for the week of July 23, 2012 for a safety review, but was anticipated to reopen the week of July 30, 2012.

Web address: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0839

**CALGB 140503**
A phase III Randomized trial of lobectomy versus sublobar resection for small (≤2cm) peripheral non-small cell lung cancer

Principle Investigator: Nasser Altorki M.D. nkaltork@med.cornell.edu
Participating Groups: RTOG; SWOG; ACOSCOG; NCI- Canada; Study supported by NCI CTSU

**Primary Objective**: Compare the disease-free survival of patients with small (≤ 2 cm) peripheral stage IA non-small cell lung cancer undergoing lobectomy vs sublobar resection (wedge resection or segmentectomy).

**Secondary Objectives**: Compare the overall survival of patients undergoing lobectomy vs sublobar resection. Compare the rates of loco-regional and systemic recurrence in patients undergoing lobectomy vs sublobar resection. Compare the pulmonary function of these patients, as measured by expiratory flow rates at 6 months postoperatively. Explore the relationship between characteristics of the primary lung cancer, as revealed by pre-operative CT scan and positron emission tomography (PET) imaging, and outcomes. Determine the false-negative rate of preoperative PET scan for identification of involved hilar and mediastinal lymph nodes. Assess the utility of annual follow-up CT scan after surgical resection in these patients.

Schema for CALGB 140503: Figure 3.

Date opened: June 15, 2007
Accrual goal: 692
Current accrual: 336

Summary to date/Problems/Issues: Initial slow accrual has picked up substantially over the past year with more centers opening study. Some patients/surgeons are reluctant to enroll given the study determines of the type of surgical procedure to be performed. Surgical equipoise on the main trial question is not unanimous which has also hampered enrollment.


**ECOG 1505**
A Phase III Randomized Trial of Adjuvant Chemotherapy with or without Bevacizumab for Patients with Completely Resected Stage IB (≥= 4 cm) - IIAA Non-Small Cell Lung Cancer (NSCLC)

ECOG Principle investigator: Heather Wakelee, MD (hwakelee@stanford.edu)
Protocol co-chair: Alan Sandler, M.D. (alan.sandler@vanderbilt.edu)

**Primary objective**: Compare overall survival of patients with completely resected stage IB (tumors ≥ 4cm)-IIIA non-small cell lung cancer treated with adjuvant chemotherapy with or without bevacizumab.
Secondary Objectives: Compare disease-free survival of patients treated with these regimens. Compare the toxicity of these regimens in these patients. Perform analyses of tissue and blood to establish factors that predict clinical outcome in patients treated with these regimens. Determine whether smoking status is linked to outcome in these patients.

Schema for ECOG 1505: Figure 4

Date opened: 6/1/2007
Accrual goal: 1500
Current Accrual: 670

Summary to date/Problems/Issues: There were 670 patients have been enrolled between August 2007 and June 2010. There has been a 15% ineligibility primarily due to inadequate lymph node sampling. There has been no statistically significant difference in the grade 5 toxicity between the two arms, but the Bevacizumab arm has a statistically higher rate of neutropenia, lymphopenia, hypertension, proteinuria, abdominal pain, hyponatremia, and hypoxia. Only one bronchopleural fistulae (non-fatal) has been seen. Enrollment is continuing at about 20 patients per month. Projected enrollment is expected to complete in 2015.


RTOG 1010
A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of Her2-Overexpressing Esophageal Adenocarcinoma

Principle Investigator: Howard Safran, MD (hsafran@lifespan.org)

Primary Objective: To determine if trastuzumab increases disease-free survival when combined with trimodality treatment (radiation plus chemotherapy followed by surgery) for patients with HER2-overexpressing esophageal adenocarcinoma

Secondary Objectives: To evaluate if the addition of trastuzumab to trimodality treatment increases the pathologic complete response rate and overall survival for patients with HER2-overexpressing esophageal adenocarcinoma; to develop a tissue bank of tumor tissue from patients with non-metastatic esophageal adenocarcinoma; to determine molecular correlates of complete pathologic response, disease-free survival, and overall survival for patients with HER2-overexpressing esophageal adenocarcinoma treated with neoadjuvant and maintenance trastuzumab; to evaluate predictors of cardiotoxicity in patients with esophageal cancer treated with trastuzumab and chemoradiation; to evaluate adverse events associated with the addition of trastuzumab to trimodality treatment for patients with non-metastatic esophageal adenocarcinoma; to determine if the addition of trastuzumab to trimodality treatment improves the patient reported Functional Assessment of Cancer Therapy for Esophageal Cancer (FACT-E)
Esophageal Cancer Subscale (ECS) score; to determine if an improvement in the FACT-E ECS score at 6-8 weeks post completion of neoadjuvant chemoradiation correlates with pathologic complete response; to determine if pathologic complete response correlates with the FACT-E ECS score at 1 year and/or 2 years from the start of chemoradiation; to determine if the addition of trastuzumab to trimodality treatment improves the Swallow Index and Eating Index Subscale scores of the FACT-E; to determine if the addition of trastuzumab to paclitaxel, carboplatin, and radiation impacts quality-adjusted survival.

Schema for RTOG 1010: Figure 5

Date opened: 12/30/2010
Accrual goal: 160
Current accrual: 139

Summary to date/Problems/Issues: The study is meeting projected accrual of about 3 HER2+ patients per month. Over 130 patients have been screened and 37% are HER2+ to date. There is likely some pre-screening occurring at institutions prior to sending in tissues, explaining the higher percentage of HER2+ than expected.

Web address: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1010

CALGB 80803 (RTOG 1175)
PET Scan Imaging in Assessing Response in Patients With Esophageal Cancer Receiving Combination Chemotherapy

Principle Investigator: Karyn A. Goodman, M.D. (goodmank@mskcc.org)

Primary objective:
To induce a complete pathologic response (pCR) rate of 20% in positron emission tomography (PET) scan non-responders treated with either induction FOLFOX or carboplatin/paclitaxel, who then crossover to the other regimen during radiotherapy.

Secondary objectives:
To compare PET/CT response between induction treatment arms; to compare pCR between induction treatment arms among PET/CT scan responders; to directly compare pCR between induction treatment arms among non-responders if both treatment regimens are found to be efficacious; to determine 8-month progression-free survival (PFS) in PET/CT scan responders, and in non-responders treated with alternative crossover chemoradiotherapy; estimate the PFS and overall survival (OS) curves, overall and among PET responders and PET/CT non-responders by induction treatment; to determine the rate of postoperative anastomotic leak after neoadjuvant chemotherapy followed by chemoradiation; to evaluate immunohistochemistry and RT-PCR of ERCC1, and genetic polymorphisms of ERCC1, XPD, and XRCC1; to evaluate status and levels of methylation of nine candidate biomarker genes as well as expression levels of selected specific microRNAs, which will be correlated with chemoradiation response; to compare the quality of life (QOL) of responders and nonresponders (as determined by PET/CT scanning) to presurgical treatment for esophageal cancer, in terms of global QOL, physical
symptoms, physical functioning, and emotional well-being; to examine the association between OS and QOL in esophageal cancer patients treated with chemotherapy, chemoradiation therapy, and surgery.

Schema for CALGB 80803 (RTOG 1175): Figure 6

Date opened: Sept 2011
Accrual goal: 204
Current accrual: 20

Summary to date/Problems/Issues: One of the main concerns expressed by some of the sites is whether the insurance companies will cover the second PET scan. This has not been a problem to date, since Medicare as a re-staging scan covers it. Also, NIH funding is available to cover repeat baseline scans if they do not meet the protocol requirements.

Web address: http://clinicaltrials.gov/ct2/show/record/NCT01333033

**NCCTG - N0849**
Randomized Phase II Trial of Extended Neoadjuvant Therapy for Locally Advanced Adenocarcinoma of the Esophagus, Gastroesophageal Junction, or Gastric Cardia

Principle Investigator: Steven R. Alberts, Mayo Clinic (alberts.steven@mayo.edu)

**Primary objective:**
To assess and compare the pathologic complete response (PCR) rate of patients in Arm A receiving the sequence docetaxel, oxaliplatin, and capecitabine (DOC) followed by 5-fluorouracil (5-FU), oxaliplatin, and radiation therapy (RT) with patients in Arm B receiving only 5-FU, oxaliplatin and RT in patients with potentially resectable ACA of the esophagus, GEJ, or gastric cardia.

**Secondary objectives:**
To assess the adverse event (AE) profile and safety of the proposed treatment in this population; to assess and compare the overall survival (OS) between treatment arms; to assess and compare the disease-free survival between treatment arms; to assess and compare the clinical tumor response rate of the proposed regimens when administered before surgery between treatment arms; to evaluate the profiles of pharmacogenetic and proteomic marker measures over time and assess the association of changes in these biomarkers induced by proposed regimens with pathologic tumor response and other outcomes of interest; to evaluate the profiles of PET measures, including standardized uptake values (SUV) and % injected dose (%ID) in the tumor volume over time, and assess the correlation of changes in PET measures with pathologic tumor response and other outcomes of interest; banking of paraffin embedded tissue blocks/slides and blood products for future studies.

Schema for NCCTG N0849: Figure 7
Date opened: February 2010
Accrual goal: 96
Current accrual: 71

Summary to date/Problems/Issues: Trial is accruing on schedule. Interim analysis planned within the next few months.

Web address: http://clinicaltrials.gov/ct2/show/NCT00938470?term=N0849&rank=1

TOP GEAR
Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma: A randomised phase II/III trial of preoperative chemoradiotherapy versus preoperative chemotherapy for resectable gastric cancer

Principle investigator: Trevor Leong (trevor.leong@petermac.org)

Primary objective: Overall survival

Secondary objective: Disease Free Survival, Toxicity as measured by adverse events, Pathological Response Rate, Surgical R0 resection rate

Schema for TOP GEAR: Figure 8.

Date opened: 3/5/2009
Accrual goal: 752
Current accrual: 53

Summary to date/Problems/Issues: Not all sites have yet been activated in Australia, with 30 planned. The EORTC and NCIC CTC will begin recruitment from Europe and Canada in the 4th quarter of this year. When all sites are activated, the intergroup collaboration will comprise over 75 centres across 15 countries. Expectation that each region (Australasia, Europe and Canada) will each recruit approximately 50 patients/year, so that the target accrual of 750 will be reached in 5 years. The inclusion criteria have recently been widened to include patients with Siewert type II GEJ tumors (originally only Gastric and Siewert III tumors).

Figure Legends:
Figure 1: Schema for ACOSOG Z4099/RTOG 1021
NSCLC – nonsmall cell lung cancer

Figure 2: Schema for RTOG 0839
NSCLC – nonsmall cell lung cancer
XRT – radiation therapy
Gy - gray
Rx – therapy

Figure 3: Schema for CALGB 140503
NSCLC – nonsmall cell lung cancer

Figure 4: Schema for ECOG 1505
NSCLC – nonsmall cell lung cancer
Vs. – versus

Figure 5: Schema for RTOG 1010
HER2 – Herceptin 2 receptor
XRT – radiation therapy
Gy – gray

Figure 6: Schema for CALGB 80803/RTOG 1175
PET – proton emission tomography
CT – computed tomography
XRT – radiation therapy
Chemo – chemotherapy

Figure 7: Schema for NCCTG N0849
XRT – radiation therapy

Figure 8: Schema for TOP GEAR
EGJ – esophagogastric junction
XRT – radiation therapy
*Attendees of the 2012 Robert Ginsberg Clinical Trials meeting of the General Thoracic Surgical Club (alphabetical order)
Mark Allen, M.D., Sharon Ben-Or, M.D., Ankit Bharat, M.D., Shanda Blackmon, M.D., Larry Cardoza, M.D., Ben Daly, M.D., Gail Darling, M.D., Frank Detterbeck, M.D., Robert Downey, M.D., L. Henry Edmunds, M.D., Jonathan Enlow, M.D., Matthew Faktor, M.D., Richard Feins, M.D., Mark Ferguson, M.D., Adela Fernandez, M.D., Chrish Fernando, M.D., Eustace Fontaine, M.D., Richard Freeman, M.D., Sid Gangadharan, M.D., Rose Ganim, M.D., George Haasler, M.D., John Handy, M.D., Jasmine Huang, M.D., David Johnstone, M.D., Hisashi Kajikuri, M.D., Kemp Kernstine, M.D., Shaf Keshavjee, M.D., Leslie Kohman, M.D., John Kicharczuk, M.D., Elbert Kuo, M.D., Rodney Landreneau, M.D., Philip Linden, M.D., Mitch Magee, M.D., Rob McKenna, M.D., Bryan Meyers, M.D., John Mitchell, M.D., Nathan Mollberg, M.D., Sara Myers, M.D., Frank Nichols, M.D., Keishi Ohtani, M.D., Jemi Olak, M.D., Raymond Osarogiabon, M.D., Roman Petrov, M.D., Philip Rascoe, M.D., Scott Reznik, M.D., David Rice, M.D., Inderpal Sarkaria, M.D., Joseph Shrager, M.D., Stephen Swisher, M.D., William Tisol, M.D., Nirmal Veeramachaneni, M.D., Dennis Wigle, M.D., Valerie Williams M.D., David Wormuth, M.D., Stephen Yang, M.D., Koichi Yoshida, M.D.
Figure 1

ACOSOG 4099/RTOG 1021

Histologically confirmed NSCLC with negative mediastinal lymph nodes → STRATIFY: Planned brachytherapy yes/no; Performance status → RANDOMIZE

Arm 1: Sublobar Resection ± Brachytherapy → FOLLOW

Arm 2: Stereotactic Body Radiation Therapy

Figure 2

RTOG 0839

Histologically Confirmed Stage IIIA (N2+) NSCLC → RANDOMIZE

ARM I: Induction Chemoradiation Paclitaxel & Carboplatin XRT 60Gy → Reassessment 4 weeks after Induction Rx

Resectable: Surgery within 6 weeks of chemotherapy

Consolidation Chemotherapy: Paclitaxel Carboplatin

Unresectable: Consolidation chemotherapy within 6 weeks of initial chemotherapy

ARM II: Induction Chemoradiation Panitumumab Paclitaxel & Carboplatin XRT 60Gy
**Figure 3**

**CALGB 140503**

- **Surgery:** Confirm path diagnosis of NSCLC and N0 by frozen section of levels 4, 7 and 10 on right and 5, 6, 7 and 10 on left.
- **Randomize:**
  - Lobectomy
  - Segmentectomy or Wedge resection

**Figure 4**

**ECOG 1505**

- **Stratification Factors**
  - Chemotherapy: Vinorelbine/cisplatin vs Docetaxel/cisplatin vs Gemcitabine/cisplatin vs Pemetrexed/cisplatin
  - Stage: IB(≥4cm) vs II vs IIIA-N2 vs IIIA-T3N1
  - Histology: Squamous cell vs other
  - Gender: Male vs female
- **Randomize:**
  - Arm A: 1 of 4 chemotherapy regimens (no bevacizumab)
  - Arm B: 1 of 4 chemotherapy regimens Plus bevacizumab
- **Follow:**
  - Completely Resected Stage IB-IIIA NSCLC
Figure 5

RTOG 1010

ARM 1
XRT (50.4 Gy)
Paclitaxel, carboplatin and Trastuzumab
Surgery
5 to 8 weeks after XRT
Maintenance trastuzumab
Every 3 weeks x 13 treatments

ARM 2
XRT (50.4 Gy)
Paclitaxel, carboplatin
Surgery
5 to 8 weeks after XRT

Figure 6

CALGB 80803(RTOG 1175)

Esophageal Cancer
Stratified by
T1-3 vs T3-4
and
N0 vs N+

Arm I

Folinic acid
Fluroracil
Oxaliplatin
(FOLFOX-6)

≥35% response
in metabolic activity

PET/CT

<35% response
in metabolic activity

Carboplatin
Paclitaxel
+ XRT x 6 weeks

Surgery
4 to 10 wks
After XRT/chemo

Arm II

Carboplatin
Paclitaxel

≥35% response
in metabolic activity

PET/CT

<35% response
in metabolic activity

Carboplatin
Paclitaxel
+ XRT x 6 weeks

FOLFOX-6
+ XRT x 6 weeks
NCCTG N0849

**Figure 7**

**Top Gear**

- **Group I (control arm):** Epirubicin, Cisplatin, 5-Fluorouracil (3 cycles)
- **Group II:** Epirubicin, Cisplatin, 5-Fluorouracil (2 cycles)

**Figure 8**

**TOP GEAR**

Resectable Adenocarcinoma of stomach or EGJ (T3/4, N1-3, M0) → Randomize

- **Group I (control arm):** Epirubicin, Cisplatin, 5-Fluorouracil (3 cycles)
- **Group II:** Epirubicin, Cisplatin, 5-Fluorouracil (2 cycles)

Surgery → XRT (45Gy) → Continuous 5-Fluorouracil