Update for Alliance Respiratory and Thoracic Surgery Studies

Lyudmila Bazhenova

Everett Vokes

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NSCLC

**Early Stage Disease**
Phase III. Sublobar resection vs. SBRT in high risk pts.
Phase III. Lobectomy vs. sublobar resection for ≤ 2 cm tumors.

**Locally Advanced Disease**
Phase I. Accelerated hypofractionated radiation concurrent with chemotherapy in unresectable stage III.

**Metastatic Disease**
Phase III. 1ˢᵗ line chemotherapy +/- COX 2 inhibition in COX expressing tumors.
Phase II. Erlotinib +/- bevacizumab in EGFR mutants.
Phase III. Sunitinib vs. placebo maintenance.
SCLC

• Phase III. Comparison of thoracic radiotherapy regimes in patients with LS SCLC
• Phase II. NTX-010 (replication competent picornavirus) after platinum induction therapy for ES SCLC.

Mesothelioma

• Phase II. Maintenance pemetrexed vs. observation in malignant pleural mesothelioma
CALGB 140503
A Phase III Randomized Trial Of Lobectomy Versus Sublobar Resection For Small (≤ 2 Cm) Peripheral Non Small Cell Lung Cancer

Study Chair: Nasser Altorki
Activated: 6/15/07
# CALGB / CTSU Sites Open: 36 / 98
Target / Current Accrual: 692 / 324
Background

- LCSG randomized 267 patients with T1N0 (AJCC 6.0) to lobectomy vs. limited resection
  - No difference in survival
  - 50% increase in local recurrence rate with limited resection.
  - Tumors up to 3 cm were included
  - Less decline in PFT at 6 months in limited resection group

- Modern retrospective and single arm prospective studies showed equivalent DFS and OS

Kodama J thor cardvasc surgery 1997
Okada J Thor Cardiovasc surgery 2005
Eligibility criteria

• Peripheral lung nodule ≤ 2 cm on CT and presumed to be lung cancer
  – Pure GGO not eligible
• Tumor location suitable for either lobar or sublobar resection
• No prior malignancy within 3 years
• Intra-operative randomization criteria
  – Histologic confirmation of NSCLC
  – Confirmation of N0 status
Peripheral tumors <2 cm

**Register**

Intraoperatively
- Confirm lung cancer diagnosis
- Confirm N0 4, 7, 10 R
  5, 6, 7, 10 L

**Randomize**

Lobectomy
- VATS or open

Sublobar resection

Off study

1º DFS
2º OS, locoregional recurrence, change in PFT
CALGB 31102
Phase I Study of Accelerated Hypofractionated Radiation Therapy with Concomitant Chemotherapy for Unresectable Stage III NSCLC

Study Chair: James Urbanic
Activated: 2/15/12
# CALGB / CTSU Sites Open: 3 /
Target / Current Accrual: 24 / 0
Locoregional failure is common after conventional radiation for stage III disease
- 35-40% as a sole site even with modern radiation technology (RTOG 94-10 and West Japan trial)

RTOG 0617 high dose arm closed for futility.

Next idea is to hypo fractionate (give higher daily doses) keeping the total dose at 60 Gy
- SBRT showed local control rates of 90% at 2-3 years.
- Aided by novel radiation technologies

Socinski, Cancer 2001
Currant, Proc ASCO 2003
Furuse, Proc ASCO 2000
Eligibility criteria

- Unresectable, treatment naïve stage IIIA and IIIB NSCLC

Endpoints

1° To determine MTD dose fraction

2°
- RR
- Rate of progression
- PFS
- OS
Study schema

**Cycle 1-3 (14 days cycle)**
- Paclitaxel 45 mg/m²
- Carboplatin AUC 2 weekly x 4,
- no chemo during Cycle 3
- Radiotherapy: 60 Gy (see cohorts below)

**Consolidation Therapy** (Cycles 4-5, q 21)
- Paclitaxel 200 mg/m²
- Carboplatin AUC 6 by IV over 30-60 minutes on day 1

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Total Dose</th>
<th>Fraction Size</th>
<th># Fractions</th>
<th>Time</th>
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<td>2.22 Gy</td>
<td>27</td>
<td>5.5 weeks</td>
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<tr>
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<td>3.00 Gy</td>
<td>20</td>
<td>4 weeks</td>
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</tbody>
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CALGB 30801
A Randomized Phase III Double Blind Trial
Evaluating Selective COX-2 Inhibition in COX-2 Expressing Advanced NSCLC

Study Chair: Martin Edelman
Activated: 2/15/10
# CALGB / CTSU Sites Open: 103 / 218
Target / Current Accrual: 297 / 140
Background

• Cox 2 in lung cancer
  – Overexpressed in NSCLC and pre-neoplasia
  – A marker of poor prognosis in NSCLC
  – Induced by tobacco carcinogens
• Preclinical studies of COX-2 inhibitors suggest antitumor and chemopreventive efficacy
• Epidemiologic data suggest subjects who routinely use NSAIDs have decreased lung cancer risk
Randomized phase II trial accrued 140 pts in 9 months.
- Negative overall.

Preplanned analysis of COX-2 and 5LOX expression
- COX-2 expression is a **negative** prognostic marker for patient who *did not* receive celecoxib.
- COX-2 expression is a **positive** predictive marker for patients who *did* receive celecoxib.
Stage IIIB (pleural effusion), IV NSCLC PS 0-1 chemo naive AND COX-2 Index >2 Index >4

**Correlates:** Urinary PGEM, pk, pharmacogenetics

*Index > 4 for primary endpoint*
Objectives

- **Primary:**
  - Determine if the addition of celecoxib to standard chemotherapy will increase progression free and overall survival.

- **Secondary:**
  - Confirm the prognostic value of COX-2 expression.
  - RR, OS, PFS etc.

- **Correlative/Biomarker**
  - Correlation of urinary PGE-M with COX-2 expression, celecoxib administration and outcome
  - Association between the -765G/C polymorphism in PTGS2 and COX-2 expression in non-small cell lung cancer specimens
  - Association of CYP2C9 germline polymorphisms and celecoxib metabolism
A Randomized Phase II Trial of Erlotinib Alone or in Combination with Bevacizumab in Patients with Non-Small Cell Lung Cancer and Activating Epidermal Growth Factor Receptor Mutations

Study Chair: Thomas Stinchcombe
Activated: 03/16/12
Target / Current Accrual: 118 / 0
Accrual Last 90 / 30 Days: 0 / 0
Planned Accrual Rate: 2 / mo
CALGB 30607
Randomized Phase III Double-Blind Placebo-Controlled Trial Of Sunitinib As Maint. Therapy In Non-progressing Patients Following An Initial Four Cycles Of Platinum-Based Combination Chemo In Stage IIIB/IV NSCLC

Study Chair: Mark Socinski
Activated: 6/15/08
# CALGB / CTSU Sites Open: 131 / 229
Target / Current Accrual: 244 / 177
CALGB 30607: Sunitinib as Maintenance Therapy in Non-progressing Advanced NSCLC Patients Following Chemotherapy

- Phase III, randomized, placebo-controlled trial
- Planned randomization: 156 patients (amended to 256)

**Patients with untreated stage IIIB/IV NSCLC and ECOG PS 0–1**

- 4 cycles of platinum-based chemotherapy*

**Randomization of responding patients or patients with stable disease stratified by prior treatment with/without bevacizumab**

- Sunitinib 37.5 mg/day
- Placebo

**Continue until disease progression†**
- Planned follow-up: 1 year

**10 Endpoint - PFS**

*Platinum-based regimen may include carboplatin/cisplatin plus paclitaxel, docetaxel, vinorelbine or gemcitabine with or without bevacizumab (bevacizumab discontinued after four cycles)

†At progression, patients receiving placebo may cross over to the sunitinib arm
Study Objectives

• Primary endpoint
  – PFS (from completion of chemotherapy in the first-line setting)

• Secondary endpoints
  – Additional responses achieved in the maintenance phase due to sunitinib therapy
  – Safety and tolerability of sunitinib vs. placebo
  – Overall survival
  – Impact of sunitinib on time to symptom progression vs. placebo (EORTC QLQ-C30 + LC13)
CALGB 30610/RTOG 0538
Phase III Comparison Of Thoracic Radiotherapy Regimens In Patients With Limited SCLC Also Receiving Cisplatin And Etoposide

Study Chair: Jeff Bogart
Activated: 3/15/08
# CALGB / CTSU Sites Open: 103 / 234
Target / Current Accrual: 690 / 183
Background

• INT 0096 showed superiority of 45 Gy BID x 3 weeks concurrently with chemotherapy over 45 Gy QD x 5 weeks
  – 5Y OS 26% with hyperfractionated XRT vs. 16% with conventional XRT
  – Local tumor relapse was 42% with twice-daily XRT vs. 75% with once-daily XRT BID XRT doubled gr 3-4 esophagitis rate 16% vs. 32%

• Study criticized for low XRT dose in control arm

• Not widely used in practice with only 10% of patients receiving BID XRT

Turrisi, NEJM 1999
Eligibility

• Treatment naïve LS SCLC.

Endpoints

• Compare median and 2y OS of 45cGY BID and investigational XRT
• To compare toxicity, local relapse, RR, QOL
NCCTG 0923
A Randomized, Double-Blinded Phase II Study of NTX-010, a Replication-Competent Picornavirus, After Standard Platinum-Containing Cytoreductive Induction Chemotherapy in Patients with Extensive Stage Small Cell Lung Cancer

Study Chair: Julian Molina
Activated: 01/15/10
# NCCTG / CTSU Sites Open: 34 / 4
Target / Current Accrual: 99 / 41*
Background

- Seneca Valley Virus (NTX-010) is a novel member of the family *Picornaviridae*.
- NTX-010 is selective and potent toward killing tumor cells having one or more neuroendocrine properties *in vitro* and *in vivo* (*CD 56, chromogranin, synaptophysin*).
- Phase I study treated 30 patients (6 small cell, 24 carcinoid). All received $10^7$ vp/kg. SCLC patients had ≥ 3 lines of therapy.
  - In SCLC patients, median PFS was 1.2 months and median OS was 4.1 months with 1 long term (19m+) survivor.
  - All patients developed neutralizing virus Ab and cleared virus effectively.
ES SCLC
Central pathology review
No previous exposure to SVV
CR, PR or SD to a first line platinum doublet.
PS 0-1

NTX 010
Single injection of $10^{11}$ vp/kg

1° PFS in patients who did not progress on the first line therapy
2° OS
CALGB 30901
Randomized Phase II Study Of Maintenance Pemetrexed Versus Observation For Patients With Malignant Pleural Mesothelioma Without Progression After First-Line Chemotherapy

Study Chair: Arkadiusz Dudek
Activated: 4/15/10
# CALGB / CTSU Sites Open: 62 / 71
Target / Current Accrual: 137 / 13
Background

- Switch and continuation maintenance with pemetrexed showed improvement in PFS
  - 4.1. vs. 2.8m in PARAMOUNT
  - PFS 2 vs. 4 months, median OS 10 vs. 13 m

- Benefit of continuation maintenance in mesothelioma is unknown.

Paz-Ares, Lancet Oncology 2012
Eligibility

- MPM any subtype
- Previous surgery or XRT is allowed
- No progression on chemotherapy.
- Chemotherapy is platinum + peme
- No more than 6 cycles of chemotherapy.
Study schema

Stratify by
- Cis vs. Carbo
- Epithelioid vs. other
- Number of cycles received
  (6 vs. < 6)

1° PFS
2° OS, Toxicity, responses.
Endorsed Intergroup Active Studies
ECOG E1505
A Phase III Randomized Trial of Adjuvant Chemotherapy with or without Bevacizumab for Patients with Completely Resected Stage IB (>= 4 cm) - IIIA NSCLC

Endorsed By: CALGB, NCCTG, NCIC, SWOG
Activation Date: 06/01/2007
Target /Current Accrual: 1500 / 1176
Current Accrual through CTSU: 589
ECOG E5508
Randomized Phase III Study of Maintenance Therapy with Bevacizumab, Pemetrexed or Both Following Carboplatin, Paclitaxel and Bevacizumab for Advanced Stage Non-Squamous Non-Small Cell Lung Cancer

Endorsed By: CALGB, NCCTG, SWOG
Activation Date: 08/23/2010
Target /Current Accrual: 1282 / 300
Current Accrual through CTSU: 126
SWOG S0819
A Randomized Phase III Study Comparing Carboplatin/Paclitaxel or Carboplatin/Paclitaxel/Bevacizumab with or without Concurrent Cetuximab in Patients with Advanced NSCLC

Endorsed By: CALGB, ECOG, NCCTG
Activation Date: 07/15/2009
Target / Current Accrual: 1700 / 726
Current Accrual through CTSU: 272