Review

# Update on International Cooperative Groups Studies in Thoracic Malignancies: The Emergence of Immunotherapy

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## Abstract

Cancer cooperative groups have historically played a critical role in the advancement of non–small-cell lung cancer therapy. Representatives from cooperative groups worldwide convene at the International Lung Cancer Congress annually. The International Lung Cancer Congress had its 17th anniversary in the summer of 2016. The present review highlights the thoracic malignancy studies discussed by presenters. The included studies are merely a sample of the trials of thoracic malignancies ongoing globally.

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## Introduction

More and more therapeutic options have become available for patients with thoracic malignancies, including non–small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), mesothelioma, and thymic malignancies. These options include improved systemic therapy and radiation techniques, such as combination regimens, targeted therapies, and immunotherapies. Cancer cooperative groups have historically played a critical role in the advancement of NSCLC therapy. The cooperative group thoracic malignancy trials that are currently accruing are listed in Table 1. Representatives from cooperative groups worldwide convene at the International Lung Cancer Congress (ILCC) annually. The ILCC held its 17th anniversary meeting in the summer of 2016. In the present review, we have highlighted the thoracic malignancy studies discussed by the presenters. The presenters included Suresh Ramalingam, MD, of the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network (ECOG-ACRIN); Karen Kelly, MD, of the Southwest Oncology Group (SWOG); Everrett Vokes, MD, of the Alliance for Clinical Trials in Oncology; Giorgio Scagliotti, MD, of the European Organization for Research and Treatment of Cancer (EORTC); Glenwood Goss, MD, of the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG); and Tony Mok, MD, presenting for the Chinese Thoracic Oncology Group (CTONG), Asia Thoracic Oncology Research Group (ATORG), and Korean Cancer Study Group. The following studies are merely a sample of the trials of thoracic malignancies ongoing worldwide.

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## ECOG-ACRIN Studies

The ECOG-ACRIN has 3 objectives for lung cancer: (1) integration of targeted agents and biomarker discovery, (2) development of novel SCLC agents, and (3) incorporation of novel imaging biomarkers.

### *Early-stage Disease*

Perhaps the greatest reduction in NSCLC mortality could be achieved by increasing the cure rates in the adjuvant setting. To this

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**Table 1 Clinical Trial Identifiers of Cooperative Group Trials**

| Trial Name | ClinicalTrials.gov Identifier |
|---|---|
| **ECOG-ACRIN** | |
| E1505 | NCT00324805 |
| ALCHEMIST | NCT02194738 |
| EA5142 | NCT02595944 |
| EA5123 | NCT02607423 |
| ECOG 5508 | NCT01107626 |
| **SWOG** | |
| S1206 | NCT01386385 |
| S1403 | NCT02438722 |
| S1400 | NCT02154490 |
| S1507 | NCT02642042 |
| **Alliance** | |
| CALGB 140503 | NCT00499330 |
| RTOG 1306 | NCT01822496 |
| RC1126 | NCT01532089 |
| AFT 09 | NCT02591615 |
| EORTC NEMO | NCT02863055 |
| EORTC 1205 | NCT02436733 |
| DENIM | NCT02395679 |
| **NRG Oncology Group** | |
| NRG 1306 | NCT01822496 |
| RTOG Foundation 3505 | NCT02768558 |
| BR.31 | NCT02273375 |
| **European trials** | |
| PEARLS | NCT02504372 |
| AIO-TRK-0214 | NCT02326285 |
| National lung matrix trial | NCT02664935 |
| SPECTAlung | NCT02214134 |
| SAFIR 02 Lung | NCT02117167 |
| NICOLAS | NCT02434081 |
| PRIMUS | NCT02564380 |
| PIPSeN | NCT02679963 |
| NICHE | NCT02369484 |
| Osimertinib with or without bevacizumab | NCT02971501 |
| EORTC NEMO | NCT02863055 |
| EORTC 1205 | NCT02436733 |
| DENIM | NCT02395679 |
| **Canadian trials** | |
| CALGB 140503 | NCT00499330 |
| IND 219 | NCT02337530 |
| NCIC-CTG IND.215 | NCT01783197 |
| IND.226 (MEDI4736) | NCT02261220 |
| BR.31 | NCT02273375 |

Abbreviations: ACRIN = American College of Radiology Imaging Network; CALGB = Cancer and Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; NCIC-CTG = National Cancer Institute of Canada Clinical Trials Group; RTOG = Radiation Therapy Oncology Group; SWOG = Southwestern Oncology Group.

end, ECOG-ACRIN has undertaken phase III randomized studies investigating the addition of angiogenesis inhibitors and targeted therapies to standard chemotherapy regimens. Regarding angiogenesis inhibitors, the results of the E1505 (chemotherapy with or without bevacizumab in patients with completely resected stage IB-IIIA non–small-cell lung cancer) study, presented at the 2016 American Society of Clinical Oncology meeting, were discussed at the 17th ILCC meeting.[1] The E1505 study focused on whether adjuvant chemotherapy with and without 1 year of adjunct bevacizumab would improve overall survival. In the study, 1500 patients with resected (lobectomy or greater) IB-IIIA NSCLC and no previous chemotherapy or planned radiation were randomized to 4 cycles of chemotherapy alone versus 4 cycles of chemotherapy with 1 year of bevacizumab. The primary endpoint of overall survival was not significantly different between chemotherapy and chemotherapy with bevacizumab (hazard ratio [HR], 0.99; $P = .90$). In addition, the study found that the investigator's choice of adjuvant chemotherapy regimens (investigator's choice: cisplatin doublet, inclusive of vinorelbine, gemcitabine, or docetaxel, with the addition of pemetrexed for patients with nonsquamous cell cancer) did not significantly affect overall survival (ie, no cisplatin doublet outperformed the other). Regarding targeted therapies, the ongoing ALCHEMIST trial, previously discussed at the 15th ILCC meeting,[2] is investigating targeted agents against EGFR- and ALK-mutant nonsquamous NSCLC. For patients with NSCLC without sensitizing EGFR mutations or ALK rearrangements, the ANVIL (adjuvant nivolumab in resected lung cancers) trial is accruing patients under the ALCHEMIST schema (EA5142). After completion of chemotherapy, patients will be randomized 1:1 to receive either nivolumab or placebo for 1 year. The primary endpoint of ANVIL will be overall survival, with a focus on disease-free survival.

Patients with stage III N2 disease are faced with several key questions on how to best manage their disease.[3] EA5123 (fludeoxyglucose F-18 PET/CT in predicting response to chemotherapy in patients with stage IIIA non–small-cell lung cancer that can be removed by surgery) was a study focusing on a cohort of 90 stage IIIA ($N2^+$) NSCLC patients to answer the question of whether chemotherapy or concurrent chemotherapy and radiation will improve disease-free survival. In addition, EA5123 sought to determine whether imaging is able to predict mediastinal nodal clearance. In the study, patients with resectable tumors with N2 disease were to undergo baseline positron emission tomography-computed tomography (PET-CT) to confirm nodal involvement. Patients would then undergo a single cycle of cisplatin-based induction therapy, followed by repeat PET-CT, followed by 2 additional cycles of cisplatin-based chemotherapy, followed by a third PET-CT scan before surgical resection and mediastinal dissection. The primary endpoint of the study was the ability of the cycle 1 PET-CT findings to predict for nodal clearance. However, the study was closed because of poor accrual.

### *Advanced-stage Disease*

Advanced-stage studies include ECOG 5508 and EA5152. ECOG 5508 is examining different maintenance chemotherapy