RESULTS

Patient disposition

One hundred and twenty-two patients were recruited from February 2004 to March 2005 at 11 sites in Japan. Sixty-five patients had lung cancer and 57 had malignant lymphoma. The patients were randomly assigned to the EPO group ($n = 63$) or the placebo group ($n = 59$). One patient in each group never received a study drug, one patient in each group never received chemotherapy and one patient in the placebo group did not have laboratory data after administration. Thus, the FAS population was 117 patients (61 patients in the EPO group, 56 patients in the placebo group).

Demographics, clinical and baseline characteristics

Patient demographics were well balanced between the two groups, except for baseline hemoglobin levels and serum erythropoietin concentrations (Table 1). The mean hemoglobin level in the EPO group was slightly lower than in the placebo group (10.0 versus 10.4 g/dl). The baseline hemoglobin level did not influence the evaluation of the primary endpoint by analysis of covariance.

Hematological evaluations

Mean change in hemoglobin level at the last evaluation significantly increased in the EPO group (1.4 ± 1.9 g/dl) than in the placebo group (−0.8 ± 1.5 g/dl) ($P < 0.001$). The hemoglobin level started to elevate in the EPO group at 3 weeks after the first administration (Figs 1 and 2). After 4–8 weeks of administration, the proportion of patients who achieved changes in hemoglobin level ≥2.0 g/dl from baseline was 42.6% (26/61) for the EPO group and 1.8% (1/56) for the placebo group ($P < 0.001$).

During the study, the proportion of patients with the hemoglobin level increased 12.0 g/dl or more was evaluated in the patients with hemoglobin level below 12.0 g/dl at baseline, the proportion was higher in the EPO group than in the placebo group [49.2% (29/59) versus 9.6% (5/52), $P < 0.001$]. The nadir hemoglobin level was 9.4 ± 1.5 g/dl in the EPO group and 8.6 ± 1.3 g/dl in the placebo group ($P = 0.002$). The proportion of patients with hemoglobin level decreased <8.0 g/dl was evaluated in the patients with hemoglobin level >8.0 g/dl at baseline, the proportion was 18.6% (11/59) in the EPO group and 32.1% (18/56) in the placebo group ($P = 0.096$).

RBC transfusion

The incidence of RBC transfusion was not different between the EPO group and the placebo group throughout the study [11.5% (7/61) versus 12.5% (7/56), $P = 0.865$] or from Week 5 to Week 8 [8.2% (5/61) versus 12.5% (7/56), $P = 0.443$]. However, the incidence of RBC transfusion or hemoglobin level <8.0 g/dL from Week 5 to Week 8 was significantly lower in the EPO group than those in the placebo group [16.4% (10/61) vs. 32.1% (18/56), $P = 0.046$], and fewer RBC transfusion units were required in the EPO group (10 units, $n = 5$) than in the placebo group (26 units, $n = 7$).

Quality of life

At the last observation, the FSS data for two patients were missing because of progressive disease (PD). The missing scores were substituted by the maximum decrease in score

Table 1. Patient demographics of full-analysis-set population

	Placebo group ($n = 56$)	EPO group ($n = 61$)
Sex		
Male	33	34
Female	23	27
Age (years), mean ± SD	62.1 ± 9.6	61.8 ± 11.9
Tumor		
Lung cancer	30	32
Small cell lung cancer	7	8
Non-small cell lung cancer	23	24
Malignant lymphoma	26	29
Hodgkin lymphoma	0	3
Non-Hodgkin lymphoma	26	26
Chemotherapy		
1st line	38	41
2nd line	6	8
3rd line	1	1
Relapse/recurrence	11	11
ECOG performance status		
0	38	33
1	17	26
2	1	2
Weight (kg), mean ± SD	54.5 ± 8.8	55.2 ± 10.0
Hemoglobin (g/dl), mean ± SD	10.4 ± 1.0	10.0 ± 1.0
Serum endogenous erythropoetin (mU/ml), mean ± SD	49.1 ± 33.4	67.3 ± 72.0
MCV (fl), mean ± SD	93.5 ± 6.0	91.9 ± 5.5
Transferrin saturation (%), mean ± SD	29.4 ± 19.8	32.4 ± 22.0
Baseline QOL: FACT-An		
Fatigue subscale (0–52), mean ± SD	33.9 ± 10.0	35.5 ± 9.7
≤36	29	29
>36	26	32
Data missing	1	0

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; QOL, quality of life; FACT-An, Functional Assessment of Cancer Therapy-Anemia; MCV, mean corpuscular volume; EPO, epoetin beta.

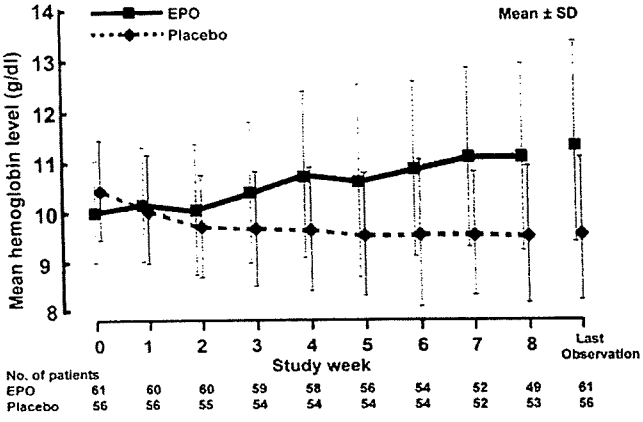

Figure 1. Hemoglobin level during the treatment period. A colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org. SD, standard deviation; EPO, epoetin beta.

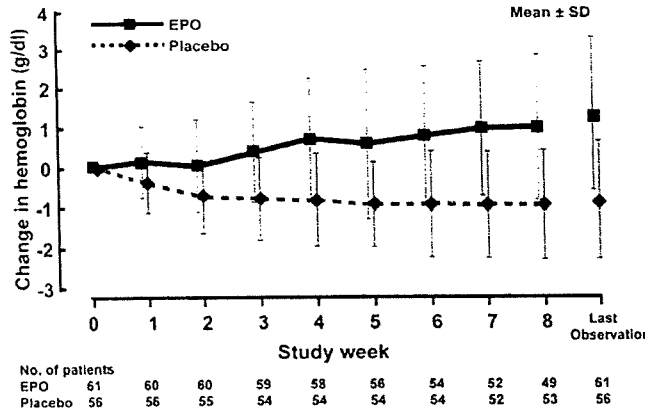

Figure 2. Change in hemoglobin level during the treatment period. A colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.

for all patients. This substitution was decided before blinded data review. The changes in FSS from baseline were less in the EPO group than those in the placebo group (Mean ± SD: -0.5 ± 9.4 versus -4.5 ± 10.0, $P = 0.031$). But excluding these two patients with missing data at the last observation, the change in FSS from baseline was not significant in the EPO group and in the placebo group (-0.5 ± 9.4 versus -3.6 ± 9.0, $P = 0.082$). The factors that influenced the change in FSS were baseline FSS, change in hemoglobin level, treatment group and PS at the last observation (analysis of variance). It has been suggested that if the baseline FSS is higher than 36, the change in FSS will decrease after administration of ESA because of the high baseline and the lack of symptoms (ceiling effect and regression to the mean) (20,21). Thus, we also analyzed patients whose baseline FSS was ≤ 36. In the baseline FSS ≤ 36 patients, change in FSS was 2.1 ± 11.7 in the EPO group and -1.3 ± 9.6 in the placebo group, so the EPO group showed improvement in FSS ($P = 0.225$). However, in the baseline FSS > 36 patients, the change in FSS was -2.9 ± 5.9 in the EPO group and -7.9 ± 9.4 in the placebo group ($P = 0.016$), so the EPO group showed suppression of the decline in FSS (Fig. 3). In subset analysis of the EPO group, the mean change in hemoglobin level did not differ in PD and non-PD patients (1.3 ± 1.8 versus 1.4 ± 2.0 g/dl), but PD patients showed a more marked decrease in FSS than non-PD patients (-6.8 ± 9.4 versus 0.2 ± 9.2).

Safety

The incidence of adverse events was evaluated for the 120 patients who receive a study drug. Adverse events were observed in 62 patients (100%) in the EPO group and 57 patients (98.3%) in the placebo group, and no significant differences were found between the two groups ($P = 0.299$). The adverse events related to the study drug were 24 events in the EPO group (17 of 62 patients, 27.4%) and 19 events in the placebo group (11 of 58 patients, 19.0%) ($P = 0.274$). Adverse drug reactions observed in at least 3% of the patients in the EPO group were increased blood pressure (6.5%), increased lactate dehydrogenase (3.2%) and increased urinary glucose (3.2%). In the placebo group, rash (3.4%), increased blood pressure (3.4%) and decreased activated partial thromboplastin time (3.4%) were reported. Grade 3 abdominal pain and Grade 3 liver dysfunction were both observed in the same patients in the EPO group. Five patients (5 events) in the EPO group and five patients (12 events) in the placebo group experienced serious adverse events. Of these, only Grade 3 liver dysfunction was considered related to EPO treatment (Table 2). One thrombovascular event (TVE), a lacunar infarction, was reported in the EPO group. No other TVEs were reported in either group. No anti-erythropoietin antibodies were reported.

Survival

A retrospective analysis of survival was performed. The median follow-up duration was 670 days for the EPO group

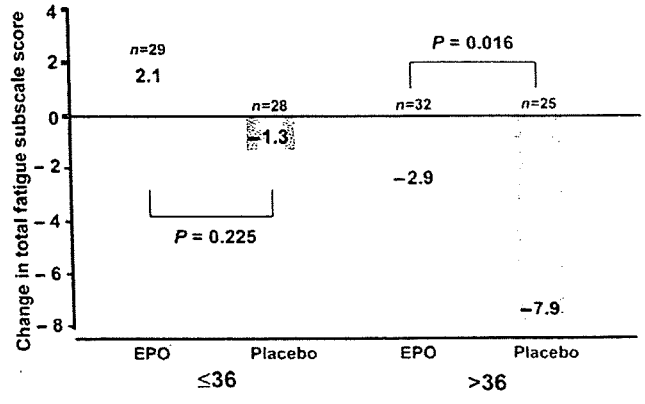

Figure 3. Mean change in FACT-An total fatigue subscale score stratified by baseline total fatigue subscale score (≤ 36, >36). A colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org. FACT-An, Functional Assessment of Cancer: Therapy-Anemia.

Table 2. Incidence of the most common adverse events

	Placebo group ($n = 58$)		EPO group ($n = 62$)	
	No. of patients	%	No. of patients	%
Adverse events	57	98.3	62	100
Adverse events with incidence ≥20% in the EPO group				
Neutropenia	47	81.0	47	75.8
Leukopenia	46	79.3	47	75.8
Thrombocytopenia	28	48.3	31	50.0
Nausea	28	48.3	27	43.5
Fatigue	26	44.8	28	45.2
Anorexia	24	41.4	27	43.5
Lymphopenia	24	41.4	32	51.6
Alopecia	17	29.3	22	35.5
Increased LDH	15	25.9	16	25.8
Constipation	10	17.2	14	22.6
Adverse drug reactions	11	19.0	17	27.4
Adverse drug reactions with incidence ≥3% in either group				
Increased blood pressure	2	3.4	4	6.5
Increased LDH	1	1.7	2	3.2
increased urinary glucose	0	0.0	2	3.2
Rash	2	3.4	0	0.0
Decreased APTT	2	3.4	0	0.0
Adverse drug reactions with severity ≥Grade 3				
Abdominal pain	0	0.0	1	1.6
Liver dysfunction	0	0.0	1	1.6

LDH, lactate dehydrogenase; APTT, activated partial thromboplastin time.

and 641 days for the placebo group. The 1-year survival population based on Kaplan–Meier estimates was 64.9% in the EPO group and 65.9% in the placebo group. The hazard ratio was 0.94 for the EPO group relative to the placebo group (95% CI: 0.57–1.53).

DISCUSSION

Improvements in hemoglobin level were observed in Japanese patients with CIA on administration of EPO 36 000 IU once a week for 8 weeks. In the evaluation of QOL, it is necessary to consider the effects of scores at baseline, such as the ceiling effect and regression to the mean (20). It has been reported that in patients with less symptoms as baseline FSS is more than 36, the change in FSS became negative (21). The results of a stratified analysis of groups with baseline FSS ≤36 and >36 (performed for reference) showed that in patients with baseline FSS ≤36 (severe anemia symptoms), the symptoms of anemia improved in the EPO group, but worsened in the placebo group. In patients with baseline FSS >36 (mild anemia symptoms), worsening occurred in both groups, but the worsening was significantly inhibited in the EPO group compared with the placebo group. In the United States, at present, the FDA has not approved the use of ESAs to improve QOL, but the results of this study suggest that EPO may be useful in the prevention of worsening of symptoms of anemia.

In the United States, it has been stressed that the purpose of using ESAs is to treat CIA in order to avoid RBC transfusions. In the present study, the incidence of RBC transfusion during administration was low and the hemoglobin level when RBC was transfused was 5.5–8.8 g/dl. In Japan, most physicians and patients are reluctant to use RBC transfusions, but in the United States and in Europe, RBC transfusions are often started when the hemoglobin level is 8.0–10.0 g/dl (22). In this study, the proportion of patients with either severe anemia requiring a RBC transfusion or hemoglobin level of <8.0 g/dl (NCI-CTC Grades 3 and 4) was examined. Evaluation of this proportion from 4 weeks after the start of administration, when ESAs exhibited hematopoietic effects (23–25), indicated that this proportion was significantly lower in the EPO group (16.4%, 10 of 61 patients) than in the placebo group (32.1%, 18 of 56 patients) ($P = 0.046$).

One TVE was observed in this study, a lacunar infarction (Grade 1) in one patient (69-year-old male with lung cancer) in the EPO group. The investigator judged without causal relationship to the study drug but by aging, because the event was observed 1 day after the first study drug administration. No other TVEs were reported. Increased blood pressure and hypertension occurred in 10 patients (six in the EPO group, four in the placebo group). Marked differences from the placebo group were not observed for other adverse events.

The FDA has issued several safety alerts regarding data that demonstrated adverse survival outcomes in ESA-treated cancer patients. In this study, however, based on the results of a survey of overall survival, the 1-year survival proportion showed no significant difference between the groups. The effects of ESAs on survival of cancer patients have been examined by the ODAC and other groups since 2007, based on new clinical trial reports. So far, the reported safety data have been insufficient to rule out the risk of mortality in chemotherapy-treated patients, but ESAs are considered a therapeutic option for the management of CIA. Clinical studies based on the doses and hemoglobin levels recommended on the labels will continue to accumulate evidence on the effects of ESAs on survival.

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Conflict of interest statement

The author, Yasuo Ohashi, receives consultation fee from Chugai Pharmaceutical Co., Ltd.: the author advises on design and data analysis of clinical trials.

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Cooperative Group Research Efforts in Thoracic Malignancies 2009: A Review From the 10th Annual International Lung Cancer Congress

Heather Wakelee,[1] Bill W. Loo, Jr.,[2] Kemp H. Kernstine,[3] Joe Bill Putnam, Jr.,[4] Martin J. Edelman,[5] Everett E. Vokes,[6] Joan H. Schiller,[7] Paul Baas,[8] Nagahiro Saijo,[9] Alex Adjei,[10] Glenwood Goss,[11] Hak Choy,[12] David R. Gandara[13]

Abstract

Critical advances in the treatment of patients with lung cancer have occurred in the past few years. The cooperative groups in North America and internationally have played crucial roles in these advances. The leaders of the groups meet on a regular basis to review the progress of their trials. However, they rarely have a chance to discuss all ongoing and planned trials, except at the annual Lung Cancer Congress held each June. This article captures this exchange from the 10th Annual Lung Cancer Congress held in June 2009. Exciting efforts are ongoing for all stages of non–small-cell lung cancer, small-cell lung cancer, and mesothelioma. A major focus of the groups at this time is a push toward more personalized medicine, as reflected in the selection criteria for many of the trials, along with planned correlates to better define populations most likely to benefit. Agents targeting the vascular endothelial growth factor (VEGF) pathway, including many tyrosine kinase inhibitors against the VEGF receptor, and those targeting the epidermal growth factor receptor pathway, are under extensive development with many combination trials ongoing.

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Introduction

Progress in therapy for thoracic malignancies has been increasing dramatically in recent years. We have known for some time that chemotherapy improves survival and quality of life compared with best supportive care for advanced-stage disease.[1] Guidelines published by the American Society of Clinical Oncology (ASCO) and the American College of Chest Physicians endorse either a platinum or nonplatinum doublet as initial therapy for patients with good performance status (PS) with newly diagnosed advanced-stage non–small-cell lung cancer (NSCLC).[2,3] For early-stage NSCLC that has been resected, both ASCO and the National Comprehensive Cancer Network endorse cisplatin-based adjuvant chemotherapy for resected stage II and IIIA NSCLC, with controversy surrounding therapy of stage I disease and the use of postoperative radiation therapy.[4-6]

For advanced-stage disease, efforts to add a third drug to the standard 2-drug doublet regimens had not met with success until recent trials that have included bevacizumab and cetuximab, both antibodies targeted to pathways now known to be important in NSCLC.[7-9] These pathways include the vascular endothelial growth factor (VEGF) pathway critical for angiogenesis targeted by bevacizumab and the epidermal growth factor receptor (EGFR) pathway targeted by cetuximab. The benefit of the addition of bevacizumab to chemotherapy was first demonstrated by E4599, a phase III trial led by one of the large cooperative oncology research

[1]Department of Medicine, Division of Oncology
[2]Division of Radiation Oncology
Stanford University Cancer Center, CA
[3]Thoracic Surgery, City of Hope, Duarte, CA
[4]Department of Thoracic Surgery, Vanderbilt University, Nashville, TN
[5]Department of Medicine, Division of Oncology, University of Maryland Greenebaum Cancer Center, Baltimore
[6]Section of Hematology/Oncology, University of Chicago Medical Center, IL
[7]Department of Medicine, Division of Oncology, The University of Texas Southwestern Medical Center, Dallas
[8]Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam
[9]Medical Oncology Division, National Cancer Center Hospital, Chiba, Japan
[10]Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY
[11]Department of Medicine, The Ottawa Hospital Cancer Centre, Ontario, Canada
[12]Department of Radiation, The University of Texas Southwestern Medical Center, Dallas
[13]Division of Hematology and Oncology, University of California Davis Cancer Center, Sacramento

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Address for correspondence: Heather Wakelee, MD, Department of Medicine, Division of Oncology, Stanford Cancer Center, 875 Blake Wilbur Dr, Stanford, CA 94305-5826
Fax: 650-724-3697; e-mail: hwakelee@stanford.edu

groups of North America, the Eastern Cooperative Oncology Group (ECOG)[8]; the National Cancer Institute of Canada Clinical Trial Group (NCIC-CTG) directed the BR.21, which led to approval of the anti-EGFR targeted agent erlotinib[10]; and one of the key trials showing a benefit from adjuvant chemotherapy in early-stage disease was led by NCIC-CTG,[11] highlighting the critical role the North American cooperative oncology groups, as well as cooperative groups abroad, have played in establishing the current standards of care for patients with NSCLC.

Within the United States, there are 4 general oncology cooperative groups active in lung cancer research sponsored by the National Cancer Institute, with member institutions scattered throughout the country: Cancer and Leukemia Group B (CALGB), ECOG, the North Central Cancer Treatment Group (NCCTG), and the Southwest Oncology Group (SWOG). Within Canada, the NCIC-CTG oversees cooperative oncology clinical trials. More modality-focused cooperative groups in North America (both in the United States and Canada) include the American College of Surgeons Oncology Group (ACOSOG) and the Radiation Therapy Oncology Group (RTOG). Europe has multiple cooperative groups within each country, but the European Organization for Research and Treatment of Cancer (EORTC) works across borders for important trials. Most Asian countries also have cooperative group efforts, with the work in Japan highlighted in this article, particularly that of the Japanese Clinical Oncology Group (JCOG).

The newest advances in lung cancer treatment have been toward more personalized therapy of the disease. Patients with activating mutations in EGFR have a known increased sensitivity to the tyrosine kinase inhibitors (TKIs) that target the pathway, gefitinib and erlotinib. The recently published IPASS (Iressa Pan Asia Study) looked at first-line gefitinib versus chemotherapy for clinically selected patients more likely to have these mutations and found that for those with the mutations, gefitinib improved progression-free survival (PFS) more than chemotherapy.[12] A recent effort from one of the Japanese cooperative groups added further to this observation in a trial that only included patients with EGFR mutations and found a very robust benefit to the first-line gefitinib.[13] Ongoing efforts within other cooperative groups are looking for other markers of benefit from the EGFR inhibitors.

Better selection of specific chemotherapy drugs for individual patients is another area of active investigation within the cooperative group system. The cooperative groups are also focused on novel therapeutic agents, particularly the TKIs targeting VEGF receptor (VEGFR) and others. Most trials looking at novel agents are also designed to determine biomarkers that will predict which patients are most likely to benefit from individual drugs.

This report explores cooperative group research strategies in NSCLC (Tables 1 and 2), small-cell lung cancer (SCLC; Table 3), and mesothelioma as presented at the 10th Annual Lung Cancer Congress. The group's efforts are presented in alphabetical order by group name. Further details about the open studies can be found online at clinicaltrials.gov.

American College of Surgeons Oncology Group

The stated purpose of the ACOSOG is to evaluate the surgical management of patients with malignant solid tumors. ACOSOG includes surgeons and other oncology specialists throughout the United States and internationally. The aims of the thoracic committee of this group are to improve local control in early-stage NSCLC and to enhance therapeutic efficacy through biologic and molecular markers.

Ongoing ACOSOG trials in early-stage NSCLC explore alternatives to lobectomy in patients who are high-risk surgical candidates. Z4032 is a randomized phase III trial of sublobar resection with or without brachytherapy in high-risk patients (based on pulmonary function and medical comorbidity) with stage IA/IB NSCLC ≤ 3 cm in size. Brachytherapy is administered by placement of a mesh with iodine-125(^{125}I) seeds at the resection margin. The study opened in July 2005 and to date has accrued over 200 of the target 226 patients, with completion expected in 2009. The primary and secondary endpoints will be time to local recurrence, treatment-related toxicity, overall survival (OS), disease-free survival (DFS), impact of complete resection, pulmonary function, and quality of life.

Z4033 is a pilot study assessing the efficacy of a nonsurgical local thermal ablation treatment modality, radiofrequency ablation, in patients with stage IA NSCLC who are not operative candidates based on poor pulmonary function or other significant comorbidities. The primary and secondary objectives are local recurrences at 2 years and regional and distant recurrence. The trial opened in September 2006 and, by June 2009, had accrued 43 patients of its target enrollment of 55, with completion expected in 2009.

There are currently 2 proposed studies in ACOSOG for patients with limited mediastinal nodal metastasis. The first is a prospective phase II trial of surgical resection and postoperative chemotherapy in patients with single-station N2 disease by clinical staging studies, ie, computed tomography (CT), positron emission tomography (PET), and mediastinoscopy and/or endobronchial ultrasound transbronchial needle biopsy. This is intended as a feasibility study with the primary objective of evaluating the effectiveness of the above clinical staging modalities. It also includes a correlative science endpoint of predicting chemotherapy sensitivity by genetic markers of chemotherapy resistance in tumor tissue.

The second addresses the role of postoperative radiation therapy (PORT) after resection of clinically early-stage NSCLC with initially unsuspected mediastinal nodal metastasis. Although uncontrolled retrospective studies suggest a survival benefit to PORT in addition to that of postoperative chemotherapy in this setting, prospective, randomized data are lacking. This question is currently being addressed in a large, international, randomized phase III study of PORT versus observation in patients with surgically detected N2 disease, the LungART (Lung Adjuvant Radiotherapy Trial), primarily involving European cooperative groups and participating institutions (discussed further in the EORTC section). The ACOSOG has proposed coordinating a North American Intergroup study of PORT, which will also be a randomized phase III trial comparing PORT (conformal radiation therapy to 50.4 Gy over 6 weeks, with a boost of 10.8 Gy if there is nodal extracapsular extension) with observation. The primary endpoint will be OS, with secondary endpoints of treatment-related toxicity, local control, DFS, and patterns of recurrence.

Although surgery typically is not a primary treatment modality for SCLC, there are data to support its role in very limited stage. A prospective study of surgery for clinical stage IA SCLC is proposed, with

Table 1 Open Cooperative Group Phase III Trials in Early-Stage Non–Small-Cell Lung Cancer

Trial	Subtype and Stage	Treatment	Outcome	Number of Patients
ACOSOG Z4032	Stage I NSCLC, poor PFT	Sublobar resection with or without brachytherapy seeds (^{125}I)	Recurrence	226
CALGB 140503	Stage IA ≤ 2 cm	Lobectomy versus sublobar resection	DFS	1297
CALGB 30506	Stage I 2-6 cm	Observation versus adjuvant chemotherapy; stratification by lung metagene score	OS	1294
ECOG 1505	Resected stage IB-IIIA	4 Cycles of adjuvant chemotherapy with or without bevacizumab	OS	1500
ECOG 5597	Resected stage I	Selenium versus placebo × 4 years	Recurrence	1960
EORTC LungART	Resected N2	With or without postoperative radiation therapy	DFS	700
JCOG0707	Stage I > 2 cm	UFT versus S-1	OS	960
JCOG0802	Stage I < 2 cm	Segmentectomy versus lobectomy	OS	1100
RTOG 0617	Locally advanced	Carboplatin/paclitaxel/XRT with or without cetuximab with or without high-dose XRT (74 Gy)	OS	500

Abbreviations: ^{125}I = Iodine-125; ACOSOG = American College of Surgeons Oncology Group; CALGB = Cancer and Leukemia Group B; DFS = disease-free survival; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; JCOG = Japanese Cooperative Oncology Group; NSCLC = non–small-cell lung cancer; OS = overall survival; PFT = pulmonary function test; RTOG = Radiation Therapy Oncology Group; UFT = uracil-tegafur; XRT = radiation therapy

endpoints being clinical to pathologic stage correlation, OS, DFS, and translational research through tissue and serum collection.

Cancer and Leukemia Group B

CALGB 9633 was a crucial trial for our understanding of the adjuvant therapy benefit in stage IB NSCLC. To date, CALGB 9633 is the only large platinum-based adjuvant chemotherapy trial exclusively targeting stage IB disease.[14,15] The study compared surgical resection with or without adjuvant paclitaxel/carboplatin. Though results failed to show a statistically significant OS benefit, patients with tumors ≥ 4 cm in size did appear to have benefit (hazard ratio [HR], 0.66; 90% CI, 0.45-0.97; $P = .04$).[16]

Other early-stage trials by CALGB include the recently completed C39904, looking at dose-escalated, accelerated, 3-dimensional conformal radiation therapy (3D-CRT) in patients with inoperable stage I NSCLC. Ongoing studies include C140203, a phase II trial assessing intraoperative sentinel lymph node mapping using Technetium Tc 99 sulfur colloid in 150 patients with stage I NSCLC, and C140503, looking at lesser resections for small stage I tumors. Lobar resection at this time is the standard approach for stage I NSCLC,[17] but in this era, especially in small peripheral primary tumors, questions have been raised about the necessity of these extensive resections. C140503 is a phase III trial with a target enrollment of nearly 1300 patients, comparing lobectomy with sublobar resection for small stage IA NSCLC (≤ 2 cm in size) with stratifications based on tumor size, histology, and smoking status. Patients are randomized to lobectomy by open thoracotomy or video-assisted thoracoscopic surgery (VATS) versus a wedge resection or anatomic segmentectomy by open thoracotomy or VATS. A preresection mediastinoscopy is required to confirm N0 status by frozen section examination of nodal levels 4, 7, and 10 on the right side and 5, 6, 7, and 10 on the left side.

Another large adjuvant therapy effort led by CALGB is C30506, a randomized phase III trial (N = 1294) for patients with resected stage I NSCLC 2-6 cm in size, who are randomized to observation or adjuvant chemotherapy after complete resection. Patients will be stratified based on a genomics prognostic model known as the lung metagene score (LMS).[18] Patients with a low LMS are felt to be at low risk for recurrence. The study will require fresh tissue collection for RNA extraction.

The CALGB has been a leader in establishing current guidelines for the therapy of stage III NSCLC and the importance of combined chemoradiation. Current efforts include C30106, looking at targeted agents as radiosensitizers, which will lead into 30605, a larger trial of induction chemotherapy with radiation and erlotinib for patients with stage III PS 2; C30407, which assessed novel chemoradiation therapy with or without cetuximab and was presented at ASCO this year[19]; and C30105, assessing high-dose radiation to 74 Gy, leading into C30609, a randomized phase III Intergroup trial discussed further in the RTOG section herein (RTOG 0617).

The eicosanoid pathway has been of particular interest to CALGB. In their first effort to modulate this pathway, the phase II CALGB 30203 trial used carboplatin/gemcitabine as a backbone regimen and added either zileuton, celecoxib, or both.[20] No OS benefit was found in any of the arms in an unselected group, and the study failed to meet its primary endpoint; however, immunohistochemistry (IHC) analysis for COX (cyclooxygenase)-2 indicated that high levels were a positive predictor for benefit with celecoxib (improved survival with an OS HR of 0.294; $P = .004$ for those with elevated COX-2 levels with or without celecoxib) but an overall negative prognostic factor for survival in all patients (OS HR, 2.51; $P = .023$ for elevated COX-2 levels). This result has led to development of CALGB 30801 for patients with previously untreated advanced-stage NSCLC with elevated COX-2 levels who receive a platinum doublet (carboplatin/gemcitabine or carboplatin/pemetrexed at investigators' discretion) and are randomized to celecoxib or placebo until progression. The selection of only those with elevated COX-2 levels is a step toward more individualized patient care.

The TALENT (Tarceva Lung Cancer Investigation outside of the United States) and TRIBUTE (Tarceva Lung Cancer Investigation within the United States) trials of erlotinib plus first-line chemotherapy failed to show a survival advantage with the combination, but the small number of never-smokers in the TRIBUTE study did show an OS advantage with the addition of erlotinib (10.1 months

Table 2 Cooperative Group Phase III Trials in Advanced-Stage Non–Small-Cell Lung Cancer

Trial	Selection	Treatment	Number of Patients
CALGB 30801	Elevated COX-2	Platinum doublet with or without celecoxib	TBD
CALGB 30607	–	Sunitinib vs. placebo maintenance	240
E5508[a]	Nonsquamous	Bevacizumab vs. pemetrexed vs. both as maintenance	TBD
EORTC-EURTAC	EGFR mutation	Erlotinib vs. platinum doublet chemotherapy	146
EORTC-BREC	First-line	Customized chemotherapy by BRCA1	432
WJTOG 3605	First-line	Carboplatin/paclitaxel vs. carboplatin/S-1	600
N0723 MARVEL	Second-line	Erlotinib vs. pemetrexed; stratified by EGFR-FISH	1200
NCIC-CTG BR.29	First-line	Carboplatin/paclitaxel with or without cediranib 20 mg	750
SWOG S0819[a]	EGFR−/IHC+	Chemotherapy (plus bevacizumab if eligible) with or without cetuximab	1545

[a]Planned.
Abbreviations: CALGB = Cancer and Leukemia Group B; COX-2 = cyclooxygenase-2; EGFR = epidermal growth factor receptor; EORTC = European Organization for Research and Treatment of Cancer; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; NCIC-CTG = National Cancer Institute of Canada Clinical Trials Group; SWOG = Southwest Oncology Group; TBD = to be determined; WJTOG = West Japan Thoracic Oncology Group

vs. 22.5 months with erlotinib).[21] CALGB 30406 was designed to further explore this observation and was a randomized phase II study of never-smoker (< 100 cigarettes in their lifetime) and light smoker (< 10 pack-years and quit over 1 year ago) smoker patients with newly diagnosed advanced-stage NSCLC. Patients were randomized to either receive daily oral erlotinib or 6 cycles of carboplatin/paclitaxel plus erlotinib followed by erlotinib. In both arms, the erlotinib was continued until disease progression. The trial is now closed to enrollment and will include extensive correlative evaluation of EGFR mutational status, *EGFR* expression by IHC and fluorescence in situ hybridization (FISH) and *KRAS* mutation status in addition to proteomic analysis.

Cancer and Leukemia Group B is focusing heavily on studies with the VEGFR TKI sunitinib. Sunitinib is approved for the treatment of patients with gastrointestinal stromal tumors and renal cell carcinoma and has demonstrated encouraging single-agent activity in NSCLC.[22] To build on this, 4 randomized trials are either under way or in development using sunitinib. CALGB 30607, a randomized phase III trial of 240 patients, will randomize patients with advanced-stage NSCLC who have stable or responding disease after 4 cycles of a platinum doublet to either sunitinib 37.5 mg/day or placebo. The maintenance therapy (sunitinib or placebo) is continued until disease progression, with a planned follow-up to at least 1 year. Progression-free survival is the primary endpoint. Patients may receive bevacizumab with the 4 cycles of chemotherapy, but the bevacizumab must be discontinued at the time of randomization to sunitinib or placebo. Patients who do not enroll in 30607 are eligible for the randomized phase II study 30704, with a target enrollment of just over 200 patients. This study is also powered to look at PFS but will enroll previously treated patients to receive either pemetrexed alone (500 mg/m^2 every 3 weeks), sunitinib alone (37.5 mg orally daily), or the combination of both agents at full doses. The other sunitinib trials are C30804, which compares sunitinib with pemetrexed in elderly patients (aged < 75 years) with a good PS; C30602, a window-of-opportunity study with the drug in extensive-stage SCLC; and C30504, a randomized phase II study of sunitinib or placebo maintenance after completion of 6 cycles of platinum/etoposide chemotherapy for patients with extensive-stage SCLC.

In SCLC, C30610 is open to patients with limited-stage disease. All patients will receive standard cisplatin/etoposide chemotherapy and prophylactic cranial irradiation (PCI). The randomization is to 1 of 3 radiation strategies, to start with the first cycle of chemotherapy. The 3 radiation regimens are standard 45 Gy twice daily over 3 weeks compared with either 61.2 Gy given on a daily fractionation schedule (no weekends) over 5 weeks or 70 Gy given in daily fractions over 7 weeks. The primary endpoint is OS.

Eastern Cooperative Oncology Group

E1505, which opened in June 2007 with an accrual goal of 1500 patients, has accrued nearly 500 patients to date and is the largest adjuvant trial within the cooperative group system. The study is open to patients with resected stage IB ≥ 4 cm)–IIIA NSCLC of any histology and stratifies by stage, histology, sex, and chemotherapy regimen. A minimum mediastinal lymph node sampling, to include level 7 for all patients, level 4 for right-sided tumors, and level 5 or 6 for left-sided tumors, is required for adequate staging. Patients receive 1 of 4 cisplatin-based doublet regimens for 4 cycles and are randomized to receive either bevacizumab 15 mg/kg every 3 weeks continued for 1 year or no additional therapy beyond the 4 cycles of chemotherapy. The primary endpoint is OS. Extensive correlate studies are planned, with blood and tissue specimens being collected from all patients.

E5597, an ongoing Intergroup chemoprevention trial, randomizes patients with completely resected stage I NSCLC, 6-36 months postresection, to 4 years of selenium supplementation (200 µg as selenized yeast) versus placebo (N = 1960). The study now allows for adjuvant chemotherapy before enrollment. Multiple correlative studies including methylation of p16 and O6-methylguanine-DNA methyltransferase are built into the trial, which is nearing its enrollment goal.

Eastern Cooperative Oncology Group's recent major effort for locally advanced NSCLC was E3598, which looked at the addition of thalidomide to concurrent chemotherapy/radiation, using a carboplatin/paclitaxel backbone. Thalidomide, an antiangiogenic agent, failed to improve either PFS or OS but led to increased thrombosis and will not be further developed in this setting.[23]

Table 3 Small-Cell Lung Cancer Phase III Trials[a]

Trial	Selection	Treatment	Number of Patients
EORTC 08072/BR.26 (CONVERT)	LS	66 Gy daily fractions vs. 45 Gy twice-daily fractions	532
JCOG0202	LS	Cisplatin/etoposide/XRT with consolidation PE vs. cisplatin/irinotecan	250
JCOG0509	ES, first-line	Cisplatin/amrubicin vs. cisplatin/irinotecan	282
JCOG0605	ES, second-line	Nogitecan vs. PE/irinotecan	180
SWOG S0938	ES	PE with or without cediranib	600

[a]Other novel agents in earlier phases of development for SCLC include GDC-0449, Hedgehog pathway inhibitor; cixutumumab (IMC-A12), insulin-like growth factor receptor inhibitor; sunitinib, vascular endothelial growth factor receptor inhibitor; and others.
Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; ES = extensive-stage; JCOG = Japanese Cooperative Oncology Group; LS = limited-stage; PE = platinum/etoposide; SCLC = small-cell lung cancer; SWOG = Southwest Oncology Group; XRT = radiation therapy

The issue of maintenance chemotherapy has become an important topic in the treatment of patients with advanced-stage NSCLC, with several trials now showing an improvement in PFS with this approach[24,25] and 1 showing a definite OS benefit.[25] The question of how long to continue bevacizumab has also been raised repeatedly, and ECOG's attempt to look further at these issues is the E5508 randomized phase III trial for patients with chemotherapy-naive, nonsquamous, bevacizumab-eligible advanced-stage NSCLC. The study will randomize patients who have at least stable disease (SD) after completing 4 cycles of carboplatin/paclitaxel/bevacizumab to bevacizumab alone, or pemetrexed alone, or a combination of the two.

Also building on the E4599 platform but focused in a select group of patients, E2507 is currently in development for patients without a smoking history with previously untreated advanced-stage NSCLC. Eligible patients will receive carboplatin/paclitaxel (with or without bevacizumab, depending on bevacizumab eligibility) with a randomization to receive concurrent erlotinib or not. In the ECOG 2507 trial, all patients receive chemotherapy with randomization to erlotinib or not, in contrast to the otherwise similar CALGB 30406, in which all patients receive erlotinib with randomization to chemotherapy or not. E3503 will also use erlotinib as first-line therapy for NSCLC, building on work with a proteomic analysis that predicts for response to erlotinib.[26]

Other novel agents under investigation include cetuximab and cixutumumab (IMC-A12), an antibody against the insulin-like growth factor receptor-1 (IGF-1R). E4508 randomizes 180 newly diagnosed patients with advanced-stage NSCLC to receive either carboplatin/paclitaxel with cetuximab, cixutumumab, or both in a "pick-the-winner" design looking for a 2-month improvement in PFS. E3508 will also look at the addition of cixutumumab in patients with newly diagnosed advanced-stage NSCLC but with the addition of bevacizumab as well. This randomized phase II study of 180 patients, looking for PFS improvement, randomized patients to receive carboplatin/paclitaxel/bevacizumab (E4599 regimen) with or without intravenous cixutumumab 6 mg/kg weekly.

Eastern Cooperative Oncology Group has recently opened E1508, looking at 2 exciting novel pathways in the therapy of SCLC. This randomized phase II study uses a backbone regimen of cisplatin/etoposide for patients with newly diagnosed extensive-stage SCLC. The 3-arm study includes a reference arm and 2 experimental arms adding either GDC-0449, an inhibitor of the Hedgehog pathway or cixutumumab, the inhibitor of IGF-1R discussed above, to the cisplatin/etoposide backbone.

European Organization for Research and Treatment of Cancer

Nearly every country in Europe has at least 1 country-based cooperative group, and most have 10-20 phase III trials open in NSCLC at the current time. The EORTC spans multiple European countries and has been a leader in several critical lung cancer trials.

There remains significant controversy about the use of PORT for resected stage IIIA NSCLC. Despite guidelines supporting the use of PORT, and encouraging data from a recent subset analysis of the ANITA (Adjuvant Navelbine International Trialist Association) trial[27] and the Surveillance, Epidemiology and End Results database,[28] prospective, randomized data supporting this modality are lacking. The LungART trial (EORTC 2205-08053), initiated by the French cooperative group, will include broad participation by the EORTC, NCIC-CTG, and others. Enrollees are randomized to receive a dose of 54 Gy in 30 fractions to the thorax or no adjuvant radiation therapy after complete resection of stage IIIA (N2 involved) NSCLC. The study is aimed for patients with unexpected N2 disease discovered at the time of surgical resection. Patients are stratified for postoperative (or preoperative) chemotherapy (to be completed before randomization to radiation). Target enrollment is > 700 to show a 10% improvement in 3-year DFS (30%-40%), with extensive correlates included.

Most of the efforts of EORTC in lung cancer are in metastatic disease. A study focused in elderly patients (aged > 70 years), EORTC 08086, is a randomized phase II trial evaluating the standard agent vinorelbine versus albumin-bound paclitaxel.

In the move toward more personalized care, many European groups, including EORTC, will be supporting the EURTAC (European Randomized Trial of Tarceva vs. Chemotherapy) study, led by the Spanish Lung Cancer Group, for newly diagnosed patients with NSCLC with known EGFR-activating mutations comparing first-line erlotinib 150 mg/day versus a standard platinum doublet (4 standard options), followed by a crossover. Additionally, EORTC is participating in the BREC (BRCA1 Expression Customization) trial, also led by the Spanish Lung Cancer Group, which is open to patients with newly diagnosed NSCLC. The study is looking at customizing chemotherapy by assigning therapy to patients on the experimental arm based on RAP80 levels and BRCA1 levels, which

predict response or lack of response to cisplatin and docetaxel, compared with a standard arm of docetaxel/cisplatin for all patients.

In SCLC, there are the EORTC08061 and EORTC08062 trials. EORTC08061 looks at the VEGFR TKI sunitinib 37.5 mg orally daily continuously as either first- or second-line therapy in patients with extensive-stage SCLC. This is a window-of-opportunity type trial in 48 patients (24 first-line and 24 second-line) with stopping after 4 weeks based on PET/CT results at that time. EORTC08062 is a nearly completed randomized phase II study looking at the new anthracycline amrubicin with or without cisplatin versus cisplatin/etoposide. The results of this study will be used to design a randomized phase III trial comparing the winning arm with standard cisplatin/etoposide. EORTC will also participate in the CONVERT (Concurrent ONce-daily VErsus twice-daily RadioTherapy; EORTC 08072) exploring 66 Gy in daily fractions versus the standard 45 Gy in twice-daily fractions with cisplatin/etoposide chemotherapy (radiation start with cycle 2) for limited-stage SCLC. It is hoped that this randomized phase III trial will enroll 532 patients.

The EORTC has also been active in mesothelioma. The results of EORTC08031 were presented at the ASCO 2009 annual meeting. This study looked at using extrapleural pneumonectomy with consolidation radiation after 3 courses of chemotherapy. The study found a 42% success rate as defined by patients being alive and without grade 3 or 4 toxicity at 90 days, which fell short of the predefined 50% success rate needed to call the trial positive.[29] E08052 is an ongoing mesothelioma single-arm phase II study of bortezomib plus cisplatin as first-line therapy and is accruing well, having passed the initial hurdle in a Simon 2-stage design with PFS at 18 weeks as the endpoint.

Japanese Cooperative Groups, Including the Japanese Clinical Oncology Group

For early-stage NSCLC, Japanese cancer cooperative groups have focused on the oral fluorinated pyrimidine uracil-tegafur (UFT) as the adjuvant therapy of choice, especially in patients with stage I adenocarcinoma. Traditionally, the drug has been given for 2 years as daily oral therapy. The HR for survival for UFT given as adjuvant therapy for patients with stage I NSCLC in a meta-analysis of 6 trials (95% stage I, N > 2000) was 0.73 (95% CI, 0.58-0.92; $P = .0066$).[30] The current major adjuvant effort is JCOG0707, open to patients with resected stage I tumors (> 2 cm), who are randomized to either 2 years of UFT or 1 year of S-1 (another 5-fluorouracil derivative) as adjuvant therapy after complete resection (N = 960). The West Japan Thoracic Oncology Group (WJTOG) 0101 study is a recently completed randomized phase III trial (N = 600) of UFT versus gemcitabine as adjuvant therapy, with results pending.

Japanese Clinical Oncology Group has several surgical-based studies for early-stage NSCLC. Patients with ground-glass opacities (GGOs) < 2 cm in size undergo a wide wedge resection, provided there is < 25% of the lesion that is solid. These lesions are considered noninvasive cancer, and the endpoint will be recurrence-free survival. For patients with invasive NSCLC (< 2 cm and ≥ 25% consolidation if the lesion is a GGO), JCOG0802 randomizes patients to limited surgery (segmentectomy) versus lobectomy, each with lymph node dissection (N = approximately 1100). The primary endpoint is OS.

For patients with locally advanced NSCLC, the phase I/II study JCOG0402 will evaluate cisplatin/vinorelbine with radiation followed by gefitinib in 37 patients. JCOG0301 is open for elderly patients with stage III NSCLC to receive radiation alone or in combination with carboplatin, with an OS endpoint (N = 200). The WJTOG recently presented a randomized phase III (WJTOG 0105) trial looking at 3 different platinum-based regimens in combination with radiation therapy in locally advanced disease and found no significant differences between the doublet and triplet regimens, but increased toxicity was observed.[31]

An ongoing randomized phase III trial, WJTOG 3605, randomizes newly diagnosed patients with advanced-stage NSCLC (N = 600) to carboplatin/paclitaxel versus carboplatin/S-1. Another ongoing study, WJOG 5108L, randomized patients, regardless of EGFR mutational status, to gefitinib versus erlotinib (N = 560). WJOG 5208L randomized patients with previously untreated squamous cell lung carcinoma to either receive cisplatin/docetaxel or nedaplatin (N = 250). JCOG has another study of elderly patients in development that will compare docetaxel alone or with cisplatin for patients with newly diagnosed advanced-stage NSCLC.

The North East Japan Gefitinib Study Group, established in 2004, completed an ongoing phase III trial (N = 320) of first-line gefitinib versus carboplatin/paclitaxel for patients with advanced-stage NSCLC with known EGFR-activating mutations. In the end, 98 patients received gefitinib, and 100 patients received chemotherapy. The overall response rate was 75% with gefitinib and 29% with the chemotherapy with a significant improvement in PFS.[13] The WJOG has a similar study, WJTOG3405, limited to patients with exon 19 deletion and L858R mutations within the EGFR, randomized to first-line gefitinib 250 mg/day or cisplatin/docetaxel every 3 weeks x 3-6 cycles. A phase II trial limited to elderly patients aged > 75 years with advanced-stage NSCLC and known EGFR-activating mutations is also ongoing.

The JCOG has 4 ongoing/planned trials in SCLC. JCOG0202 is the primary effort in limited-stage disease. This phase III study of 250 patients will look for an OS benefit for cisplatin/etoposide with concurrent radiation therapy (1 cycle given with twice-daily fractioned radiation) followed by consolidation with 3 cycles of cisplatin/irinotecan compared with the standard cisplatin/etoposide with concurrent radiation therapy followed by consolidation with the same cisplatin/etoposide regimen for 3 cycles. For patients with extensive-stage SCLC, the first-line option is the phase III JCOG0509, which looks for an OS benefit with cisplatin 60 mg/m^2 on day 1 plus amrubicin 40 mg/m^2 days 1-3 compared with cisplatin 60 mg/m^2 on day 1 plus irinotecan 60 mg/m^2 on days 1, 8, and 15 in 282 randomized patients. The chemotherapy is given in 4-week cycles for 4 cycles. For those with sensitive relapsed SCLC, JCOG0605 is a phase III trial for 180 patients comparing nogitecan with the triplet of cisplatin/etoposide/irinotecan. Finally, in patients with refractory/relapsed SCLC, a study in development will look at the response rate in 80 patients receiving single-agent amrubicin.

National Cancer Institute of Canada Clinical Trials Group

The NCIC-CTG BR.10 trial remains one of the most positive adjuvant chemotherapy trials, even now, with 9 years of follow-up.[32]

The follow-up trial, BR.19, explored the use of adjuvant gefitinib and enrolled > 500 patients before closing prematurely in 2005 based on other negative gefitinib trials (ISEL [Iressa Survival Evaluation in Lung Cancer][33] and SWOG 0023[34]). The primary endpoint of OS is expected to be available in the next year or so after a data-lock in April 2009. Extensive correlates with tumor tissue and blood are ongoing. The NCIC-CTG is involved in E1505 as well as E5597. The NCIC-CTG is also leading a separate economic analysis of E1505, with health utilization data collected prospectively for all Canadian patients. The NCIC-CTG will also participate in LungART (BR.27) and CALGB 140503, among other Intergroup efforts.

For patients with medically inoperable localized NSCLC, NCIC-CTG BR.25 is a just-completed study of accelerated hypofractionated 3D-CRT at doses ≤ 60 Gy administered over 2.5-3 weeks. The 80 accrued patients will be followed by 5 years.

First-line advanced-stage NSCLC efforts of the NCIC-CTG thoracic group have been focused on VEGFR TKI cediranib. BR.24, a randomized phase II/III trial of first-line carboplatin/paclitaxel with or without cediranib, met its primary efficacy endpoint in phase II but with excessive toxicity observed in the cediranib arm, despite dose reductions to 30 mg daily (down from 45 mg daily). Based on those results, BR.24 was closed, but BR.29 is now open, using the same randomized phase II/III design but with a 20-mg dose of cediranib.

The predominant second-line effort of the NCIC-CTG thoracic committee will be participation in N0723 (MARVEL). For SCLC, the recently completed BR.20 looked at vandetanib, a dual EGFR and VEGFR TKI. The drug did not show superiority to placebo in this trial and will not be further developed in this manner. For limited-stage SCLC, the NCIC-CTG will participate in the CONVERT trial, discussed in the EORTC section, known within the NCIC-CTG as BR.26.

For mesothelioma, a phase II study of sunitinib is in development. The NCIC-CTG has an extensive team for correlate studies, which are an important part of all trials run within the group.

North Central Cancer Treatment Group

The NCCTG, centered at the Mayo Clinic in Minnesota, has participating centers in 30 states, Puerto Rico, and 2 provinces in Canada. The group is actively participating in the E1505 study for early-stage disease and other Intergroup efforts. For locally advanced NSCLC, N0321 is a phase I/II study examining the use of bortezomib in combination with paclitaxel/carboplatin and radiation therapy. Another trial in development in locally advanced disease, N0921, is for patients aged ≥ 70 years with stage III NSCLC who will receive pemetrexed and cetuximab with concurrent radiation therapy.

The VEGFR TKI sorafenib is being studied as an addition to pemetrexed for second-line therapy of nonsquamous NSCLC in the N0626 trial. This randomized phase II study of pemetrexed with or without sorafenib has reached 50% of the accrual goal. N0528 is a randomized phase II first-line trial of gemcitabine and carboplatin with or without cediranib (AZD2171), another VEGFR TKI. Accrual goal is just under 100 patients, using a dose of cediranib of 30 mg.

N0723, also known as the MARVEL (MARker Validation of Erlotinib in Lung cancer) study, is the largest NCCTG effort. This study, which opened in October 2008, randomizes patients to either erlotinib or pemetrexed as second-line therapy for advanced NSCLC and is focused on whether PFS is improved in subsets of patients based on various biomarkers, in particular EGFR overexpression by FISH. Target accrual is 1200 patients, with the hope of finding 956 with FISH results (required for randomization). It is expected that 30% of the patients will be EGFR FISH positive and 70% will not. The study is now being modified to register patients before initiation of first-line chemotherapy, with the FISH analysis and randomization performed on all patients with ≥ SD after completion of 4 cycles of a platinum doublet. This modification is in accordance with treatment pattern changes with maintenance therapy.

The only cooperative group trial focused on oligometastatic advanced-stage disease is N0724, a phase II study that randomizes patients to either observation or radiation therapy to known sites of disease after completion of 4 cycles of platinum-based chemotherapy. Another focused advanced-stage NSCLC study is N0821, a phase II study of pemetrexed, carboplatin, and bevacizumab in patients with good PS who are aged ≥ 70 years.

Other concepts in development are exploring MK-0426 in advanced-stage squamous cell lung cancer, up-front thoracic radiation therapy in bulky advanced-stage NSCLC, and a phase II study of γ-secretase inhibitor R04929097 in patients with advanced-stage NSCLC.

The NCCTG has a small-cell study examining the IGF-1R antibody cixutumumab in combination with carboplatin and etoposide for extensive-stage NSCLC, N0922. All patients receive 4 cycles of carboplatin/etoposide, and all patients receive maintenance cixutumumab, with a randomization to receive the antibody either concurrently with the chemotherapy or after completion of the chemotherapy. Another small-cell study in development is N0923, using NTX-010, a replication-competent picornavirus, given after completion of chemotherapy.

Radiation Therapy Oncology Group

The stated mission of the RTOG is to improve the survival and quality of life of patients with cancer through the conduct of high-quality clinical trials that focus primarily on optimizing radiation therapy. The RTOG has a broad portfolio of trials in lung cancer from early to locally advanced stages that address the role of treatment intensification through radiation dose escalation or hypofractionation and/or combination with systemic therapies.

In early-stage lung cancer, RTOG 0236 was the first North American cooperative group trial of stereotactic body radiation therapy (SBRT), a treatment modality involving high-precision delivery of highly conformal and dose-intensive radiation therapy to small-volume tumors, as an alternative to resection in strictly medically inoperable patients with peripherally located T1-3 tumors (< 5 cm in size without lymph node or distant metastasis). The dose was 54 Gy (corrected) in 3 fractions over 8-14 days. Between May 2004 and October 2006, the trial completed its target accrual of 55 evaluable patients. As reported at the 2009 World Congress on Lung Cancer, at a median follow-up of 25 months, the 2-year local control was 98% (with a single local failure), regional control was 100% (with 2 regional relapses that occurred after 2 years), and the OS rate was 72%. There were no treatment-related deaths and only 2 protocol-defined grade 4 toxicities.

This has led to the initiation of RTOG 0618, a phase II study of the same SBRT regimen in patients with the same tumor characteristics but who are physiologically able to tolerate complete resection. Since December. 2007, the trial has accrued approximately half of its target of 33 patients and is likely to be completed by 2010. If results are encouraging, the plan is to move forward with a randomized phase III trial of surgery versus SBRT.

Because of concerns of increased toxicity of SBRT in more centrally located tumors, the RTOG is also exploring a slightly less dose-intensive approach for tumors close to the proximal bronchial tree. RTOG 0813 is a phase I/II dose-escalation trial designed for medically inoperable patients with centrally located stage I NSCLC, with a starting dose of 50 Gy in 5 fractions. The study was activated in February 2009, with an accrual goal of 94 patients. Future plans include a randomized trial of different dose/fractionation SBRT regimens for medically inoperable early-stage lung cancer.

In locally advanced lung cancer, the RTOG completed a phase I/II study of an escalated radiation dose (74 Gy) with concurrent chemotherapy, RTOG 0117, as well as a phase II trial of escalated systemic therapy (carboplatin/paclitaxel plus cetuximab) with concurrent radiation therapy (63 Gy), RTOG 0324. In both of these studies, patients with predominantly inoperable stage IIIA/IIIB NSCLC had median survival times of 21.6 months and 22.7 months, respectively—highly promising compared with the 17-month median survival observed in RTOG 9410, the study that established concurrent chemoradiation therapy as the standard of care for locally advanced NSCLC in the RTOG. Thus, the RTOG has initiated and is the coordinating group for the Intergroup study RTOG 0617, a 4-arm phase III randomized trial of standard-dose (60 Gy) versus high-dose (74 Gy) radiation with concurrent carboplatin/paclitaxel with or without cetuximab for patients with unresectable stage IIIA/IIIB NSCLC. The study opened in November 2007 and has accrued 123 of 500 planned patients to date.

The RTOG has also coordinated a randomized phase III Intergroup study of PCI versus observation for patients without evidence of brain metastases and without progression after initial treatment for locally advanced NSCLC. RTOG 0214 closed early after failing to meet its original accrual goal of 1058 patients, but analysis of 340 randomized patients revealed a statistically significant reduction of the rate of brain metastasis from 18% to 7.7% at 1 year with PCI.[35] This was at the cost of decreased performance on a verbal learning test in the PCI group, but there was no significant difference in mini–mental status examination and quality of life. With the limited accrual, there was insufficient power to detect a difference in PFS or OS.

Protocols currently under development will focus on multimodality therapy. RTOG 0839 is a proposed study that will study carboplatin/paclitaxel/cetuximab with full-dose concurrent radiation therapy (61 Gy) as preoperative therapy for resectable stage IIIA disease with minimal N2 nodal metastasis. RTOG 0937 is a proposed randomized phase II study of consolidative radiation therapy to thoracic and limited extrathoracic sites after chemotherapy and PCI for extensive-stage SCLC. In addition, all of the currently active and proposed protocols include a translational research component to investigate the predictive and/or prognostic value of blood and/or urine biomarkers.

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Building on earlier work in superior sulcus (Pancoast) tumors, S0920 will explore the addition of cetuximab to the regimen studied in the recently completed S0220 but will include patients with more advanced disease (IIB, IIIA, and IIIB, including ipsilateral supraclavicular nodal disease, all T3 or T4). Enrolled patients will receive cisplatin 50 mg/m^2 on days 1, 8, 29, and 36 and etoposide 50 mg/m^2 on days 1-5 and 29-33 with concurrent thoracic radiation therapy of 54 Gy (the SWOG standard NSCLC regimen) in combination with cetuximab 250 mg/m^2 weekly after a loading dose. Patients will then proceed to surgical resection, with additional consolidation chemotherapy. The primary endpoint is the pathologic complete response rate.

Also for early-stage NSCLC, SWOG is participating in E1505 and E5597 and has other SWOG-led studies, in particular S0720, focused on personalizing adjuvant chemotherapy. S0720 is founded on work by Zheng et al,[36] as well as others[37] demonstrating that ERCC1 and RRM1 levels provide both prognostic value and predictive value for platinum-based chemotherapy in NSCLC. S0720 will test the feasibility of pharmacogenomically directed adjuvant therapy by accruing patients with completely resected stage I NSCLC (≥ 2 cm in size) and assigning therapy based on assessment of ERCC1 and RRM1 levels from the surgical specimen. The primary endpoint of S0720 is feasibility, defined by the percentage of patients who can be assigned treatment appropriately, reflecting the adequacy of tumor specimen collection and analysis.

Another early-stage NSCLC study is S0424, which is investigating the molecular epidemiology of early-stage NSCLC in smoking and nonsmoking men and women. By performing extensive tissue- and blood-based analyses on multiple pathways, this study assesses the influence of smoking, hormonal factors, and other exposures on sex differences in lung cancer. The study is nearly completed but requires more never-smoking men to finish accrual.

The major first-line NSCLC trial for SWOG is S0819, a phase III trial that will randomize patients to carboplatin/paclitaxel (plus bevacizumab in eligible patients) with or without cetuximab. The 4-drug regimen was studied in S0536 with encouraging results and promising correlate trial work.[38] SWOG's initial work with cetuximab, S0342, combined the agent with carboplatin/paclitaxel in different schedules with favorable results in the concurrent arm, especially in patients with EGFR overexpression by FISH analysis.[39] EGFR FISH analysis will be an important component of S0819, which aims to screen 1545 patients to identify adequate number of patients with EGFR expression by IHC (required for study entry) and 618 FISH-positive patients.

For patients with poor PS with advanced-stage NSCLC, S0709 will evaluate erlotinib versus erlotinib plus chemotherapy using a serum proteomics pattern suggestive of erlotinib benefit.[26] Patients on the chemotherapy arm will received carboplatin/paclitaxel on day 1 then erlotinib on days 2-16 of each 21-day cycle to allow for "pharmacodynamic separation," as previously piloted at University of California, Davis.[40]

Another agent that SWOG is studying is conatumumab (AMG 655), a proapoptotic agent that directly activates TRAIL-TR-2. S0810 will enroll 60 patients per arm who will be randomized to conatumumab 15 mg/kg every 3 weeks or the same dose plus pemetrexed

500 mg/m^2. Conatumumab is also being added to standard first-line cisplatin/pemetrexed chemotherapy either with (S0814) or without (S0813) bevacizumab with maintenance conatumumab in both studies after completion of 6 cycles of chemotherapy. S0814 will also include maintenance bevacizumab. The accrual goal is 70 patients per trial.

In SCLC, SWOG is looking at a trial of large-volume chemoradiation for limited-stage disease (S0908), and in extensive-stage disease, cediranib will be combined with cisplatin/etoposide in a randomized phase III study, S0938. S0938 will enroll 600 patients who will be randomized to standard cisplatin/etoposide chemotherapy with or without cediranib (which will be continued as a single agent after completion of 4 cycles of chemotherapy), with an OS endpoint. The study has embedded marker validation with a biomarker-embedded design. Aflibercept (VEGF Trap) and topotecan combination therapy will be studied for recurrent SCLC in S0802.

Patients with newly diagnosed mesothelioma will be eligible for S0905, which will randomize patients to cisplatin/pemetrexed with cediranib or placebo after completion of the phase I dose-escalation period. This study is building on encouraging single-agent activity of second-line cediranib for mesothelioma in the S0509 study presented at the ASCO 2009 annual meeting.[41] Also in mesothelioma, S0722 is exploring the use of everolimus (RAD001).

Conclusion

The cooperative group system plays a vital role in the advancement of therapy for NSCLC, SCLC, and mesothelioma. The cooperative groups of North America have been pivotal in showing benefit with the anti-VEGF agent bevacizumab and the anti-EGFR drug erlotinib, as well as the importance of adjuvant chemotherapy among other advances. As outlined in this article, the portfolios of the groups and international cooperative groups are full of varied and important studies. The use of an antiangiogenesis approach, as seen in E1505 with adjuvant bevacizumab, in BR.29 with first-line cediranib, and in multiple other trials incorporating anti-VEGFR TKIs, is a primary focus. The groups are also very involved in investigating therapies in the EGFR pathway, including cetuximab, and better understanding of how to use erlotinib and gefitinib in patients with activating mutations and other indicators of benefit such as proteomic profiles.

The cooperative groups provide a mechanism for asking critical questions such as the value of postoperative radiation therapy and the role of lesser resections for smaller stage I tumors that would be very difficult in any other setting. One of the incredible strengths of the cooperative groups is the breadth and depth of translational science possible within trials. This translational strength is seen in the multitude of trials currently active or in development looking at real-time sample analysis of EGFR mutations, RRM1 expression, and others in the move toward personalized therapy. Multiple other targeted agents, including those targeting IGF-1R, Hedgehog, and direct inducers of apoptosis are also in trials within the cooperative group system. Within the context of the cooperative group system, the future of thoracic malignancy therapy looks promising.

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Treatment after the Failure of Gefitinib in Patients with Advanced or Recurrent Non-small Cell Lung Cancer

RIICHIROH MARUYAMA, HIROSHI WATAYA, TAKASHI SETO and YUKITO ICHINOSE

Department of Thoracic Oncology, Kyushu Cancer Center, Fukuoka, Japan

Abstract. *Background: The optimal treatment for patients with progressive non-small cell lung cancer who initially show a good response to gefitinib is unclear. Patients and Methods: This study retrospectively analyzed 60 consecutive patients who experienced treatment failure after achieving disease control with gefitinib and thereafter underwent post initial gefitinib treatment either with or without continuing gefitinib. Results: Continuing gefitinib was independently associated with a good survival based on multivariate analyses (hazard ratio (HR)=0.51; 95% confidence interval (CI)=0.26-0.98; p=0.0426), and performance status at the failure of gefitinib (0.05; 0.02-0.17; p<0.0001). The adjusted HR of continuing gefitinib based on Cox regression analysis and a propensity score of 0.61 (95% CI, 0.41-0.92) indicated an association between a prolonged survival and the continuation of gefitinib. Conclusion: In addition to post gefitinib treatment, continuing the administration of gefitinib should be considered in patients who previously achieved disease control with gefitinib, even after a failure of gefitinib.*

Gefitinib (Iressa™; AstraZeneca, London, UK) is an orally active and selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that blocks signal transduction pathways. International phase II studies (IDEAL-1 and -2) have been conducted on the efficacy of gefitinib as a second- or third-line treatment in patients with advanced non-small cell lung cancer (NSCLC). These studies demonstrated the response rate to be 18% and 12%, respectively (1, 2). The Iressa Survival Evaluation in Lung Cancer (ISEL) trial was a randomized, placebo-controlled phase III trial conducted to investigate the effect of gefitinib on survival as a second-line or third-line treatment for patients with locally advanced or metastatic NSCLC (3). Treatment with gefitinib was not associated with a significant improvement in survival in comparison to a placebo in this study. However, a subgroup analysis showed there was a greater treatment effect among never-smokers (median time to treatment failure 5.6 months for gefitinib and 2.8 months for placebo; hazard ratio (HR) 0.55; 95% confidence interval (CI) 0.42-0.72; $p<0.0001$) than among former and current smokers (HR 0.89; 95% CI 0.78-1.01; $p=0.0707$), and among patients of Asian origin (median time to treatment failure 4.4 months for gefitinib and 2.2 months for placebo; HR 0.69; 95% CI 0.52-0.91; $p=0.0084$) than among those of non-Asian origin (HR 0.86; 95% CI 0.76-0.98; $p=0.0197$) (3). Recently, our group (4) and Kim *et al.* (5) reported the definitive data of two trials comparing gefitinib with docetaxel in second-line treatment of metastatic NSCLC. In the former trial (V-15-32), gefitinib did not reach non-inferiority in comparison with docetaxel (4). Conversely, in the latter trial (INTEREST), non-inferiority was reached using a more powered clinical and statistical design (5).

Unfortunately, most patients who are initially sensitive to gefitinib ultimately relapse. In addition, patients often experience a rapid progression of the disease once gefitinib administration is terminated following a relapse. The molecular mechanism of acquired resistance to gefitinib has been reported (6, 7). However, there have so far been few studies addressing treatment after the failure of gefitinib. The present study retrospectively evaluated the clinical value of continuing gefitinib administration after the failure of initial gefitinib treatment.

Patients and Methods

Patients. This institute had 62 consecutive pretreated patients with cytologically or histologically diagnosed advanced NSCLC or postoperative recurrence, who initially achieved disease control with gefitinib, but thereafter developed resistance to the treatment and underwent post initial gefitinib therapy from October 2002 to November 2007. Two patients who received gefitinib as a first-line treatment were excluded from the present study. Gefitinib was orally administered, at a daily dose of 250 mg. The clinical or pathological stage of the disease was based on the TNM classification of the Union Internationale Contre Cancer (UICC) (8). The histological analysis of the tumors was based on the WHO classification for cell types (9). The clinicopathological characteristics of the patients are

Correspondence to: Riichiroh Maruyama, MD, Ph.D., Department of Thoracic Oncology and Surgery, Nippon Steel Yawata Memorial Hospital, 1-1-1, Harunomachi, Yahatahigashi-ku, Kitakyushu 805-8508, Japan. Tel: +81 936719312, Fax: +81 936719447, e-mail: maruyama.r@ns.yawata-mhp.or.jp

Key Words: Non-small cell lung cancer, gefitinib, treatment failure, post initial gefitinib therapy.

Table I. *Clinicopathological characteristics of the patients.*

Parameter	n=60
Median age, years (range)	64 (34-77)
Gender, female/male	34/26
Histological type, ad/other	56/4
Smoking status, never/current or former smoker	38/22
Performance status at failure (ECOG), 0-1/≥2	51/9
No. of prior chemotherapy regimens, 1/2/>3	37/14/9
Response to prior chemotherapy, PR/SD	27/24
Response to gefitinib, CR/PR/SD	2/34/24
Median duration of disease control with gefitinib (months) (range)	12 (1-27)
Reason for PD with gefitinib, progression of the pre-existing target lesions/appearance of new lesions	17/43
Post initial gefitinib treatment, chemotherapy alone/radiotherapy alone/combination	22/16/22

ad, Adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

shown in Table I. Of these, 36 patients continued to receive gefitinib while the remaining 24 patients received other types of therapy due to their physician's decision.

Prior treatment and therapy after the failure of initial gefitinib. All patients received at least one prior chemotherapy regimens (platinum-doublet consisting of a so-called new cytotoxic agent) before the administration of gefitinib as shown in Table I. Approximately half of all patients had a partial response (PR) as the best response to prior chemotherapy. The majority of the patients had received gefitinib as a second-line therapy. After the failure of the initial gefitinib treatment, the patients received various therapies. Radiation therapy included palliative therapy for bone metastases and whole brain irradiation or gamma-knife surgery for brain metastases. Most of the chemotherapy regimens after the failure of the initial gefitinib therapy were single agent or a combination of new non-platinum agents, such as docetaxel, gemcitabine or vinorelbine and so on. Platinum-based combination regimens were selected for patients who had a good performance status (PS).

Tumor assessment during and after treatment. The change in disease was assessed by computed tomography (CT) findings of the chest every two months. The measurability of target lesions at baseline and the response criteria were based on the Response Evaluation Criteria in Solid Tumors (RECIST) (10).

Statistical analysis. The overall survival time in the current study was defined as the time from the date of failure of the initial gefitinib treatment to the date of death due to any cause. Patients who were alive on the date of the last follow-up were censored on that date. The duration of disease control with the initial gefitinib therapy was defined as the time from the initial date of gefitinib administration to the date of progression of the disease, the discontinuation of treatment, or death due to any cause and was censored at the date of the last follow-up visit for patients who did not discontinue, who were still alive and who did not have disease progression. Because the distribution of the duration time was rightly-skewed, this variable was dichotomized at the median value of 10 months. The distribution of the baseline clinical factors was compared using Fisher's exact test for categorical parameters and by pooled *t*-test for continuous parameters. Survival curves were estimated using the nonparametric Kaplan-Meier method (11, 12). A univariate Cox proportional hazards regression (13) was used to evaluate the possible association between the baseline covariates and patient prognosis.

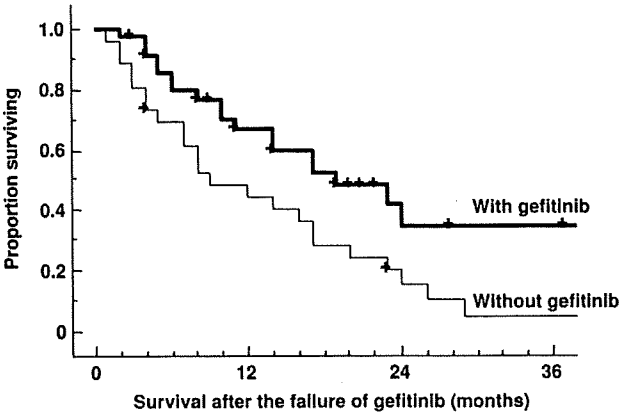

Figure 1. *The overall survival curves after the failure of gefitinib in the patients who underwent post initial gefitinib treatment with continued administration of gefitinib or other therapies alone.*

The primary scope of this study was to evaluate the value of continuing gefitinib therapy in patients with progressive NSCLC that initially responded to gefitinib. To reduce any possible selection bias due to an imbalance of clinical factors, whether continuing gefitinib or not, a covariate adjustment was performed using the propensity score (14). In this method, the propensity score (on the probability scale) and a variable denoting the continuation of gefitinib administration were entered in the Cox proportional hazards regression. The prognostic effect of continuing the drug was thus determined according to the regression coefficient. The propensity scores were estimated using a logistic regression model. All *p*-values reported as two-tailed and statistical significance was defined as $p<0.05$. The analyses were conducted using StatView statistical software program (Abacus Concepts, Inc., Berkeley, CA, USA) and SAS (SAS Institute Inc., Cary, NC, USA).

Table II. *Univariate Cox analysis for overall survival after the failure of gefitinib treatment.*

Variable	Referent	HR	95% CI	*p*-Value
Age (years)	<65 *vs.* ≥65	0.67	0.36-1.27	0.222
Gender	Female *vs.* Male	0.81	0.43-1.52	0.506
Smoking history	No *vs.* Yes	1.00	0.53-1.90	0.998
ECOG PS at the failure of gefitinib	0-1 *vs.* ≥2	0.05	0.02-0.15	<0.0001
No. of prior chemotherapy regimens	1 *vs.* ≥2	0.74	0.39-1.41	0.359
Response to prior chemotherapy	Yes *vs.* No	0.70	0.37-1.33	0.277
Response to gefitinib	CR/PR *vs.* SD	0.74	0.39-1.40	0.351
Duration of disease control with gefitinib (months)	≥10 *vs.* <10	0.41	0.21-0.80	0.009
Gefitinib continued	Yes *vs.* No	0.49	0.26-0.91	0.025

ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

Table III. *Multivariate Cox analysis with covariates selected by univariate analysis.*

Variable	Referent	HR	95% CI	*p*-Value
ECOG PS at the failure of gefitinib	0-1 *vs.* ≥2	0.05	0.02-0.17	<0.0001
Duration of disease control with gefitinib (months)	≥10 *vs.* <10	0.57	0.28-1.15	0.1145
Gefitinib continued	Yes *vs.* No	0.51	0.26-0.98	0.0426

Results

Treatment and response after the relapse of gefitinib. The response rate (RR) and disease control rate (DCR; PR plus stable disease, SD) for post-treatment after the failure of gefitinib was 13.3% (8/60) and 33.3% (20/60), respectively. The RR was 11.1% (4/36) and 16.7% (4/24) of patients with gefitinib and without gefitinib, respectively and the DCR was 27.8% (10/36) and 41.7% (10/24), respectively. There was no significant difference between the two groups (p=0.40).

Survival after the failure of gefitinib. The median follow-up duration from the failure of initial gefitinib treatment was 12 months (range: 1-41 months). The survival curves with or without continuing gefitinib are shown in Figure 1. There was a statistically significant difference between the patients who underwent therapy after the failure of initial gefitinib therapy with and without gefitinib (HR=0.48; 95% CI, 0.26-0.88). A univariate Cox analysis was used to determine the prognostic effect of covariates including age, gender, smoking status, PS at failure, the number of prior chemotherapy regimens, the response to prior chemotherapy, the response to gefitinib, the duration of disease control with initial gefitinib and the continuation of gefitinib administration. Of these, in addition to continuing gefitinib, PS at failure (HR=0.05; 95% CI, 0.02-0.15) and duration of disease control with initial gefitinib (HR=0.61; 95% CI, 0.42-0.89) indicated a possible independent association with the overall survival (Table II). Continuing gefitinib (HR=0.51; 95% CI, 0.26-0.98) and PS at the failure of gefitinib (HR=0.05; 95% CI, 0.02-0.17) indicated an independent association with the overall survival using a multivariate Cox analysis (Table III).

Table IV. *Adjusted hazard ratio of continuing gefitinib administration by using propensity score analysis.*

Parameter	HR	95% CI	*p*-Value
Gefitinib continued			
No	1.00		
Yes	0.61	0.41-0.92	0.0196
Propensity score	0.73	0.57-0.94	0.0148

The prognostic effect of continuing gefitinib was adjusted for known, measurable confounders using propensity score methods. The propensity score with regard to continuing gefitinib treatment was assigned to each patient by a logistic regression model with seven covariates (age, gender, smoking status, PS at failure, the number of prior chemotherapy regimens, the response to prior chemotherapy, the response to gefitinib, and the duration of disease control with initial gefitinib). Since the prognostic factors were not distributed evenly in the two groups with/without continuing gefitinib, the propensity scores were therefore different between them. The median propensity score (on the

probability scale) was 0.74 (range, 0.14-0.96) for the group without continuing gefitinib in comparison to 0.87 (0.39-0.99) for the group with continuing gefitinib. The adjusted HR of continuing gefitinib which was obtained by the Cox regression and the propensity score was 0.61 (95% CI, 0.41-0.92) indicating a prolonged survival associated with the continuation of gefitinib (Table IV).

Discussion

Two subsequent phase III trials randomized previously untreated patients with advanced NSCLC into standard platinum-based chemotherapy alone or that with the addition of two different doses of gefitinib (15, 16). These trials demonstrated no difference in the response rate, time to progression, or either 1-year or overall survival with the addition of gefitinib to standard chemotherapy. Therefore, no discernible improvement was observed in the outcome following the addition of gefitinib to standard cytotoxic chemotherapy. However, the effects of gefitinib in combination with cytotoxic chemotherapy in the refractory patients who have disease control with gefitinib remains unknown. Shoji *et al.* reported the characteristics and failure pattern of gefitinib responders with postoperative recurrence of pulmonary adenocarcinoma. Most responders failed due to the appearance of new lesions without progression of the pre-existing target lesions (17). Some gefitinib-resistant tumors develop new lesions while some gefitinib-sensitive tumors remain. It is possible that gefitinib may suppress the initial target lesions even after the appearance of new lesions. Therefore, the careful consideration of both gefitinib treatment for the gefitinib-sensitive lesions and additional treatment for gefitinib-resistant lesions is therefore recommended.

Riely *et al.* reported prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in NSCLC patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus, an inhibitor of mammalian target of rapamycin. Thirteen patients had 18-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography/CT and CT scans at baseline, 3 weeks after stopping erlotinib or gefitinib, and 3 weeks after restarting erlotinib or gefitinib. Three weeks after restarting erlotinib or gefitinib, everolimus was added to their treatment (18). Although the addition of everolimus failed to shrink tumors further in their clinical setting, this prospective study of 10 patients who previously responded to erlotinib or gefitinib suggested that these patients continued to benefit from treatment with erlotinib or gefitinib despite documented progression of disease by RECIST. When patients with acquired resistance to erlotinib or gefitinib discontinued EGFR-TKI treatment, the majority of patients had worsening in lung cancer symptoms, an increase in tumor size, and an increase in tumor FDG uptake. Just 3 weeks after resuming the EGFR-TKI, the majority of patients had stabilization or improvement in symptoms, a decrease in tumor size and a reduction in tumor FDG uptake. Disease progression generally implies resistance to therapy and leads to a change in the therapy regimen. However, this theory might not apply to EGFR-TKIs. Gefitinib administration should not be terminated following a relapse so as not to experience a rapid progression of the disease or worsening symptoms caused by lung cancer.

Grothey *et al.* reported same results as our study concerning the survival benefit of exposure to molecular targeting agents beyond progression in BRiTE, the first-line Bevacizumab Regimens: Investigation of Treatment Effects and Safety, a large observational study in patients with metastatic colorectal cancer. In this study, all patients received bevacizumab, a recombinant monoclonal antibody against vascular endothelial growth factor (VEGF), as part of first-line therapy. Patients who had first progression were grouped into 3 subgroups: i) no treatment, ii) post-progression treatment without bevacizumab, and iii) post-progression treatment with bevacizumab by physician decision not randomization. In multivariate analysis, exposure to bevacizumab beyond first progression and exposure to any second-line chemotherapy were independently associated with increased overall survaival (both $p<0.001$) (19).

Cho *et al.* reported a phase II study of erlotinib in advanced NSCLC after the failure of gefitinib. The erlotinib produced a greater clinical benefit in patients who had shown SD with prior gefitinib therapy in their study (20). The standard doses of 250 mg gefitinib and 150 mg erlotinib are not equivalent. Erlotinib was administered at its maximum-tolerated dose, whereas gefitinib was administered at approximately one third of its maximum-tolerated dose. Instead of gefitinib, the administration of another EGFR-TKI such as erlotinib may lead to a clinical benefit in patients who initially achieved disease control while receiving gefitinib.

A secondary mutation that substitutes methionine for threonine at position 790 (T790M) in the EGFR kinase domain (6, 7) and *MET* amplification with or without T790M mutation (21, 22) are associated with the acquisition of resistance to EGFR-TKI. A novel mutation, which leads to the substitution of tyrosine for aspartic acid at position 761 (D761Y) was found in a brain metastasis (23). Further mutation analyses are ongoing.

In conclusion, post initial gefitinib treatments with the continued administration of gefitinib should therefore be considered in those patients who achieved disease control by gefitinib, even after the failure of gefitinib therapy. A prospective randomized clinical trial is necessary to evaluate the benefits of the continued use of gefitinib after relapse in patients who initially achieved disease control by gefitinib.

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Prognostic factors in previously treated non-small cell lung cancer patients with and without a positive response to the subsequent treatment with gefitinib

Hiroshi Wataya[a], Tatsuro Okamoto[a], Riichiroh Maruyama[a], Takashi Seto[a], Koji Yamazaki[a], Tetsuzo Tagawa[a], Seiichi Fukuyama[a], Atsushi Osoegawa[a], Jiro Ikeda[b], Munetsugu Nishimura[b], Takeharu Yamanaka[c], Yukito Ichinose[a,*]

[a] Department of Thoracic Oncology, National Kyushu Cancer Center, Notame 3-1-1, Minami-ku, Fukuoka 811-1395, Japan
[b] First Department of Internal Medicine, Kurume University School of Medicine, Japan
[c] Cancer Biostatistics Laboratory, Institute for Clinical Research, National Kyushu, Cancer Center, Fukuoka, Japan

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ABSTRACT

Gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, has been reported to have a certain anti-tumor effect in previously treated patients with non-small cell lung cancer (NSCLC). However, the prognostic factors in those patients with and without a positive response to gefitinib treatment remain unclear. A retrospective chart review was performed in 131 advanced NSCLC patients who received 250 mg of gefitinib as either a second-line or even later stage treatment from July 2002 to December 2005. The clinical factors including age, gender, performance status (PS), stage, histology, the number of prior types of chemotherapy, and the response to first-line chemotherapy were analyzed. One and 38 patients experienced a complete and partial response, respectively, to gefitinib treatment with an overall response rate of 30%. The median survival time (MST) of all patients receiving gefitinib treatment was 10 months while the MST was 28 months in the 39 gefitinib responders and 6 months in the 92 non-responders. Among the 39 gefitinib responders, the predominant prognostic factor was found to be the effectiveness of the first-line chemotherapy. The MST of the 20 patients with a response to the first-line chemotherapy was 32 months while the MST of the 19 patients without a response to the chemotherapy was 22 months ($p = 0.025$). Among the 92 gefitinib non-responders, the predominant prognostic factor was the PS ($p < 0.001$). The effectiveness of the first-line chemotherapy was therefore found to be a prognostic factor in the gefitinib responders with previously treated NSCLC, while the PS was shown to be a prognostic factor in the gefitinib non-responders.

1. Introduction

Patients with metastasized advanced non-small cell lung cancer (NSCLC) have a poor prognosis with a 5-year survival rate ranging from 1% to 5%[1]. A recent meta-analysis demonstrated that the platinum-based combination chemotherapy using a third generation drug is currently considered to be the most effective treatment for advanced NSCLC [2]. A second-line chemotherapy such as docetaxel has been proven to give a small but significant survival benefit [3]. No conventional chemotherapy regimen has yet been proven to be effective as a third-line treatment. Retrospective analyses have suggested that the response to third-line chemotherapy was only 2%, and the median survival time (MST) was only 4 months [4].

Molecular-targeting agents have been recently introduced for the treatment of NSCLC. One of them is gefitinib, which is an orally active, selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that blocks the signal transduction pathways. An international phase II study and the trial in the United States using gefitinib were conducted as a second- or third-line treatment in patients with advanced NSCLC [5,6] and they demonstrated response rates of 18% and 12%, respectively. Although a survival benefit of gefitinib for previously treated advanced NSCLC has not been confirmed by a randomized placebo-controlled multi-institutional study [7], a recent randomized phase III trial comparing gefitinib to docetaxel as a second- or third-line treatment demonstrated the non-inferiority of gefitinib relative to docetaxel in terms of survival [8].

Several studies have revealed a female gender, never-smoker, adenocarcinoma, and Asian origin to be good predictive factors for a response to gefitinib treatment [7,9]. Lynch and Paez revealed that mutation of the EGFR tyrosine kinase domain predicts

* Corresponding author. Tel.: +81 92 541 3231 fax: +81 92 551 4585.
E-mail address: yichinos@nk-cc.go.jp (Y. Ichinose).

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