CALGB 140503 - A Phase III Randomized Trial of Lobectomy versus Sublobar Resection for Small (≤ 2 cm) Peripheral Non-Small Cell Lung Cancer

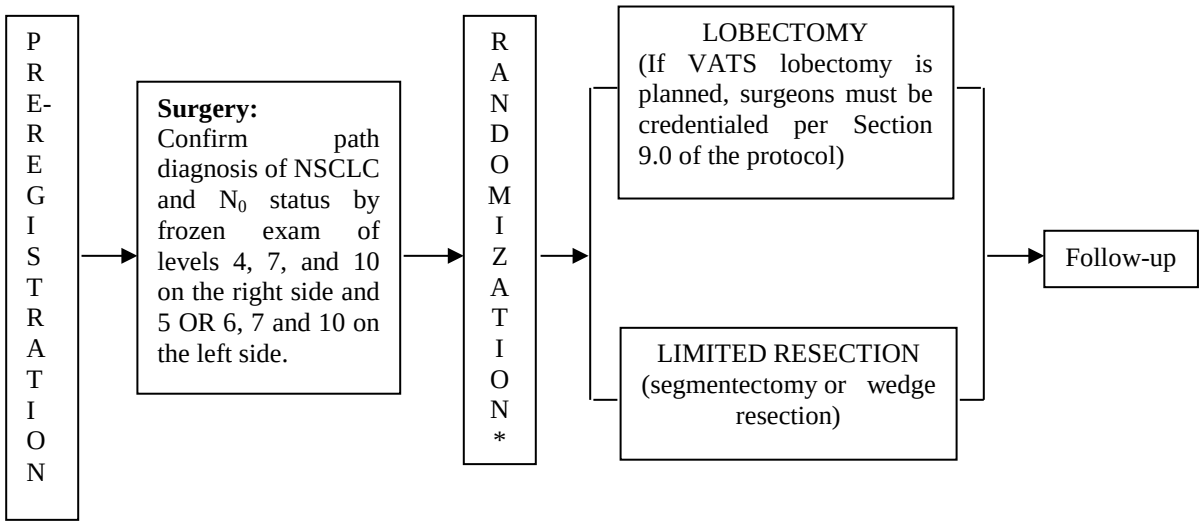
Committee: Respiratory
Study Chair: Nasser Altorki, M.D
Study Statisticians: Xiaofei Wang, Ph.D.
Junheng Gao, M.S.

1.0 OBJECTIVES

Primary:
To determine whether disease-free survival after sublobar resection (segmentectomy or wedge) is non-inferior to that after lobectomy in patients with small peripheral (≤ 2 cm) NSCLC.

Secondary:
1. To determine whether overall survival (OS) (after sublobar resection) is non-inferior to that after lobectomy.
2. To determine the rates of loco-regional and systemic recurrence (exclusive of second primaries) after lobar and sublobar resection.
3. To determine the difference between the two arms of the study in pulmonary function as determined by expiratory flow rates measured at 6 months post-operatively.
4. Imaging Substudy: To explore the relationship between characteristics of the primary lung cancer, as revealed by pre-operative CT and PET imaging, and outcomes; a determination of the false-negative rate of the pre-operative PET scan for identification of involved hilar and mediastinal lymph nodes; and an assessment of the utility of annual follow-up CT imaging after surgical resection of small stage IA NSCLC.

2.0 CURRENT SCHEMA



* Randomization is done intra-operatively after determining patient eligibility. CALGB CRAs must be able to access the web-based CALGB registration system during surgery to obtain treatment assignment and inform the surgeon of the assignment at the site. Patients who are not randomized intraoperatively will not be considered "on-study" and should follow the instructions in Section 6.1 of the protocol document.

3.0 ELIGIBILITY CRITERIA

Pre-registration eligibility criteria

- Peripheral lung nodule ≤ 2 cm on preoperative CT scan and presumed to be lung cancer (see Section 4.1.1 of the protocol document).
- Tumor location must be suitable for either lobar or sublobar resection (wedge or segment).
- ECOG performance status of 0-2.
- No prior malignancy within 3 years (see Section 4.1.4 of the protocol document).
- No prior chemotherapy or radiation therapy for this malignancy.
- No evidence of locally advanced or metastatic disease.
- Age ≥ 18 years.

Intra-operative randomization eligibility criteria

- Histologic confirmation of NSCLC (if not already obtained).
- Confirmation of N_0 status (see Section 4.2.2 of the protocol document).

4.0 TREATMENT SCHEDULE

The treatment schedule is described in detail in the Study Schema (Section 2.0 of this report).

5.0 STUDY DESIGN

5.1 Study Phase/Type of Design/Stratification Factors

This is a randomized phase III trial. Three stratification factors are used for the randomization: radiographic tumor size (< 1 cm, 1-1.5 cm, and > 1.5-2.0 cm); histology (SCC, adenocarcinoma and other); smoking status (never, former, and current). A stratified permuted block randomization schema will be used to accomplish treatment assignment.

5.2 Primary Endpoint

The primary endpoint of this phase III trial is the disease-free survival.

A maximum of 1258 patients will be pre-registered to the study. With allowance of 45% ineligibility rate due to either intraoperative benign diagnosis or anatomical location mandating a lobectomy, 692 eligible patients will be randomized with equal probability to one of two treatment regimens: the lobectomy (Arm A) and the limited resection (Arm B).

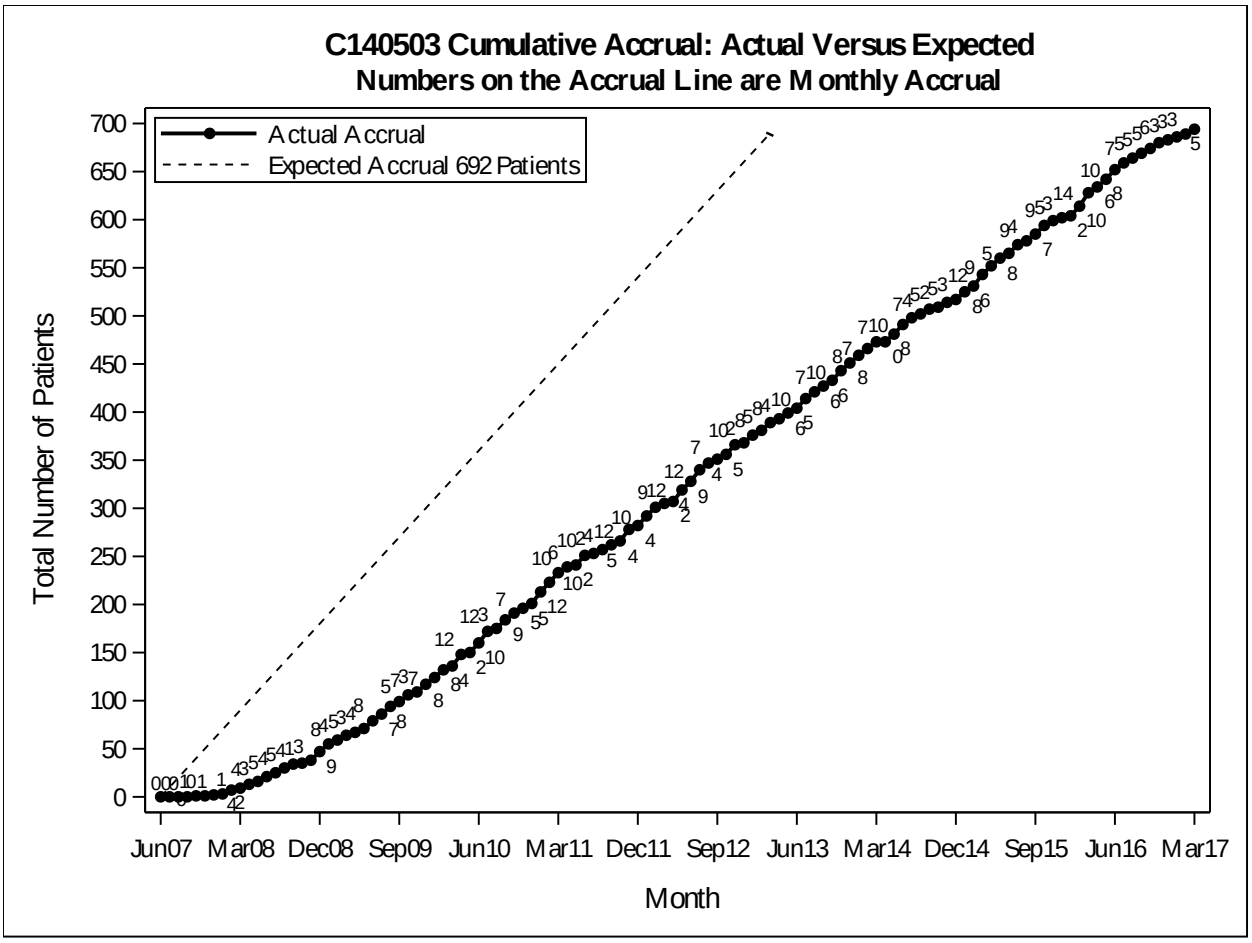
The study has approximately 80.4% power to reject the null hypothesis $\lambda_B / \lambda_A \geq 1.306$ at a one-sided type I error of 0.05.

5.3 Target Accrual

The study will pre-register a total of 1258 patients. Assuming a 45% ineligibility rate among pre-registered patients, a total of 692 eligible patients will be randomized. At an accrual rate of 10 randomized patients per month, it will take 5.8 years to reach the accrual target.

6.0 CURRENT ACCRUAL

Study Activation Date	6/15/2007
Closed Date:	03/13/17
Target Accrual	1258 pre-registered / 692 registered
Final Accrual	1080 pre-registered / 697 registered



7.0 CURRENT STUDY STATUS

CALGB 140503 was activated on 6/15/2007, and was closed on 3/13/2017. The target accrual is 692 randomized patients. The final accrual was 697. The study is following up patients for the study endpoints.

8.0 PATIENT CHARACTERISTICS

The demographic data for the randomized patients are shown in Table below.

Table 8a. Demographics

	Limited resection (N=340)	Lobectomy (N=357)	Total (N=697)
Age			
N	340	357	697
Mean (SD)	67.2 (8.7)	67.1 (8.7)	67.2 (8.7)
Median	68.3	67.6	67.9
Q1, Q3	61.6, 73.0	61.1, 73.3	61.2, 73.1
Range	(37.8-89.7)	(43.2-88.9)	(37.8-89.7)
Race			

	Limited resection (N=340)	Lobectomy (N=357)	Total (N=697)
Unknown	6 (1.8%)	8 (2.2%)	14 (2.0%)
White	314 (92.4%)	313 (87.7%)	627 (90.0%)
Black or African American	16 (4.7%)	29 (8.1%)	45 (6.5%)
Asian	2 (0.6%)	4 (1.1%)	6 (0.9%)
American Indian or Alaska Native	0 (0.0%)	1 (0.3%)	1 (0.1%)
Not Reported	1 (0.3%)	1 (0.3%)	2 (0.3%)
More than one race	1 (0.3%)	1 (0.3%)	2 (0.3%)
Gender			
Male	150 (44.1%)	147 (41.2%)	297 (42.6%)
Female	190 (55.9%)	210 (58.8%)	400 (57.4%)

Table 8b. Stratification Factors

	Limited resection (N=340)	Lobectomy (N=357)	Total (N=697)
Tumor Size (cm)			
<1.0	28 (8.2%)	30 (8.4%)	58 (8.3%)
1.0-1.5	174 (51.2%)	180 (50.4%)	354 (50.8%)
>1.5-2.0	138 (40.6%)	147 (41.2%)	285 (40.9%)
Histology			
Squamous Cell Carcinoma	45 (13.2%)	53 (14.8%)	98 (14.1%)
Adenocarcinoma	218 (64.1%)	226 (63.3%)	444 (63.7%)
Other	77 (22.6%)	78 (21.8%)	155 (22.2%)
Smoking Status			
Never	28 (8.2%)	35 (9.8%)	63 (9.0%)
Former	172 (50.6%)	177 (49.6%)	349 (50.1%)
Current	140 (41.2%)	145 (40.6%)	285 (40.9%)

9.0 ADVERSE EVENTS

9.1 Adverse Event Summary

A total of 693 patients are evaluable for surgical complication analyses (355 patients from lobectomy arm; 338 from limited resection arm). Five deaths were deemed related to the surgery. Four were on the lobectomy arm and one was on the limited resection arm. On the lobectomy arm, the causes of death include – 2 adult respiratory distress syndrome (ARDS), and 2 deaths not associated with CTCAE term; on the limited resection arm the cause of death was cardiac ischemia/infarction. One patient died from ARDS within 30 days from the surgery (limited resection) but deemed not contributing to the death.

See below for a summary and a list of surgical complications possibly, probably, or definitely attributed to surgeries. Surgical complications on this study are reported using CTCAE version 3.

Arm A: Lobectomy
Arm B: Limited resection

Table 9a. Summary of Grade 3+ Adverse Events

Summary of Grade 3+ Adverse Events At least possibly related Number of Evaluable Patients: Arm A=355 Arm B=338			
Patients with a maximum:	**Arm**	**n**	**(%)**
Total			
Grade 3 Event	A	32	*(9.0%)*
	B	38	*(11.2%)*
Grade 4 Event	A	9	*(2.5%)*
	B	3	*(0.9%)*
Grade 5 Event	A	4	*(1.1%)*
	B	1	*(0.3%)*
Hematologic Adverse Events			
Grade 3 Event	A	0	*(0.0%)*
	B	2	*(0.6%)*
Grade 4 Event	A	0	*(0.0%)*
	B	0	*(0.0%)*
Grade 5 Event	A	0	*(0.0%)*
	B	0	*(0.0%)*
Non-Hematologic Adverse Events			
Grade 3 Event	A	32	*(9.0%)*
	B	38	*(11.2%)*
Grade 4 Event	A	9	*(2.5%)*
	B	3	*(0.9%)*
Grade 5 Event	A	4	*(1.1%)*
	B	1	*(0.3%)*
Note: Summaries are based on available patient data			

Table 9b. Listings of Grade 3+ Adverse Events

Listing of Grade 3+ Adverse Events Max Grade Per Patient Per Event At least possibly related Number of Evaluable Patients: Arm A=355 Arm B=338						
		Grade of AdverseEvent				
	Arm	3-Severe		4-LifeThr		5-Lethal
		n	(%)	n	(%)	n (%)
Hematologic Adverse Events						

Listing of Grade 3+ Adverse Events
Max Grade Per Patient Per Event
At least possibly related
Number of Evaluable Patients:
Arm A=355 Arm B=338

		Grade of AdverseEvent					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Blood/Bone Marrow							
Hemoglobin	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
Platelets	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
Non-Hematologic Adverse Events							
Cardiovascular							
Cardiac ischemia/infarction	A	3	(1%)	2	(1%)	0	(0%)
	B	0	(0%)	0	(0%)	1	(0%)
Cardiac troponin I (cTnI)	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
Cardiac troponin T (cTnT)	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
Hypotension	A	0	(0%)	0	(0%)	0	(0%)
	B	2	(1%)	0	(0%)	0	(0%)
Supraventricular and nodal arrhythmia	A	4	(1%)	0	(0%)	0	(0%)
	B	3	(1%)	0	(0%)	0	(0%)
Constitutional Symptoms							
Constitutional Symptoms - Other Spec	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
Death							
Death not associated with CTCAE term	A	0	(0%)	0	(0%)	2	(1%)
	B	0	(0%)	0	(0%)	0	(0%)
Gastrointestinal							
Dysphagia (difficulty swallowing)	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
Ileus, GI	A	2	(1%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
Nausea	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
Hemorrhage							
Hemorrhage assoc w/surg, intra-op/postop	A	6	(2%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
Max Grade Per Patient Per Event
At least possibly related
Number of Evaluable Patients:
Arm A=355 Arm B=338

		Grade of AdverseEvent					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
	B	8	*(3%)*	0	*(0%)*	0	*(0%)*
Infection/Febrile Neutropenia							
Infection - Other (Specify, __)	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*
Infection w/ normal or Grade 1/2 ANC	A	9	*(3%)*	1	*(0%)*	0	*(0%)*
	B	6	*(2%)*	0	*(0%)*	0	*(0%)*
Infection with Grade 3 or 4 ANC	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
Infection with unknown ANC	A	1	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*
Lymphatics							
Edema:trunk/genital	A	1	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
Metabolic/Laboratory							
Calcium, serum-low (hypocalcemia)	A	1	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
Glucose, serum-high (hyperglycemia)	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*
Magnesium, serum-high (hypermagnesemia)	A	1	*(0%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
Potassium, serum-high (hyperkalemia)	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
Sodium, serum-low (hyponatremia)	A	3	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
Neurology							
Confusion	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	0	*(0%)*	0	*(0%)*	0	*(0%)*
Pain							
Pain	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	4	*(1%)*	0	*(0%)*	0	*(0%)*
Pulmonary							

Listing of Grade 3+ Adverse Events
Max Grade Per Patient Per Event
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Number of Evaluable Patients:
Arm A=355 Arm B=338

		Grade of AdverseEvent					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Adult Respiratory Distress Syndrome	A	0	(0%)	5	(2%)	2	(1%)
	B	1	(0%)	0	(0%)	0	(0%)
Atelectasis	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
Dyspnea (shortness of breath)	A	3	(1%)	1	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
Fistula, pulmonary/upper respiratory	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
Hypoxia	A	4	(1%)	1	(0%)	0	(0%)
	B	11	(4%)	0	(0%)	0	(0%)
Obstruction/stenosis of airway	A	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	1	(0%)	0	(0%)
Pleural effusion (non-malignant)	A	2	(1%)	0	(0%)	0	(0%)
	B	2	(1%)	0	(0%)	0	(0%)
Pneumonitis/pulmonary infiltrates	A	0	(0%)	1	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
Pneumothorax	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
Prlngd chst tb drn/airlk aftr pulm rsctn	A	8	(3%)	0	(0%)	0	(0%)
	B	3	(1%)	0	(0%)	0	(0%)
Pulmonary/Upper Respiratory - Other Spec	A	0	(0%)	2	(1%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
Voice changes/dysarthria	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
Renal /Genitourinary							
Renal failure	A	1	(0%)	1	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
Surgery/Intra-Op Injury							
Intra-operative Injury - Other Spec	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
Intra-operative injury	A	1	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
Max Grade Per Patient Per Event
At least possibly related
Number of Evaluable Patients:
Arm A=355 Arm B=338

		Grade of AdverseEvent					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Vascular							
Thrombosis/thrombus/embolism	A	0	*(0%)*	1	*(0%)*	0	*(0%)*
	B	1	*(0%)*	2	*(1%)*	0	*(0%)*

10.0 IMBEDDED CORRELATIVES

There is one imaging study within CALGB 140503. This imbedded study, CALGB 580602, is required and does not require separate IRB approvals. See Section 1.0 of this report for the objectives of the correlative study.

As of 9/6/2016, 672 patients have been enrolled to CALGB 580602.