The NCCTG Lung Committee continues to work on new therapeutic treatment trials so as to provide a broader menu of options for patients with lung cancers. The membership of this committee includes research base investigators, community treating physicians, statisticians and research base operation group members. The committee meets monthly to review accrual and progress of ongoing trials, as well as brainstorm new ideas and proposals. The committee also meets face to face twice a year in conjunction with the NCCTG semi-annual meetings to review the portfolio of trials, discuss strategies to improve accrual to our trials as well as discuss strategic partnerships and other initiatives. One of the main goals of the lung committee is to review the suggestions and ideas for trials and treatments arising from the discussions at the NCCTG lung meetings and strive to develop new trials that address these suggestions directly. The NCCTG Lung Committee also works closely with other cooperative groups in promoting joint trials and setting national agendas.

In 2010, the NCCTG lung committee worked on a total of eight new concepts / LOI, of which none was approved. See the complete listing below.

<table>
<thead>
<tr>
<th>Concept / LOI Number</th>
<th>PI</th>
<th>Title</th>
<th>Reason for disapproval</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1021</td>
<td>Adjei</td>
<td>Randomized Phase II Study with a Safety Lead-in of the Small Molecule IGF-1R Inhibitor, OSI-906 in Combination with Carboplatin/Etoposide (C/E) vs. C/E Alone in Previously Untreated Pts with Extensive Stage SCLC</td>
<td>Withdrawn by CTEP.</td>
</tr>
<tr>
<td>N1025</td>
<td>Molina</td>
<td>Randomized Phase II Study Comparing Two Dosing Schedules of R04929097 in Patients with Stage IV NSCLC</td>
<td>Disapproved by CTEP due to duplicate studies at MD Anderson.</td>
</tr>
<tr>
<td>N1027</td>
<td>Molina</td>
<td>Randomized Phase II Screening Trial of the Hedgehog Inhibitor GDC-0449 plus Erlotinib versus Erlotinib Alone in Previously Treated Patients with Stage IV NSCLC</td>
<td>Drug company was conducting their own study.</td>
</tr>
<tr>
<td>N1028</td>
<td>Molina</td>
<td>Randomized Phase II Study of Two Dose Schedules of Sorafenib in Combination with Paclitaxel, Carboplatin and Bevacizumab as First Line Treatment of Patients with Metastatic NSCLC</td>
<td>Disapproved by Thoracic Malignancies Steering committee (TMSC).</td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td>N1029</td>
<td>Molina</td>
<td>Randomized Phase II Study of Pazopanib Versus Pemetrexed Plus Cisplatin as First Line Treatment of Patients with Malignant Pleural Mesothelioma</td>
<td>Disapproved by TMSC.</td>
</tr>
<tr>
<td>N102B</td>
<td>Chen</td>
<td>Randomized Phase II Study of Gemcitabine and Carboplatin with or without Entinostat as First Line Therapy in Advanced Squamous Cell Lung Cancer</td>
<td>LOI disapproved by CTEP Protocol Review Committee.</td>
</tr>
<tr>
<td>N102C</td>
<td>Dy</td>
<td>Randomized Phase II Trial of Cisplatin and Pemetrexed with or without the VEGF/FGF/PDGF Receptor Tyrosine Kinase Inhibitor BIBF1120 as First Line Therapy in Patients with Advanced Nonsquamous NSCLC</td>
<td>Disapproved by TMSC.</td>
</tr>
<tr>
<td>N102D</td>
<td>Adjei</td>
<td>Randomized Phase II Study with a Safety Lead-in of the Small Molecule IGF-1R Inhibitor, OSI-906 in Combination with Carboplatin/Etoposide in Previously Untreated Patients with Extensive SCLC</td>
<td>Mass solicitation LOI disapproved.</td>
</tr>
</tbody>
</table>

**Accrual**

As of March 31, 2011, a total of 31 patients have been accrued to NCCTG and intergroup trials since January 1, 2011. The total accrual for the year 2010 was 142, which is considerably lower than our target accrual goal of 300 patients.

**Small Cell Lung Cancer (SCLC)**

CALGB, 30610, the Phase III Comparison of Thoracic Radiotherapy Regimens with Cisplatin and Etoposide in Limited Small Cell Lung Cancer, is open to accrual, with 9 patients accrued through NCCTG thus far. N0923 is a randomized double-blind phase II placebo controlled study of NTX-010, a replication-competent picornavirus, after standard platinum containing induction regimens of cytoreductive chemotherapy. After receiving 4-6 cycles of standard chemotherapy, the eligible non-PD patients will be randomized to one single dose of NTX-010 or placebo ≤12 weeks after the last dose of
chemotherapy, followed by PCI. As of March 31, 2011, 14 patients have been randomized to this trial, and 29 pre-registered. Both ECOG and CALGB have endorsed this trial, and will be soon be available for accrual by these groups.

A phase II study of single agent TH-302 in refractory and sensitive 2nd line extensive-stage small cell lung cancer (SCLC) patients is currently in development.

**Non-Small Cell Lung Cancer**

N0821 is a phase II first-line study of a combination of pemetrexed, carboplatin and bevacizumab in advanced nonsquamous NSCLC evaluating efficacy and tolerability in elderly patients (age $\geq$70 years) with good performance status (PS <2). This study was closed in October 2010 after having met its accrual objective of 60 patients.

S0819 is open to patient enrollment through CTSU. It is a randomized, phase III study comparing carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab with or without concurrent cetuximab in patients with advanced NSCLC. As of March 31, 2011, 41 patients have been accrued to this trial through NCCTG. CALGB 30801 was opened to NCCTG on October 5, 2010 and has enrolled 3 NCCTG patients. It is a randomized phase III double-blind trial evaluating selective COX-2 inhibition in COX-2 expressing advanced NSCLC. In January, E5508, a randomized phase III study of maintenance therapy with bevacizumab, pemetrexed, or a combination of bevacizumab and pemetrexed following carboplatin, paclitaxel and bevacizumab for advanced non-squamous NSCLC was made available to patient enrollment through CTSU. To date, NCCTG has contributed 6 patients.

For second line, N0626, the randomized Phase II study of pemetrexed combined with sorafenib versus pemetrexed alone as second-line therapy, permanently
closed to patient accrual as of April 9, 2010 after meeting the target accrual. The trial accrued a total of 110 patients and results will be presented at ASCO 2011. There are at least 2 studies in development for this population of patients: the first is a randomized, phase 2 study of the safety and efficacy of TH-302 in combination with docetaxel versus docetaxel alone in patients with relapsed stage IV NSCLC is currently in development, and the second, N1122, is a randomized phase II study of erlotinib with or without entinostat in patients with non-small cell lung carcinoma after failure of up to two prior chemotherapeutic regimens. N1122 is a biomarker-driven study that will prospectively test for E-cadherin values before randomization between the treatment arms.

*For Stage IIIA/B unresectable NSCLC (locally advanced NSCLC)*, we currently have one active study. N0628 (RTOG 0617) is a randomized Phase III trial to compare standard RT (63Gy) versus high-dose conformal RT (74Gy) w/ concurrent and consolidation carboplatin/paclitaxel in patients with stage IIIA/IIIB NSCLC. 18 patients have been accrued through NCCTG to date.

*For Stage IB-IIIA NSCLC*, E1505 is a randomized Phase III trial of adjuvant chemotherapy w/ or w/o bevacizumab for patients w/ completely resected stage IB-IIIA NSCLC. It opened June 26, 2007 and NCCTG has contributed 33 patients.

N0927 (RTOG 0915), the randomized phase II study comparing 2 stereotactic body radiation therapy (SBRT) schedules for medically inoperable patients w/ stage I peripheral NSCLC, was closed on March 22, 2011 with 4 NCCTG patients.

In March 2011, CALGB 140503 was added to the CTSU menu for NCCTG sites. This is a phase III randomized trial of lobectomy versus sublobar resection for small peripheral NSCLC. NCCTG has contributed 1 patient to date.
Mesothelioma

CALGB 30901 is currently in development for malignant pleural mesothelioma. This is a randomized phase II study of maintenance pemetrexed versus observation for patients without progression after first-line chemotherapy.

Miscellaneous Projects

In order to properly design future trials, it is critical that we understand the lessons learned from previous studies including patients treated for a particular disease. We are using data from multiple NCCTG NSCLC and SCLC trials, as well as collaborating with other groups to answer important questions relating to patient prognosis. With targeted therapies that prolong disease stabilization, progression-free survival (PFS) has become accepted alternate endpoints to tumor response. We formally investigated the relationships between response, PFS and survival, and found that PFS status or failure free survival status assessed at 12 weeks better predicts patient survival than tumor response in NSCLC (published in the Journal of Thoracic Oncology), and PFS status as early as 4 months is a better predictor of subsequent patient survival than tumor response in SCLC (published in Cancer). In SCLC, PFS also showed promise as a potential surrogate for OS, and further validation using data from a larger number of randomized phase 3 trials is underway. We are currently exploring the impact of the algorithm for declaring exact progression date on progression-free survival (PFS) estimates in advanced lung cancer clinical trials. At ASCO 2010, we reported that the PFS estimates are significantly impacted by the approach used for declaring disease progression date with the magnitude of difference being large enough to alter trial conclusions. An updated analysis including data from 14 NCCTG and 7 SWOG trials has been accepted for oral presentation at ASCO 2011. Finally, we have an active ongoing
collaboration with the Gustave-Roussy Institute, Villejuif, France, on the assessment of
disease-free survival as surrogate endpoint for overall survival for trials of adjuvant
chemotherapy in operable non-small cell lung cancer, and in locally advanced lung
cancer. Two abstracts will be presented at ASCO 2011 from this collaboration.
Open Trials

Small Cell Lung Cancer
- N0923: A Randomized Double-Blinded Phase II Study of NTX-010, a Replication-Competent Picornavirus, After Standard Platinum Containing Induction Regimens of Cytoreductive Chemotherapy for Patients With Extensive Stage Small Cell Lung Carcinoma
- CALGB 30610: Phase III Comparison of Thoracic Radiotherapy Regimens with Cisplatin and Etoposide in Limited Small Cell Lung Cancer

Non-small Cell Lung Cancer
- Stage IIIA/IIIB
  - N0628 (RTOG 0617): Randomized Phase III Comparison of Standard RT (63Gy) Versus High-dose Conformal RT (74Gy) w/ Concurrent and Consolidation Carboplatin/Paclitaxel in Patients w/ Stage IIIA/IIIB NSCLC
- Stage IIIB/IV
  - S0819 (SWOG): A Randomized, Phase III Study Comparing Carboplatin/Paclitaxel or Carboplatin/Paclitaxel/Bevacizumab with or without Concurrent Cetuximab in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)
  - 30801 (CALGB): Randomized Phase III Double-Blind Trial Evaluating Selective COX-2 Inhibition in COX-2 Expressing Advanced NSCLC
  - E5508 (ECOG): Randomized Phase III Study of Maintenance Therapy with Bevacizumab, Pemetrexed, or a Combination of Bevacizumab and Pemetrexed Following Carboplatin, Paclitaxel and Bevacizumab for Advanced Non-squamous NSCLC

Surgical Adjuvant Therapy
- E1505 (ECOG): Phase III Randomized Trial of Adjuvant Chemotherapy w/ or w/o Bevacizumab for Patients w/ Completely Resected Stg IB-IIIA NSCLC.
- 140503 (CALGB): Phase III Randomized Trial of Lobectomy versus Sublobar Resection for Small (≤2 cm) Peripheral NSCLC

Mesothelioma
- None
Trials in Development

Non-small Cell Lung Cancer

- N102F (NCCTG): Randomized phase II trial of radiation and pemetrexed with or without carboplatin for stage IIIA and IIIB non-squamous NSCLC in patients +/- 70 years of age.

- N1122 (NCCTG): Randomized phase II study of erlotinib with or without entinostat in patients with NSCLC after failure of up to two prior chemotherapeutic regimens for advanced disease.

- NCCTG: Randomized, Phase 2 Study of the Safety and Efficacy of TH-302 in Combination with Docetaxel versus Docetaxel Alone in Patients with Relapsed Stage IV Non-Small Cell Lung Cancer

Small Cell Lung Cancer

- NCCTG: A Phase II Study of Single Agent TH-302 in Refractory and Sensitive 2nd line Extensive-Stage Small Cell Lung Cancer (SCLC) patients

Mesothelioma

- 30901 (CALGB): Randomized phase II study of maintenance pemetrexed versus observation for patients with malignant pleural mesothelioma without progression after first-line chemotherapy.