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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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Keywords: Clinical trials, Mesothelioma, Non–small-cell lung cancer, Small cell lung cancer, Thymic carcinoma

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); Everett 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.

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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International Cooperative Group Study Update

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 (MED)4736)	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 (fluorodeoxyglucose 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

regimens after 4 cycles of first-line chemotherapy with carboplatin, paclitaxel, and bevacizumab. The trial enrolled 1515 stage IIIB/IV nonsquamous NSCLC patients stratified by smoking status, gender, histologic features, best response, and stage. These patients will receive 4 cycles of first-line chemotherapy followed by randomization for the patients without progression to receive either bevacizumab or pemetrexed, or a combination of bevacizumab and pemetrexed, for maintenance therapy until progression. The primary endpoint is overall survival. The study has completed accrual but has not yet yielded results. EA5152, which opened in March 2018, is a randomized phase II trial of nivolumab versus cabozantinib plus nivolumab in patients with previously treated nonsquamous NSCLC and no mutations in EGFR, ALK, MET (exon 14 or amplification), ROS1, or RET (Figure 1). The study is designed to enroll 169 patients randomized 1:1 to either nivolumab alone or nivolumab with cabozantinib. The primary endpoint is progression-free survival (PFS).

To address advanced-stage NSCLC with EGFR mutations, specifically EGFR exon 20 insertions, a study using osimertinib is under development. EGFR exon 20 mutations constitute ~ 4% to 10% of all EGFR mutations in NSCLC and are generally refractory to currently available EGFR targeted therapies. In vitro models have shown efficacy of osimertinib against EGFR exon 20 insertion models. A Simon 2-stage design with a planned sample size of 40 will be used. The primary endpoint is the response rate. If the 2-stage test rejects the null hypothesis after completion of accrual, the study can be amended to allow for a third stage.

SWOG Studies

The overall objectives of SWOG are to (1) transform standards of care through phase III trials, (2) optimize therapy for individual

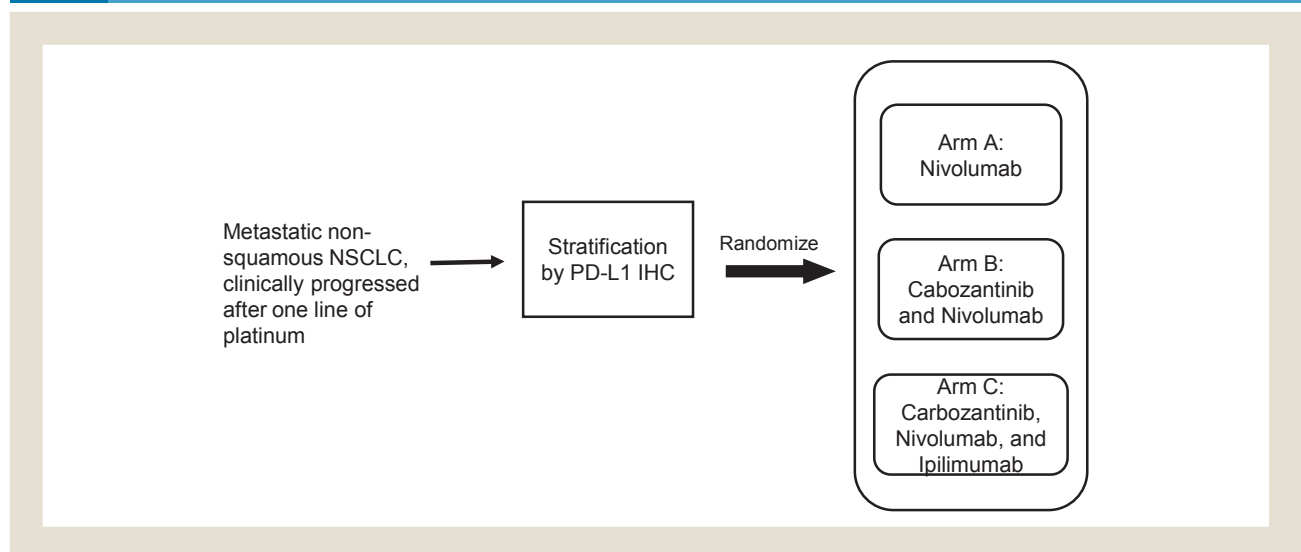
patients and patient subsets, and (3) enhance our biologic understanding of thoracic malignancies.

Early-stage Disease

It is well known that failure to perform systemic nodal staging or inadequate staging is associated with inferior survival. The SILENT study (S1700: strategies to improve lymph node examination of non-small cell lung tumors) uses a surgical lymph node specimen collection kit to overcome this problem. Patients will be randomized to either (1) routine surgical lymph node collection (conventional arm); or (2) special surgical lymph node collection (intervention arm). The special surgical lymph node collection is a more systematic approach to ensure comprehensive lymph node sampling to detect lymph node metastases. The primary endpoint is disease-free survival. In a pilot study conducted by the principal investigator, the use of the kits resulted in a > 50% increase in the detection of nodal metastases and influenced survival.⁴ The SILENT study is in its final stages of development.

Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors have been shown to be efficacious in diseases with genomic instability such as BRCA1/2 mutant breast and ovarian cancers. Given that genomic instability is associated with tobacco-related diseases, including NSCLC, and given that veliparib has been shown to result in favorable responses and survival in phase II studies when combined with platinum in metastatic NSCLC,⁵ the S1206 study is investigating the PARP inhibitor veliparib combined with concurrent chemoradiotherapy in inoperable stage III NSCLC. The study is composed of 2 phases: the first is a dose-finding study and the second is a randomized phase II trial (Figure 2). The phase I dose-finding study has been completed. Three doses of veliparib were evaluated, 40 mg, 80 mg, and 120 mg orally, twice daily, with

Figure 1 The EA5152 Study by Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network (ECOG-ACRIN) Will Compare Nivolumab Alone to Nivolumab With Cabozantinib and Nivolumab With Cabozantinib and Ipilimumab in Patients With Metastatic, Nonsquamous Non–Small-cell Lung Cancer (NSCLC). Intended Sample Size Is 96 Patients, and the Primary Outcome Measure Is Progression-Free Survival



Abbreviations: IHC = immunohistochemistry; PD-L1 = programmed cell death ligand 1.

International Cooperative Group Study Update

low-dose paclitaxel and carboplatin and 60 Gy of thoracic radiation. Veliparib at 120 mg was not associated with any dose-limiting toxicity and was recommended for phase II evaluation. The randomized phase II trial is ongoing, with a primary objective of disease-free survival.

Advanced-stage Disease

Compared with NSCLC adenocarcinoma, squamous cell carcinoma has a paucity of precision medicine strategies available. To address this unmet need, the S1400 Lung-MAP study is a master protocol for squamous NSCLC that screens patients for biomarker-driven substudies for targeted therapies or, in the absence of a candidate biomarker, immunotherapy in the second line and beyond setting. Per design, the study schema is continually evolving as studies open and close. The overarching goal of Lung-MAP is to provide a streamlined drug evaluation platform that can lead to Food and Drug Administration drug approval. As of August 2017, 1359 patients were enrolled in the screening study. The full schema of the Lung-MAP study was discussed at the 16th ILCC meeting and described in our previous review.² The current updated schema is shown in Figure 3.

In adenocarcinoma, despite the relative abundance of targeted options, KRAS, the most common driver oncogene, remains an elusive target. In an attempt to address this need, S1507 is examining the combination of docetaxel with the MEK inhibitor trametinib in KRAS-mutant NSCLC. Patients receive docetaxel 75 mg/m² on day 1 in conjunction with trametinib 2 mg on days 1 to 21. The primary objective is the overall response rate for all patients, with the secondary objective the overall response rate in KRAS G12C-mutant patients. The first phase of this trial has met its accrual goal and is undergoing data analysis.

Regarding lung adenocarcinoma, SWOG discussed 2 trials focusing on targeted therapy and immunotherapy. For targeted therapy, S1403 (afatinib dimaleate with or without cetuximab in treating patients with newly diagnosed stage IV or recurrent, EGFR mutation positive non-small-cell lung cancer) is examining the combination of afatinib and cetuximab versus afatinib alone in the

first-line treatment of advanced EGFR-mutant NSCLC. The hypothesis is that the combination will prevent and/or delay drug resistance, resulting in an increased PFS. Patients receive afatinib 40 mg daily alone or afatinib 40 mg daily plus cetuximab dosed at 500 mg/m² every 2 weeks. Repeat biopsy specimens are obtained at progression for translational endpoints, including the creation of PDX models that will allow for future drug development evaluation. For immunotherapy, a proposed front-line immunotherapy trial jointly sponsored by ECOG and SWOG is in development to investigate questions related to chemotherapy and immunotherapy combinations. The study is still in development and the objectives have not yet been finalized.

Alliance for Clinical Trials in Oncology

Early-stage Disease

To ascertain the disease outcomes from differing surgical approaches, Cancer and Leukemia Group B (CALGB) 140503 is a phase III randomized trial of lobectomy versus sublobar resection for small (≤ 2 cm) peripheral NSCLC. Patients are randomized to either lobectomy or wedge or segmental resection with stratification by tumor size, histologic type, and smoking status. The study objectives are to (1) correlate the preoperative CT and PET characteristics with outcome; (2) determine the false-negative rate for PET findings in hilar and mediastinal nodal metastases; and (3) determine the utility of annual follow-up CT scans after resection. Similar to SWOG, the Alliance is also investigating the role of PARP inhibitors in NSCLC treatment. A phase I/II trial evaluating veliparib combined with carboplatin and paclitaxel and thoracic radiation therapy for unresectable stage IIIA and stage IIIB NSCLC is nearing completion. The regimen consists of weekly carboplatin and paclitaxel with veliparib dosing levels increasing from 40 mg twice daily to 200 mg twice daily. At the conclusion of concurrent chemoradiation with veliparib, 2 cycles of carboplatin and paclitaxel combined are administered with veliparib 120 mg twice daily. The primary endpoints are toxicity and disease-free survival.

Figure 2 The Southwestern Oncology Group S1206 Study Is Designed to Study Chemoradiotherapy With and Without Veliparib in 132 Patients With Stage IIIA/B Unresectable NSCLC. The Primary Outcome Measure Is Improvement in Progression-Free Survival

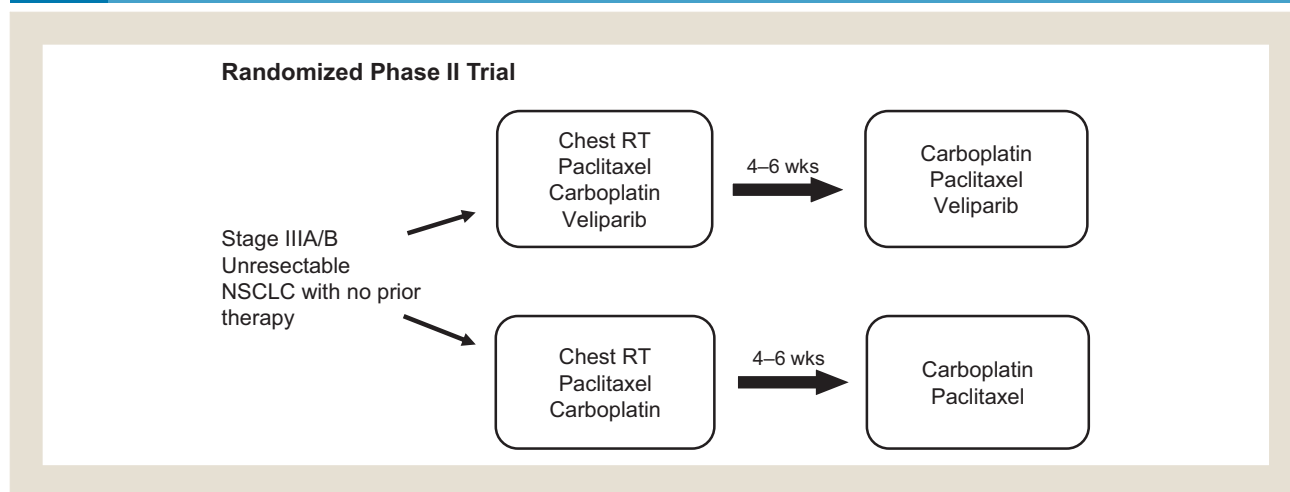
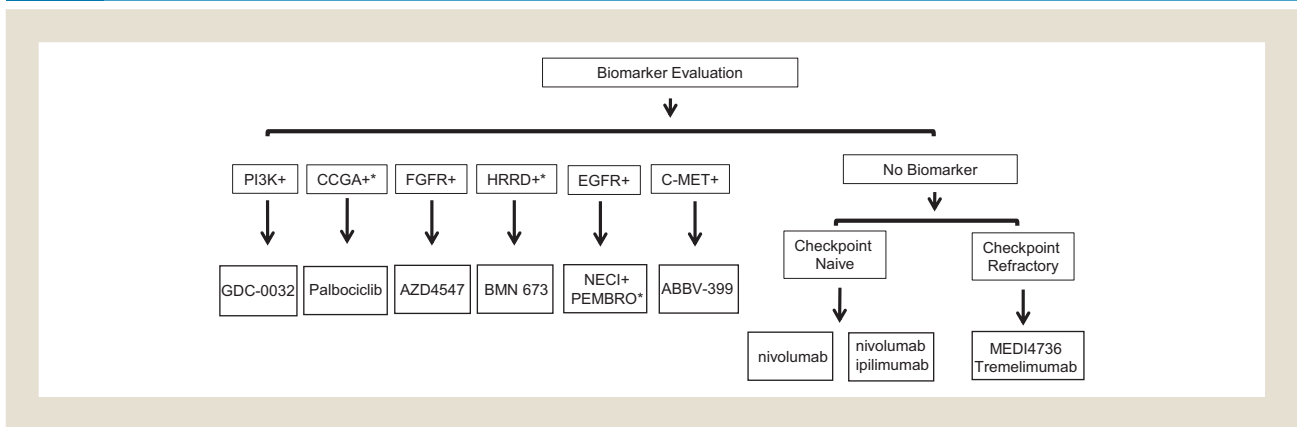


Figure 3 The S1400 Lung-MAP Study, Led by the Southwestern Oncology Group, Is Continually Evolving as Substudies Open and Close. As of August 2017, 1359 Patients Had Been Enrolled. The Study Screens Patients for Biomarker-Driven Studies of Targeted Therapies With the Intention of Providing a Streamlined Drug Evaluation Platform that Can Lead to Food and Drug Administration Drug Approval. The Current Schema Is Shown



Advanced-stage Disease

ACCRU RC1126, similar to the BELIEF (bevacizumab and erlotinib in EGFR mut+ [mutation-positive] NSCLC) study by the European Thoracic Oncology Platform,⁶ is a randomized phase II study of erlotinib alone or combined with bevacizumab in EGFR-mutant NSCLC. Patients without brain metastases and without previous chemotherapy or tyrosine kinase inhibitor treatment will be randomized to erlotinib alone or erlotinib with bevacizumab. The primary endpoint is PFS. Accrual to the trial has been completed.

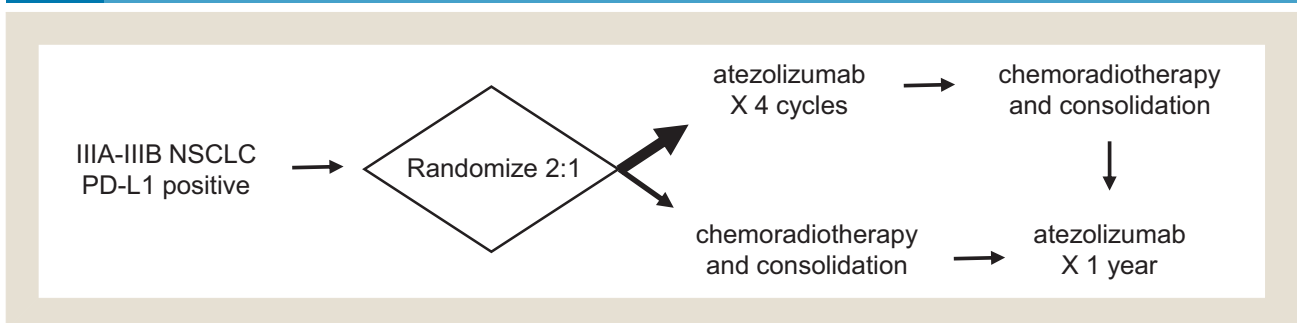
AFT (Alliance Foundation Trials) 09 is a randomized phase II trial evaluating the optimal sequencing of programmed cell death 1 (PD-1) inhibition with MK-3475 and platinum-based chemotherapy in the front-line setting of metastatic NSCLC. Treatment-naïve patients (those with treated brain metastases are eligible) are randomized to 2 arms: chemotherapy for 4 cycles, followed by MK-3475 for 4 cycles, versus MK-3475 for 4 cycles, followed by chemotherapy for 4 cycles. Both arms then transition to maintenance MK-3475 until disease progression or 1 year. The primary endpoint is the objective response rate.

With the recent phase I evidence of neoadjuvant immunotherapy activity with anti-PD-1 agents in resectable disease,⁷ the AFT-16

trial (induction immunotherapy in locoregionally advanced unresectable IIIA-IIIB disease) is using the anti-programmed cell death ligand 1 (PD-L1) therapeutic agent, atezolizumab, before curative intent chemoradiotherapy (Figure 4). The primary objective is the disease control rate of neoadjuvant atezolizumab therapy. Patients will undergo restaging after cycle 2, and those without progression will receive a total of 4 cycles of atezolizumab, followed by chemoradiation, followed by consolidation chemotherapy. Subsequently, patients will receive adjuvant atezolizumab for 1 year. In the event that patients do not respond and develop disease progression during neoadjuvant atezolizumab treatment, those patients will be assigned to receive immediate concurrent chemoradiation, followed by consolidation chemotherapy.

Finally, to evaluate the use of immunotherapy in patient populations at increased risk of autoimmune complications, A081601 is a proposed phase I/II study of pembrolizumab in compromised populations such as those with organ dysfunction, malnutrition, autoimmune disease, and human immunodeficiency virus-positive status. This phase I study will follow a 3+3 dose escalation design to test the hypothesis that pembrolizumab can be administered safely to this cohort of patients.

Figure 4 AFT-16, Led by Alliance, Studies the Use of Atezolizumab before Curative Intent Chemoradiotherapy in Patients With Stage IIIA/IIIB, Programmed Cell Death Ligand 1 (PD-L1)-Positive Non-Small-Cell Lung Cancer. The Primary Outcome Measures Are Disease Control Rate With Neoadjuvant Atezolizumab. The Intended Sample Size Is 63 Patients



International Cooperative Group Study Update

NRG Oncology Studies

The specific research questions for NRG addressed at the 17th ILCC were (1) whether radiotherapy can be further improved with the better use of functional imaging and the testing of proton therapy; and (2) whether new systemic therapies can help whether targeted to a mutation subgroup or not targeted to a specific NSCLC subgroup.

Early-stage Disease

The Radiation Therapy Oncology Group (RTOG) Foundation 3505 is a phase III trial of concurrent chemoradiotherapy with or without adjuvant nivolumab. For this study, treatment-naïve stage III NSCLC of any histologic type and without EGFR or ALK mutations will be subjected to concurrent chemoradiation with ≤ 60 Gy and the EP (etoposide, cisplatin) 50/50 regimen (cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² on days 1-5 and 29-33).⁸ Next, the patients will be randomized to either nivolumab or placebo for either 1 year or until disease recurrence or progression. The co-primary endpoints for the study are survival and PFS, and the target enrollment is 660 patients. The present study is currently active but not recruiting.

In collaboration with Alliance, the RTOG 1306-Alliance 31101 is a randomized phase II study of individualized combined modality for stage III NSCLC. Unresectable nonsquamous NSCLC with pathologically confirmed N2/N3 disease will be randomized to the following according to the cohort. The EGFR-mutant NSCLC

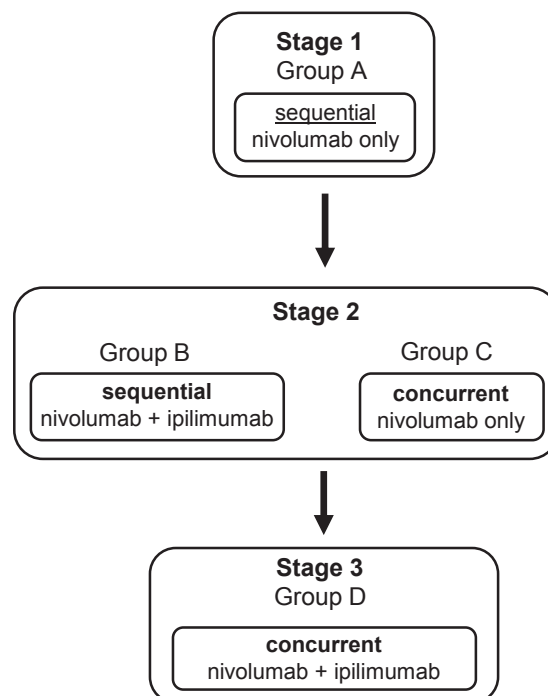
group will be randomized to receive either erlotinib induction therapy for 12 weeks followed by concurrent chemoradiotherapy or concurrent chemoradiotherapy alone. The ALK translocation NSCLC group will be randomized to either crizotinib induction therapy for 12 weeks, followed by concurrent chemoradiotherapy or concurrent chemoradiotherapy alone.

Advanced-stage Disease

To examine the role of reirradiation in conjunction with checkpoint blockade with anti-PD-1 therapy for recurrent NSCLC, the following pilot study has been proposed. The study will enroll patients with recurrent disease within the 50% isodose line after previous chemoradiotherapy with a platinum regimen and who are also candidates only for systemic therapy (ie, no curative intent options such as surgery or stereotactic radiotherapy). The study will be composed of a phase I safety assessment with patients receiving 60 Gy radiation with intensity-modulated radiotherapy or proton beam therapy and adjuvant anti-PD-1. In the phase II randomized study, PFS will be assessed between radiotherapy as above in conjunction with anti-PD-1 therapy versus anti-PD-1 therapy alone.

ARCHON-1 is a phase I study of accelerated hypofractionation radiotherapy combined with immunotherapy in locally advanced NSCLC. The primary objective of the study is to determine the safety of accelerated hypofractionation radiotherapy with immunotherapy according to the incidence of grade ≥ 3 radiation

Figure 5 ARCHON-1, Led by NRG, Is Assessing the Safety of Accelerated Hypofractionation Radiotherapy (ACRT) With Immunotherapy in Locally Advanced Non-Small-Cell Lung Cancer. The Maximum Sample Size Is 80. Safety Is the Primary Outcome Measure. Secondary Outcome Measures Include Biomarker Correlates to Overall Survival and Progression-Free Survival, Overall Survival, and the Incidence of Grade ≥ 3 Thoracic Radiation Pneumonitis Within 15 Weeks of the Start of ACRT



pneumonitis. The study design (Figure 5) will be composed of 3 stages: (1) 60 Gy of radiotherapy in 15 fractions; (2) sequential or concurrent immunotherapy and chemotherapy regimens; and (3) administration of nivolumab to all patients for ≤ 48 weeks until disease progression or intolerance. Safety will be evaluated in a 10+10 design for each treatment group, with the first cohort of 10 not receiving induction chemotherapy and the second cohort of 10 receiving induction chemotherapy. The first stage will evaluate 4 doses of nivolumab sequentially administered after radiotherapy. Should the incidence of grade 3 pneumonitis or other adverse effects occur at an acceptably low level, the study will advance to stage 2, in which patients will either receive sequential nivolumab combined with ipilimumab or concurrent nivolumab with the previously described radiotherapy regimen. Again, the safety of both regimens will be evaluated in a 10+10 design. Finally, if the toxicity profile is acceptable, the study will advance to stage 3, in which nivolumab combined with ipilimumab will be administered concurrently with radiotherapy.

European Trials

Early-stage Disease

The PEARLS [study of pembrolizumab (MK-3475) versus placebo for participants with non–small-cell lung cancer after resection with or without standard adjuvant therapy [MK-3475-091/KEYNOTE-091] is a randomized, phase III trial with pembrolizumab versus placebo for patients with early-stage NSCLC after resection and completion of standard adjuvant therapy. Patients will be randomized 1:1 to receive pembrolizumab or placebo for 1 year. The co-primary endpoints are disease-free survival in the PD-L1–strong subgroup and disease-free survival in the overall population. Correlative studies will focus on the immune landscape through T-cell receptor sequencing and serum biomarker measurements. AIO-TRK-0214 Neo-INTERCAL [induction therapy with intercalated tyrosine kinase inhibitor (TKI) and chemotherapy

in NSCLC with activating epidermal growth factor receptor (EGFR) mutation in stages II–IIIb] is a phase II trial involving stage II–IIIb EGFR-mutant NSCLC with neoadjuvant treatment with gefitinib (250 mg/d) for 12 days, followed by 3 cycles of neoadjuvant chemotherapy with cisplatin, docetaxel, and intercalated gefitinib. The primary endpoint is the rate of pathologic complete response.

Advanced-stage Disease

The UK National Lung Matrix Trial involves matching the aberration to the drug (Table 2). Each cohort is involved in a phase II study design, with 20 different molecular cohorts defined by specific somatic alterations matched to 8 different investigational agents.

The SPECTAlung (screening patients with thoracic tumors for efficient clinical trial access) study involves first obtaining informed consent for screening and exploratory/future research, followed by standard of care treatment or experimental treatment. Human biological material will be collected for a central biobank where it can be accessed by research laboratories for exploratory and future research or by diagnostic laboratories for biomarker testing. The screening results will be compiled into a SPECTA database. The database will aid in providing information on suitable downstream trials and obtaining informed consent for therapeutic trials.

For patients with stage IV NSCLC without EGFR or ALK mutations, the SAFIRO2L trial will evaluate patients after 2 cycles of first-line chemotherapy for comparative genome hybridization or next-generation sequencing. If no molecular alteration is detected or the patients have progressive disease after 4 cycles of first-line chemotherapy, the patients will exit the trial. Otherwise, patients will be randomized to 1 of 2 arms: (1) mutation or “bioguided” therapy with molecular therapies (including AZD2014, AZD4547, AZD5363, AZD8931, selumetinib, and vandetanib) or (2) standard chemotherapy maintenance with pemetrexed for nonsquamous histologic cancer or erlotinib for squamous histologic cancer.

The NICHE study examined PFS with afatinib in pretreated HER2-mutated stage IIIB/IV NSCLC. The study was stopped prematurely after 13 patients had been recruited because the stopping boundary was crossed. The results were presented at the American Society of Clinical Oncology 2017 meeting and have been summarized in the present review. The 12-week disease control rate and PFS rate was 54% and 51%, respectively, and the median PFS was 13 weeks (95% confidence interval [CI], 6 weeks to not estimable).⁹

For T790M-mediated resistance in EGFR-mutant NSCLC, the BOOSTER study will examine the role of bevacizumab combined with osimertinib in improving survival. Stage IIIB/IV NSCLC patients with progression due to T790M secondary mutations in EGFR-mutant disease will be randomized to receive either osimertinib alone or osimertinib plus bevacizumab. The primary endpoint is PFS. For RET-driven stage IIIB/IV NSCLC, a randomized study has been planned to study second-line alectinib versus second-line chemotherapy, with the latter arm allowed to crossover to alectinib at progression. The primary endpoint is the objective response rate.

The emergence of immunotherapy has opened new avenues of investigation to improve survival of patients with NSCLC without actionable mutations. The NICOLAS (nivolumab combination

Table 2 UK National Lung Matrix Trial Matches Actionable Mutations to Specific Therapeutic Agents

Agent	Actionable Mutation
AZD4547	FGFR1/2
AZD2014	TSC1/2 LKB1
Palbociclib	RB1 and p16 loss
	RB1 and CDK4 gain RB1 and CCND1 gain
	RB1 and KRAS RB1 and LKB1
Crizotinib	MET ROS1
Selumetinib	NF1 NRAS
AZD5363	PIK3CA PTEN AKT
AZD9291	EGFR
MEDI4736	None

International Cooperative Group Study Update

with standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B non–small-cell lung carcinoma) study aims to determine the feasibility of nivolumab consolidation after standard first-line chemoradiotherapy for locally advanced stage IIIA/B NSCLC. Patients will be assigned to either 3 cycles of concurrent radiotherapy, followed by 4 doses of nivolumab, or 3 cycles of chemotherapy, followed by radiotherapy concurrent with 8 doses of nivolumab. Both arms will subsequently receive nivolumab on a monthly basis for 1 year or until progressive disease. The primary endpoint is the grade ≥ 3 pneumonitis-free rate.

Similarly, the PRIMUS study (study of pembrolizumab maintenance following first-line platinum based chemotherapy in patients with metastatic squamous non–small-cell lung cancer) is examining the role of pembrolizumab in stage IIIB/IV squamous NSCLC patients who have experienced a response of stable disease or better after ≥ 2 cycles of platinum-based chemotherapy. Patients will be randomized to receive either pembrolizumab or placebo every 3 weeks, and the primary endpoint will be PFS. PIPSeN (trial evaluating maintenance olaparib in patients with platinum-sensitive advanced non–small-cell lung cancer) is a randomized, double-blind phase II study evaluating maintenance with the PARP inhibitor, olaparib, versus placebo in NSCLC patients who have received 6 cycles of platinum-based chemotherapy. The primary endpoint is PFS.

Canadian Trials

Early-stage Disease

CALGB 140503 is examining stage I T1a tumors randomized to either lobectomy or limited resection (wedge or segmental resection) for noninferiority, disease-free survival. Patients will be stratified by tumor size, histologic type, and smoking status. BR.31 is a phase III, randomized, placebo-controlled trial of the anti–PD-L1 antibody, durvalumab, in completely resected stage IB–IIIA NSCLC. Patients with completely resected stage IB (≥ 4 cm), II, or IIIA NSCLC will be randomized to either MEDI4736 or placebo. The primary endpoint is disease-free survival in PD-L1⁺ expression patients.

Advanced-stage Disease

As previously stated, despite being one of the most prevalent driver mutations in NSCLC adenocarcinoma, KRAS mutations remain unactionable. To overcome this, the NCIC-CTG IND.215 (study of selumetinib in patients with previously treated or untreated advanced/metastatic NSCLC) study is investigating the use of selumetinib, an inhibitor of the downstream KRAS effector, MEK. NCIC-CTG IND.215 is a multiarm phase I trial to evaluate the dose and schedule of a first-line platinum doublet (either cisplatin/pemetrexed or carboplatin/paclitaxel) with intermittent selumetinib in NSCLC adenocarcinoma. This part of the study will then be followed by an expansion cohort of KRAS-mutant only NSCLC with continuous dosing selumetinib. To further study the treatment of KRAS-mutant NSCLC, IND.219 is a randomized phase II trial of selumetinib in patients receiving standard pemetrexed and cisplatin chemotherapy for the treatment of advanced/metastatic KRAS wildtype or unknown nonsquamous NSCLC. The primary endpoint is the objective response rate, with secondary endpoints of PFS, overall survival, toxicity, and correlatives between KRAS status and molecular signatures.

IND.226 (a phase 1 study of MEDI4736 in combination with tremelimumab in subjects with advanced solid tumors) is a phase IB study of durvalumab (MEDI4736) with or without tremelimumab in patients with advanced incurable solid malignancies receiving standard chemotherapy regimens. Patients considered suitable for 1 of the chemotherapy regimens in the protocol are given durvalumab with or without tremelimumab and a standard chemotherapy regimen. The primary objective is to confirm the recommended phase II dose of the addition of durvalumab with or without tremelimumab. The secondary objectives include (1) assessing the safety and toxicity profile of durvalumab with and without tremelimumab; (2) exploring the efficacy of durvalumab with and without tremelimumab; (3) characterizing the immunogenicity of durvalumab with and without tremelimumab; (4) exploring the predictive and prognostic value of PD-L1 expression, circulating PD-L1, and common mutations; and (5) characterizing the pharmacokinetics of durvalumab with and without tremelimumab.

Asian Research

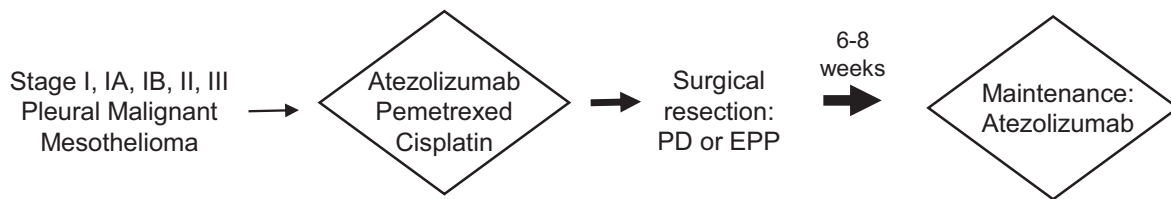
CTONG Studies

The objectives for CTONG are to conduct studies for (1) academic purposes and (2) internationally and (3) domestically produced pharmaceutical agents.

Early-stage Disease. CTONG 1504 is investigating sublobar resection versus lobectomy in NSCLC patients aged > 70 years stratified by factors including age, histologic type, and tumor size. Patients with tumors ≤ 3 cm and negative lymph node involvement will be randomized to lobectomy or wedge resection, with the primary endpoint being disease-free survival. Another study examining improved disease-free survival, CTONG 1104, involves the use of adjuvant EGFR inhibitors in resectable lung cancer. Patients with completely resected stage II–IIIA NSCLC with either EGFR exon 19 deletions or L858R mutations will be randomized to either 250 mg/d of gefitinib for 24 months (or until disease progression or unacceptable toxicity) or 4 cycles of cisplatin and vinorelbine. CTONG 1104 randomized 222 patients, 111 to each arm. The study found that the median disease-free survival was longer with gefitinib (28.7 months, 95% CI, 24.9–32.5 months) than with vinorelbine plus cisplatin (18.0 months; 95% CI, 13.6–22.3; HR, 0.60; 95% CI, 0.42–0.87; $P = .0054$).¹⁰ To evaluate the role of EGFR inhibitors in the neoadjuvant setting, CTONG 1103 will randomize stage IIIA–N2, EGFR mutant-positive NSCLC patients to erlotinib for 6 weeks, followed by surgery and 1 year of adjuvant erlotinib versus 2 cycles of neoadjuvant cisplatin and gemcitabine, followed by surgery and 2 additional cycles of adjuvant cisplatin and gemcitabine. The primary endpoint of the study is the objective response rate, and secondary endpoints include lymph node downgrade rate, complete resection rate, pathologic complete response, PFS, overall survival, and quality of life.

Advanced-stage Disease. CTONG 1509 is a randomized controlled, open-label, multicenter study to compare bevacizumab combined with erlotinib versus erlotinib alone in Chinese NSCLC patients harboring activating EGFR mutations. The expected sample size is 310 patients. Treatment-naïve patients with stage IIIB/IV disease will be randomized 1:1 to either 150 mg of erlotinib

Figure 6 The Southwestern Oncology Group S1619 Study Is Evaluating Neoadjuvant Cisplatin and Pemetrexed With Atezolizumab in Combination and as Maintenance for Resectable Malignant Pleural Mesothelioma in an Estimated 28 Patients. Primary Outcome Measures Include Modified Response Evaluation Criteria In Solid Tumors, Progression-Free Survival, and Overall Survival



daily or 150 mg of erlotinib with 15 mg/kg bevacizumab administered every 3 weeks. The primary endpoint is PFS. To further study EGFR mutations, CTONG 1510 is a randomized phase II study of an expected 150 patients assessing second-line therapy after progression with an EGFR tyrosine kinase inhibitor. EGFR-mutant NSCLC patients will be randomized to cisplatin and pemetrexed versus pemetrexed alone plus cisplatin, with the primary endpoint of grade 4 PFS. Neither CTONG 1509 nor 1510 have begun recruiting.

CTONG 1405 is a single-arm, open-label study evaluating the efficacy and safety of first-line gefitinib for advanced-stage NSCLC patients with EGFR mutations detected in tumor circulating free DNA. The primary endpoint is the objective response rate.

ATORG Studies

The ATORG, founded in 2015, will focus its debut study on stage IV EGFR-mutant patients with T790M-mediated resistance to first-line tyrosine kinase inhibitor therapy. Patients are to receive osimertinib and will be evaluated by dynamic monitoring of T790M by tumor circulating free DNA in conjunction with conventional CT scanning to determine the response rate.

Small Cell Lung Cancer

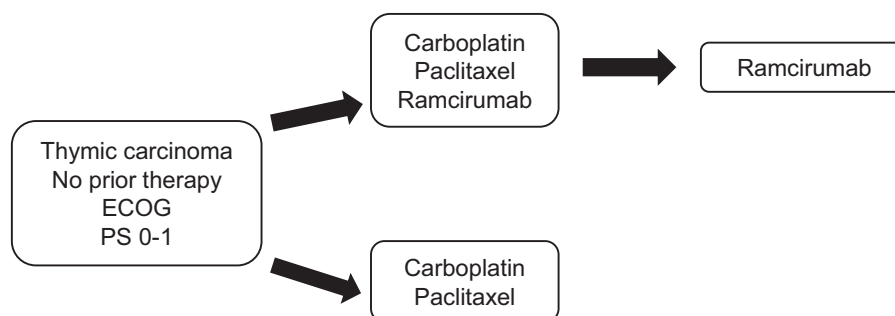
Although most National Clinical Trials Network groups have SCLC trials in development, the cooperative groups that presented

updates on SCLC included ECOG-ACRIN and NCIC-CTG. An update was presented for E2511,¹¹ a phase I/II study (now in phase II) examining the role of veliparib in conjunction with cisplatin and etoposide chemotherapy for extensive-stage SCLC. Patients were randomized to receive either 100 mg veliparib or placebo during days 1 to 7 of each cycle of chemotherapy (total, 4 cycles). IND.226 is an umbrella study examining the role of the anti-PD-L1 antibody, durvalumab, combined with the anti-CTLA4 antibody, tremelimumab, for advanced cancer. The SCLC phase Ib substudy is examining the role of these agents subsequent to 3 cycles of carboplatin and etoposide in extensive-stage SCLC. The study will have a dose-finding period, after which the primary objective, identifying the recommended phase II dose, will be determined.

Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) had the largest increase of studies between the 15th and 16th ILCC meetings. Cooperative groups that presented trials for this disease included ECOG-ACRIN, SWOG, EORTC, NCIC-CTG, and Alliance. These studies will investigate systemic therapies in the context of neo- or adjuvant or first- or second-line metastatic disease.¹² For neoadjuvant therapy, S1619 (SWOG) will assess the feasibility, safety, and tolerability of atezolizumab in conjunction with neoadjuvant cisplatin-pemetrexed for resectable MPM (pleurectomy/

Figure 7 The S1701 Study Is Evaluating Carboplatin and Paclitaxel With and Without Ramucirumab in Patients With Thymic Carcinoma. The Intended Sample Size Is 60 Patients. The Primary Outcome Measure Is Progression-Free Survival



International Cooperative Group Study Update

decortication or extrapleural pneumonectomy; Figure 6). Maintenance atezolizumab will be given for 1 year. To examine the role of immediate (ie, surgical intervention without neoadjuvant therapy) versus delayed pleurectomy/decortication, EORTC 1205 will randomize patients to undergo surgical intervention followed by 3 cycles of cisplatin and pemetrexed versus 3 cycles of neoadjuvant cisplatin and pemetrexed followed by surgery. The primary objective is the feasibility of the treatment arms to determine which could serve as a comparator to a control arm (involving either no surgery or extrapleural pneumonectomy).

In the setting of metastatic therapy, PrE505 is a single-arm phase II study evaluating the role of the anti-PD-L1 antibody, durvalumab, combined with first-line cisplatin and pemetrexed. The primary objective is overall survival, and the secondary objectives include the response rate, safety, and correlative studies. To examine the role of immunotherapy in second-line metastatic therapy, a proposed trial by Alliance and SWOG is a randomized phase III study to compare the PFS benefit with pembrolizumab versus investigator's choice for second-line chemotherapy. Another study examining immunotherapy in second-line therapy is PROMISEm, which will assess pembrolizumab versus standard chemotherapy (vinorelbine or gemcitabine) in patients with advanced, pretreated MPM. The primary endpoint is PFS.

A second-line therapy study involving a small molecule agent is NEMO, a phase II/III trial of 114 patients assessing PFS with the multifunctional tyrosine kinase inhibitor, nintedanib, as maintenance treatment of MPM. Finally, the DENIM [dendritic cells loaded with allogeneous cell lysate in mesothelioma patients (MesoCancerVa)] trial is a randomized, open-label phase II/III study of dendritic cells loaded with allogeneic tumor cell lysate as maintenance treatment after first-line chemotherapy for patients with unresectable MPM.

Thymic Carcinoma

Thymic carcinoma (World Health Organization type C) is a rare malignancy that arises from the thymus. To date, few trials have evaluated front-line chemotherapy regimens for thymic carcinoma. From retrospective analyses and small phase II non-randomized trials, carboplatin-paclitaxel is the preferred regimen for thymic carcinoma. Several case reports and phase I subgroup analyses of patients with refractory disease demonstrated responses with antiangiogenic therapies. In addition, several biomarkers of the angiogenic pathway (VEGF-A, VEGFR-1, and VEGFR-2) are overexpressed in thymic carcinoma, and high immunohistochemistry expression levels have been correlated with tumor invasiveness and clinical stage. S1701 is a

randomized, phase II trial of carboplatin-paclitaxel with or without ramucirumab for patients with locally advanced, recurrent, or metastatic thymic carcinoma (Figure 7). PFS is the primary endpoint of the study.

Conclusion

Cooperative groups have contributed to the increase in treatment options for thoracic malignancies, especially with the increase in immunotherapy studies for patients without actionable mutations. For these trials, as well as immunotherapy in general, cooperative groups have led and will continue to lead the correlative studies and translational research to identify immunotherapy biomarkers and predictors of response necessary to advance patient survival and other clinical outcomes.

References

1. Wakelee HA, Dahlberg SE, Keller SM, et al. E1505: Adjuvant chemotherapy +/- bevacizumab for early stage NSCLC—outcomes based on chemotherapy subsets. *J Clin Oncol* 2016; 36(suppl), abstract 8507.
2. Salahudeen AA, Patel MI, Baas P, et al. Overview of thoracic oncology trials in cooperative groups around the globe. *Clin Lung Cancer* 2017; 18: 5-12.
3. Harris JP, Patel MI, Loo BW, Wakelee HA, Diehn M. A population-based comparative effectiveness study of chemoradiation regimens and sequences in stage III non-small cell lung cancer. *Lung Cancer* 2017; 108:173-82.
4. Osarogiabon RU, Yu X. Mediastinal lymph node examination and survival in resected early-stage non-small-cell lung cancer in the Surveillance, Epidemiology, and End Results database. *J Thorac Oncol* 2012; 7:1798-806.
5. Ramalingam SS, Blais N, Mazieres J, et al. Randomized, placebo-controlled, phase II study of veliparib in combination with carboplatin and paclitaxel for advanced/metastatic non-small cell lung cancer. *Clin Cancer Res* 2017; 23: 1937-44.
6. Stahel RA, Dafni U, Gautschi O, et al. A phase II trial of erlotinib (E) and bevacizumab (B) in patients with advanced non-small-cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations with and without T790M mutation: the Spanish Lung Cancer Group (SLCG) and the European Thoracic Oncology Platform (ETOP) BELIEF trial. 2015 European Cancer Congress, Vienna, Austria, 2015. *Eur J Cancer* 2015; 51(suppl 3):S711-2.
7. Chaft JE, Forde PM, Smith KN, et al. Neoadjuvant nivolumab in early-stage, resectable non-small cell lung cancers. *J Clin Oncol* 2017; 35(suppl), abstract 8508.
8. Albain KS, Crowley JJ, Turrisi AT III, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. *J Clin Oncol* 2002; 20:3454-60.
9. Smit EF, Peters S, Dziadziuszko R, et al. A single-arm phase II trial of afatinib in pretreated patients with advanced NSCLC harboring a HER2 mutation: the ETOP NICHE trial. *J Clin Oncol* 2017; 35(suppl), abstract 9070.
10. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIA (N1–N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. *Lancet Oncol* 2017; 19:139-48.
11. Owonikoko TK, Dahlberg SE, Khan SE, et al. A phase I safety study of veliparib combined with cisplatin and etoposide in extensive stage small cell lung cancer: a trial of the ECOG-ACRIN Cancer Research Group (E2511). *Lung Cancer* 2015; 89:66-70.
12. Mancuso MR, Neal JW. Novel systemic therapy against malignant pleural mesothelioma. *Transl Lung Cancer Res* 2017; 6:295-314.