Table 4 Response

Group	Dose level (mg/m^2)	No. of patients	Response				PR	
			CR	PR	SD	PD	Sq.	Non-sq.
Group A (Ccr ≥60 mL/min)	80	7	0	2	3	2	2	0
	100	15	0	4	6	5	4	0
Group B (40 ≤ Ccr < 60 mL/min)	60	6	0	3	2	1	2	1
	80	6	0	3	1	2	3	0
	100	5	0	1	1	3	1	0
Total		39	0	13	13	13	12	1

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *Sq.* squamous cell carcinoma, *Non-sq.* non-squamous cell carcinoma

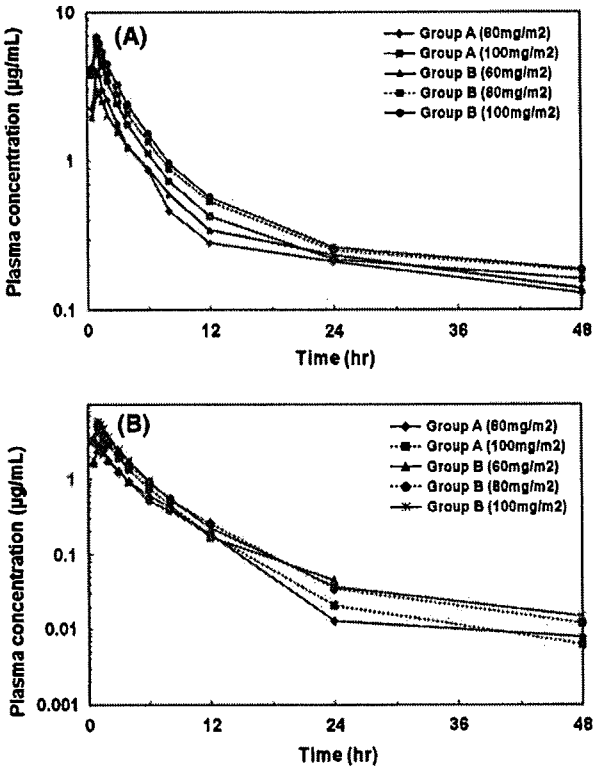

Fig. 1 Mean plasma concentration–time profiles for: **a** total-Pt and **b** free-Pt of nedaplatin

an additional nine patients were enrolled at the dose level of 100 mg/m^2 in Group A. First, the favorable antitumor response was observed in squamous cell carcinoma and we intended to evaluate the antitumor response mainly for squamous cell carcinoma. Then, five of nine additional patients enrolled had squamous cell carcinoma. Second, the recommended dose was determined as 100 mg/m^2 in Group A, which was the same dose in younger patients. We intended to confirm the toxicity and pharmacokinetic profiles in this elderly subgroup.

In the development of chemotherapy for elderly patients, the selection of appropriate agents is extremely important. Candidate agents must have confirmed antitumor activities and acceptable toxicity profiles in younger patients (e.g., aged ≤70 years). In this study, we investigated nedaplatin as it had a lower incidence of associated emesis and nephrotoxicity, compared with cisplatin, and favorable antitumor activity in NSCLC patients aged ≤70 years. Furthermore, the current standard treatment for elderly patients with advanced NSCLC, that is, third-generation single-agent chemotherapy such as vinorelbine, gemcitabine or docetaxel, had not been established at the time of planning of the study [15–17]. The DLT of nedaplatin in patients aged ≤70 years was reported to be thrombocytopenia, which is correlated with renal function; therefore, we expected that nedaplatin could be safely administered to elderly patients by stratifying the patients according to renal function. Patients with a Ccr ≥40 mL/min were eligible for inclusion in this study based on the results of a previous PK analysis examining the correlation between the nadir platelet count and renal function (described in "Introduction") [11]. When younger patients with a Ccr ≥40 mL/min were treated with 100 mg/m^2 of nedaplatin, the predicted nadir platelet count was ≥50,000/mm^3. Therefore, the initial doses of nedaplatin in Group A (Ccr ≥60 mL/min) and Group B (40 ≤ Ccr < 60 mL/min) were determined to be 80 and 60 mg/m^2, respectively. The dose escalation over 100 mg/m^2 was not planned, because the recommended dose in younger patients (aged ≤70 years) had already been determined at 100 mg/m^2.

In this study, milder criteria of DLT was applied, compared with that used in conventional phase I studies. In this developmental strategy, we pursued "the recommended dose with moderate and acceptable toxicities for the majority of elderly patients", instead of "the recommended dose with the severe toxicities in a small and limited number of patients, as per most conventional phase I studies", because the physiological and pharmacological function of elderly patients is highly variable.

Table 5 Pharmacokinetic parameters of total-Pt and free-Pt

Group	Dose level (mg/m^2)	No. of patients	No. of assessables for PK analysis	C_{max} (μg/mL)	AUC (μg/mL h)	V_{dss} (L)	$T_{1/2}$ (h)	CL (L/h)
PK parameters of total-Pt								
Group A (Ccr ≥60 mL/min)	80	7	2[a]	4.02 (3.49, 4.57)	22.58 (13.46, 31.69)	64.24 (35.27, 93.21)	14.15 (3.25, 25.04)	6.00 (3.60, 8.40)
	100	15	13	5.94 ± 1.38	21.65 ± 4.54	31.50 ± 13.40	3.28 ± 1.35	7.63 ± 1.74
Group B (40 ≤ Ccr < 60 mL/min)	60	6	2[a]	3.02 (2.91, 3.12)	19.78 (14.87, 24.68)	57.05 (33.21, 80.89)	10.77 (4.08, 17.46)	5.21 (4.16, 6.25)
	80	6	6	6.35 ± 1.11	25.99 ± 9.68	29.29 ± 13.18	7.88 ± 8.97	6.10 ± 1.13
	100	5	5	6.83 ± 1.20	32.11 ± 7.86	32.84 ± 22.00	6.62 ± 4.55	5.01 ± 1.57
PK parameters of free-Pt								
Group A (Ccr ≥60 mL/min)	80	7	2[a]	2.72 (2.13, 3.31)	10.56 (7.05, 14.06)	42.30 (37.98, 46.62)	3.49 (2.70, 4.28)	12.08 (8.11, 16.04)
	100	15	13	5.11 ± 1.51	16.20 ± 3.34	32.26 ± 11.17	3.51 ± 4.02	10.26 ± 2.46
Group B (40 ≤ Ccr < 60 mL/min)	60	6	2[a]	2.55 (2.46, 2.64)	11.59 (11.38, 11.79)	49.33 (33.22, 65.43)	6.16 (2.98, 9.34)	8.45 (7.89, 9.01)
	80	6	6	5.52 ± 1.25	18.53 ± 7.12	29.51 ± 9.11	3.40 ± 0.65	7.25 ± 2.21
	100	5	5	5.91 ± 1.21	20.69 ± 5.52	29.63 ± 12.32	2.92 ± 0.66	7.87 ± 2.71
Patients ≤70 years [14]	100	5	5		15.9			

Data are shown as mean ± SD excepting the dose level of 80 mg/m^2 in Group A and 60 mg/m^2 in Group B

PK pharmacokinetics, *total-Pt* total platinum, *free-Pt*, free platinum, C_{max} maximum plasma concentration, *AUC* area under the plasma concentration versus time curve, V_{dss} volume of distribution at steady-state, $T_{1/2}$ terminal half life, *CL* systemic clearance

[a] Data are shown as mean (actual data)

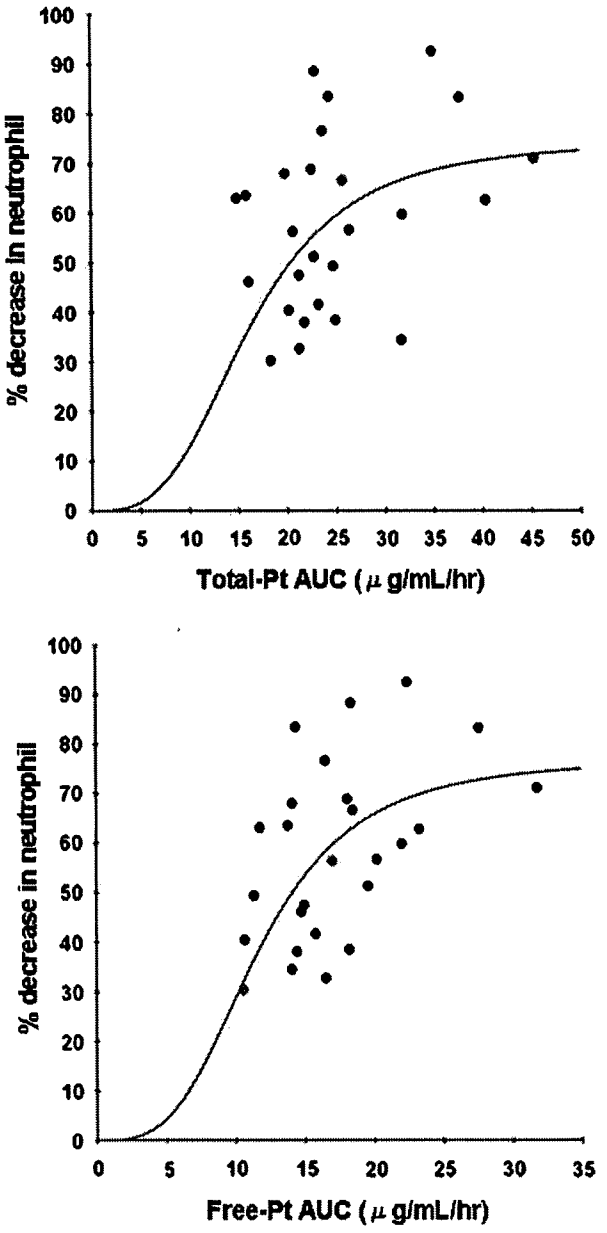

Fig. 2 Relationship between AUCs of total/free-Pt and the percentage decrease in the neutrophil count

In the pharmacokinetic analysis, the free-Pt AUC at a dose of 100 mg/m^2 in Group A seemed similar to that of 80 mg/m^2 in Group B, and there was no significant difference between these two treatment subgroups ($P = 0.336$). These results endorsed an almost equivalent drug exposure in both patient groups, stratified according to renal function. Furthermore, the AUC values in both groups seemed similar to historical data (obtained in a study with a small sample size) for patients aged ≤70 years [14]. However, a significant correlation was not observed between the renal function (i.e., the Ccr value) and the nadir platelet count, as in a previous report examining younger patients. These were possibly attributed to the wide inter-patient physiological and pharmacological variability among elderly patients or just the consequence of the adaptation of dose [11]. For elderly patients, a strict dose calculation of nedaplatin based on renal function, such as the dose calculation for carboplatin using the Calvert formula [18], is not required, and a simple dose selection of nedaplatin stratified according to renal function is considered to be reasonable.

A total of 13 (33%) of the 39 patients achieved partial responses. In this study, 21 patients with squamous cell carcinoma were enrolled, 12 patients achieved PR and the response rate was 57%. The biological mechanism responsible for the antitumor activity of nedaplatin against squamous cell carcinoma of the lung remains unknown. In the pharmacokinetic analysis, no significant differences were observed in responding patients with squamous cell carcinoma compared with non-responding others. However, nedaplatin also has a favorable antitumor activity against head and neck cancer and esophageal cancer, which also have a high frequency of squamous cell histology [19–22]. Although antitumor activity was evaluated only in elderly patients in this study, the development of this activity is worthwhile in the treatment of NSCLC with squamous cell histology. Furthermore, a translational study to identify the biological and/or genetic mechanism responsible for the antitumor activity of nedaplatin against squamous cell carcinoma is also warranted.

In conclusion, the recommended doses of nedaplatin for elderly patients with NSCLC were determined based on renal function, a dose of 100 mg/m^2 every 4 weeks was recommended for patients with a Ccr ≥60 mL/min, and a dose of 80 mg/m^2 every 4 weeks was recommended for patients with 40 ≤ Ccr < 60 mL/min. Nedaplatin can be safely administered to elderly patients with an acceptable level of toxicity and favorable antitumor activities against NSCLC, especially squamous cell carcinoma.

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References

1. Kaneko S, Ishikawa KB, Yoshimi I et al (2003) Projection of lung cancer mortality in Japan. Cancer Sci 94:919–923
2. Schiller JH, Harrington D, Belani CP et al (2002) Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 346:92–98
3. Ohe Y, Ohashi Y, Kubota K et al (2007) Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for

advanced non-small cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 18:317–323
4. Kubota K, Watanabe K, Kunitoh H et al (2004) Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. J Clin Oncol 22:254–261
5. Oshita F, Kurata T, Kasai T et al (1995) Prospective evaluation of the feasibility of cisplatin-based chemotherapy for elderly lung cancer patients with normal organ functions. Jpn J Cancer Res 86:1198–1202
6. Yamamoto N, Tamura T, Maeda M et al (1995) The influence of ageing on cisplatin pharmacokinetics in lung cancer patients with normal organ function. Cancer Chemother Pharmacol 36:102–106
7. Kanzawa F, Matsushima Y, Nakano H et al (1988) Antitumor activity of a new platinum compound (glycolate-*O*,*O*′) diammineplatinum (II) (254-S), against non-small cell lung carcinoma grown in a human tumor clonogenic assay system. Anticancer Res 8:323–327
8. Suzumura Y, Kato T, Ueda R et al (1989) Effect of treatment schedule on antitumor activity of glycolate-*O*, *O*′-diammineplatinum(II), a new platinum derivative: comparison with *cis*-diamminedichloroplatinum(II). Anticancer Res 9:1083–1088
9. Hida S, Okada K, Yoshida O (1990) Advantages in combination chemotherapy using cisplatin and its analogues for human testicular tumor xenografts. Jpn J Cancer Res 81:425–430
10. Furuse K, Fukuoka M, Kurita Y et al (1992) A phase II clinical study of *cis*-diammine glycolato platinum, 254-S, for primary lung cancer. Gan To Kagaku Ryoho 19:879–884
11. Sasaki Y, Fukuda M, Morita M et al (1990) Prediction from creatinine clearance of thrombocytopenia and recommended dose in patients receiving (glycolato-*O*,*O*′)-diammine platinum (II) (NSC 375101D). Jpn J Cancer Res 81:196–200
12. LeRoy AF, Wehling ML, Sponseller HL et al (1977) Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry. Biochem Med 18:184–191
13. Yamaoka K, Nakagawa T, Uno T (1978) Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. J Pharmacokinet Biopharm 6:165–175
14. Sasaki Y, Tamura T, Eguchi K et al (1989) Pharmacokinetics of (glycolate-*O*,*O*′)-diammine platinum (II), a new platinum derivative, in comparison with cisplatin and carboplatin. Cancer Chemother Pharmacol 23:243–246
15. The Elderly Lung Cancer Vinorelbine Italian Study Group (1999) Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small cell lung cancer: The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 91:66–72
16. Gridelli C, Perrone F, Gallo C et al (2003) Chemotherapy for elderly patients with advanced non-small cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 95:362–372
17. Kudoh S, Takeda K, Nakagawa K et al (2006) Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small cell lung cancer: results of the West Japan Thoracic Oncology Group trial (WJTOG 9904). J Clin Oncol 24:3657–3663
18. Calvert AH, Newell DR, Gumbrell LA et al (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748–1756
19. Kato H, Fukuchi M, Manda R et al (2003) Efficacy and toxicity of nedaplatin and 5-FU with radiation treatment for advanced esophageal carcinomas. Anticancer Res 23:3493–3498
20. Kodaira T, Fuwa N, Tachibana H et al (2006) Phase I study of S-1 and nedaplatin for patients with recurrence of head and neck cancer. Anticancer Res 26:2265–2268
21. Yoshioka T, Sakayori M, Kato S et al (2006) Dose escalation study of docetaxel and nedaplatin in patients with relapsed or refractory squamous cell carcinoma of the esophagus pretreated using cisplatin, 5-fluorouracil, and radiation. Int J Clin Oncol 11:454–460
22. Kanai M, Matsumoto S, Nishimura T et al (2007) Retrospective analysis of 27 consecutive patients treated with docetaxel/nedaplatin combination therapy as a second-line regimen for advanced esophageal cancer. Int J Clin Oncol 12:224–227

Cooperative Group Research Endeavors in Small-Cell Lung Cancer: Current and Future Directions

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Abstract

The International Lung Cancer Congress (ILCC), now in its ninth year, is a key forum for representatives of cooperative groups in North America, Europe, and Japan to discuss ongoing and planned clinical trials in lung cancer. Many of the significant strides in lung cancer treatment often originate from investigations designed within the cooperative group system and were a feature of the 2008 ILCC. Small-cell lung cancer (SCLC) represents 15% of all lung cancers diagnosed annually and is characterized by rapid growth kinetics, disseminated metastases, and development of chemotherapy resistance. Many questions remain regarding the optimal use of radiation therapy and approaches for enhancing the effects of chemotherapy to improve clinical outcomes. Herein, we explore and outline the scientific vision of each cooperative group's SCLC research portfolio, as presented at the 2008 ILCC. Highlights include an ongoing Intergroup phase III study exploring differing radiation therapy schemes for limited-stage SCLC and a Southwest Oncology Group 0124 trial establishing platinum/etoposide as the standard of care for untreated extensive-stage SCLC in North America. Continued research efforts sponsored by these groups will represent the future of SCLC diagnosis and management.

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Introduction

Lung cancer is a strikingly prevalent malignancy and is the leading cause of cancer-related death in worldwide. Small-cell lung cancer (SCLC) represents 15% of all lung cancers, and in 2009, an estimated 32,000 new cases will be diagnosed in the United States.[1] Small-cell lung cancer is characterized by aggressive growth kinetics and disseminated metastases, with 60%-70% of patients presenting with advanced- (or "extensive-") stage disease. Despite high initial tumor response rates following platinum-based chemotherapy, SCLC rapidly develops drug resistance, subsequently leading to tumor progression and patient death. Unfortunately, progress in SCLC management has been agonizingly slow, with a glaring lack of therapeutic advances, despite a wealth of new chemotherapeutic drug classes and targeted agents. With median survivals of 7-11 months and a 2-year survival rate of < 5% for patients with extensive-stage disease, the need to improve outcomes is apparent.[2]

The US cooperative groups, sponsored by the taxpayer-supported National Cancer Institute, as well as cooperative groups from Canada, Europe, and Asia, all play a critical role in overcoming the slow progress in SCLC drug development by incorporating SCLC-specific clinical trials into their respective research portfolios. Within the United States, there are 4 general oncology cooperative groups active in lung cancer research: the Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), North Central Cancer Treatment Group (NCCTG), and the Southwest Oncology Group (SWOG).[3] The CALGB, ECOG, and SWOG include member institutions from throughout the country, whereas NCCTG is a regional cooperative group centered at the Mayo Clinic. Within Canada, the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) oversees cooperative oncology efforts. In addition, a focused cooperative oncology

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group that plays a pivotal role and crosses the US/Canadian border is the Radiation Therapy Oncology Group (RTOG). The 2008 International Lung Cancer Congress (ILCC), now in its ninth year, provides a unique forum to gather representatives from the North American cooperative groups as well as international groups such as the European Organization for Research and Treatment of Cancer (EORTC) and the Japan Clinical Oncology Group (JCOG). This article, the fourth in a series that outlines the scientific vision of each group, will focus on clinical research in SCLC.

To provide a foundation for discussion, one must first consider current treatment perspectives in SCLC. The standard therapeutic approach for patients with limited-stage SCLC (LS-SCLC) who are not candidates for a clinical protocol is 4 cycles of chemotherapy with concurrent thoracic irradiation. Based on its preclinical synergy and superiority in efficacy and tolerability with concomitant irradiation, cisplatin and etoposide chemotherapy has supplanted alkylator/anthracycline–based regimens as the chemotherapy backbone.[4] Thoracic irradiation results in local control and a survival benefit; however, the timing of radiation appears critical.[5,6] For example, early concurrent chemoradiation yields a small, but significant, survival advantage when compared with late concurrent or sequential thoracic irradiation; yet, the optimal radiation dose and fractionation regimen remains controversial.[7,8] For patients with excellent performance status and an adequate baseline pulmonary reserve, administration of twice-daily thoracic irradiation to 45 Gy with cisplatin/etoposide has shown encouraging long-term survival results.[9] However, in practice, this schedule is logistically difficult to administer and yet unknown to be superior to a biologically equivalent dose of a once-daily thoracic irradiation regimen. Patients with LS-SCLC who attain a complete response (CR) after concurrent chemoradiation are offered prophylactic cranial irradiation (PCI) based on a meta-analysis reporting a 5.4% improvement in 3-year overall survival (OS; 20.7% PCI-treated vs. 15.3% control) and a 25% reduction in the incidence of brain metastases (33.1% PCI-treated vs. 58.6% control).[10]

In North America and Europe, the cornerstone of treatment for extensive-stage SCLC (ES-SCLC) consists of platinum (cisplatin or carboplatin) and etoposide chemotherapy. The primary role of radiation therapy is for palliating symptomatic sites of disease. Recently, PCI has been incorporated into the treatment algorithm on the basis of results from a phase III clinical trial randomizing 286 patients with ES-SCLC with any response to initial chemotherapy to either PCI or observation.[11] At 1 year, PCI significantly reduced the incidence of symptomatic brain metastases (14.4% PCI-treated vs. 40.4% control; hazard ratio [HR], 0.27; $P < .001$) and increased OS (27.1% PCI-treated vs. 13.3% control; [HR], 0.68; $P = .003$). Indeed, this has led to the recommendation that PCI be offered for patients with ES-SCLC who respond to first-line chemotherapy, after a thorough discussion of the potential risks and benefits.

Unfortunately, the disease recurs in the majority of patients shortly after initial treatment. Although second-line chemotherapy can result in tumor regression, responses are short-lived, and median survival is often < 6 months.[2] A key factor guiding the selection of future therapy, and its possible efficacy, is the type of response gained after exposure to a first-line platinum-based regimen. Historically, patients are classified into 1 of 3 groups of relapsed disease: platinum sensitive, platinum resistant, or refractory. Platinum sensitivity is arbitrarily defined as a chemotherapy-free interval > 90 days, whereas patients with platinum-resistant disease have recurrent disease within 90 days of completing chemotherapy.[2] Refractory SCLC refers to those who do not respond to, or progress during, first-line chemotherapy. Patients with platinum-resistant and refractory disease are often grouped together and generally have poor responses to subsequent chemotherapy (≤ 10%) and shorter median survivals than patients with platinum-sensitive disease. Although there is no standard second-line treatment option, a number of agents have shown single-agent activity, such as the camptothecin analogues (topotecan, irinotecan), paclitaxel, vinorelbine, and gemcitabine.[2] Multiple-agent regimens, such as retreatment with platinum/etoposide, are also a common treatment choice for platinum-sensitive tumors. In the late 1990s, a randomized phase III trial for patients with recurrent SCLC compared single-agent topotecan with cyclophosphamide, doxorubicin, and vincristine (CAV) and found topotecan to be equally efficacious but with greater palliative effects on common lung cancer symptoms.[12] Topotecan, as a result of its US Food and Drug Administration (FDA) approval for second-line SCLC therapy in platinum-sensitive relapsed disease, has emerged as the standard of comparison in most phase III clinical trials.[13]

These perspectives highlight the current state of SCLC management, which has not changed significantly in the past decade. We will now explore the scientific progress and research endeavors pursued by the large multi-institutional cooperative groups.

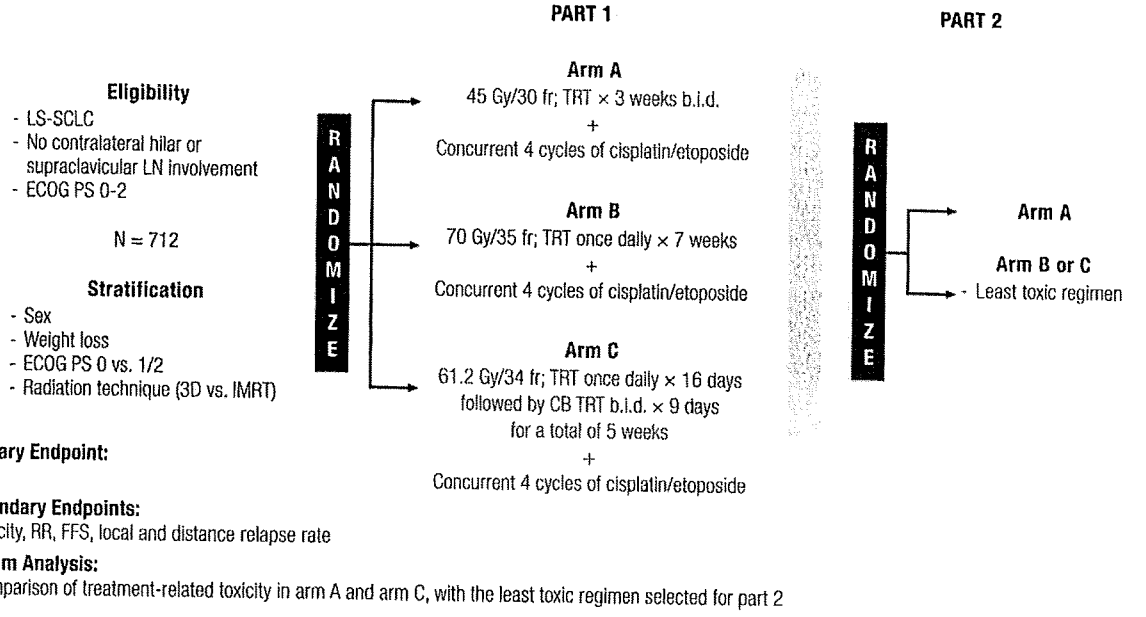
Cancer and Leukemia Group B

In 1987, the CALGB published a seminal report (CALGB 8083) describing the benefits of thoracic irradiation when given concurrently with chemotherapy for patients with LS-SCLC.[14] Improvements in local control, failure-free survival, and OS strengthened the case for shifting the standard of care to a chemoradiation therapy approach. Unfortunately, in 2009, many questions still remain unanswered regarding the optimal dose and delivery of thoracic irradiation.

Cancer and Leukemia Group B has been instrumental in exploring the 70-Gy maximum-tolerated dose (MTD) of once-daily radiation therapy in a phase II setting.[13,15] For example, CALGB conducted CALGB 39808, in which 57 patients with LS-SCLC were treated with 70 Gy in 35 once-daily fractions concurrently with carboplatin/etoposide following 2 cycles of induction paclitaxel and topotecan.[16] The reported 2-year survival was 48%, and the incidence of grade 3 dysphagia was 16%. However, the experience with 70 Gy of concurrent thoracic chemoradiation remains limited and, as a consequence, the de facto practice still calls for once-daily radiation therapy to be delivered at a total dose of 50-60 Gy in 1.8-2.0–Gy fractions.

Hyperfractionating radiation therapy is believed to offer additional clinical benefits. An Intergroup 0096 phase II trial randomized 417 patients to receive 4 cycles of cisplatin/etoposide with either 45 Gy of concurrent thoracic irradiation given twice daily over 3 weeks or once-daily for 5 weeks. Thoracic irradiation was scheduled to coincide with the start of chemotherapy. This pivotal trial found a significant 5-year OS benefit favoring twice-daily

Figure 1 **CALGB 30610/RTOG 0538 Treatment Schema: Phase III Trial Comparing Thoracic Radiation Therapy Regimens in Limited-Stage Small-Cell Lung Cancer**



Abbreviations: 3D = 3-dimensional conformal radiation therapy; b.i.d. = twice daily; CALGB = Cancer and Leukemia Group B; CB = concomitant boost; ECOG = Eastern Cooperative Oncology Group; FFS = failure-free survival; fr = fractions; IMRT = intensity-modulated radiation therapy; LN = lymph node; LS-SCLC = limited-stage small-cell lung cancer; OS = overall survival; PS = performance status; RR = response rate; RTOG = Radiation Therapy Oncology Group; TRT = thoracic radiation therapy

thoracic irradiation compared with once-daily fractionation (26% vs. 16%; $P = .04$) and a lower incidence of local failure (36% vs. 52%; $P = .06$).[9] Grade 3 esophagitis was the most significant toxicity with twice-daily radiation therapy (26% twice-daily vs. 11% once-daily), but the incidence of grade 4 esophagitis did not differ between regimens.

Radiation Therapy Oncology Group has examined an alternative fractionation scheme using a concomitant boost technique to escalate dose while keeping the total treatment duration at 5 weeks. Initially, thoracic irradiation is administered once-daily for 3 weeks, followed by 2 weeks of twice-daily thoracic irradiation. This dose/fractionation regimen is hypothesized to counteract accelerated repopulation, the increased tumor cell growth rate that is known to often occur several weeks into treatment. The MTD for the concomitant-boost technique, when combined with cisplatin/etoposide chemotherapy, has been determined at 61.2 Gy.[17] Thus, there are 3 plausible treatment regimens for delivering concurrent thoracic radiation therapy in LS-SCLC at relatively similar biologically effective doses: (1) CALGB's 70-Gy once-daily fractionation for 7 weeks, (2) the Intergroup 0096 regimen of 45-Gy twice-daily fractionation for 3 weeks, and (3) RTOG's 61.2-Gy concomitant-boost technique for 5 weeks duration.

To address the important radiation therapy questions of optimal dose and fractionation schemes, CALGB 30610, an Intergroup study, has now been developed (Figure 1). This pivotal phase III trial for patients with treatment-naive LS-SCLC is the first of its kind in well over a decade. It consists of 2 parts; part 1 has 3 treatment arms with patients randomized in a 1:2:2 fashion: arm A, 45 Gy (1.5 Gy twice daily × 3 weeks); arm B, 70 Gy (2.0 Gy once daily × 7 weeks); arm C, 61.2 Gy (1.8 Gy once daily × 16 days followed by 1.8 Gy twice daily × 9 days for a total duration of 5 weeks). Four cycles of cisplatin and etoposide are given concurrently, starting on day 1 of radiation therapy for all arms of this study. After interim analysis for toxicity assessment, only 1 experimental arm (arm B or arm C) will be selected for further accrual in part 2 of the study. The primary endpoint will be OS, and the projected total accrual is approximately 712 patients.

Several randomized trials have attempted to build on the platform of platinum/etoposide chemotherapy for ES-SCLC; however, these attempts have been met with disappointing results. For example, the addition of topotecan consolidation, paclitaxel, BEC2 vaccination, or thalidomide to the platinum/etoposide backbone have not shown any significant survival advantage.[18-22] Furthermore, CALGB 30103, a randomized phase II trial, evaluated the Bcl-2 antisense oligonucleotide, oblimersen (G3139), in combination with carboplatin/etoposide in 56 chemotherapy-naive patients with ES-SCLC. Although Bcl-2 is an overexpressed apoptotic inhibitor implicated in SCLC oncogenesis and chemotherapy resistance, CALGB 30103 suggested poorer clinical outcomes for patients who received oblimersen than for those who did not (1-year OS rates, 24% and 47%).[23]

Sunitinib, an oral small-molecule, multitargeted receptor tyrosine kinase inhibitor, has been FDA approved for the treatment of patients with renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumors. It has potent inhibitory effects of the platelet-derived growth factor receptors (PDGFRs)-α and

-β, vascular endothelial growth factor receptors (VEGFRs)-1, -2, and -3, stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT-3), colony stimulating factor receptor (CSF)-1R, and the glial cell line–derived neurotrophic factor receptor (RET). Given its promiscuity in inhibition, sunitinib is hypothesized to affect multiple hallmarks of cancer, including angiogenesis and tumor cell proliferation. CALGB 30504 is an ongoing phase I/II clinical trial investigating the combination of sunitinib plus cisplatin/etoposide for patients with ES-SCLC. The phase I portion of the trial will determine the MTD to be used for the phase II portion. Sunitinib will be given daily concurrent with 6 cycles of cisplatin/etoposide, followed by maintenance sunitinib until the development of progressive disease (PD) or excessive toxicity. The phase II portion of the trial will randomize patients, after initial treatment with sunitinib plus cisplatin/etoposide, to maintenance therapy with either sunitinib or placebo. The primary endpoint will be progression-free survival (PFS), with an accrual goal of 107 patients.

Eastern Cooperative Oncology Group

Bevacizumab, a monoclonal antibody (MoAb) targeting VEGF, has shown to improve survival when combined with chemotherapy in patients with advanced NSCLC, as described in the ECOG 4599 trial.[24] Given these positive results, further evaluation of bevacizumab was felt to be warranted in SCLC because of its high degree of vascularization and VEGF expression.[25] ECOG 3501, a phase II trial of bevacizumab with cisplatin/etoposide in ES-SCLC, has completed accrual. A 21-day cycle of intravenous (I.V.) cisplatin 60 mg/m^2 day 1, etoposide 120 mg/m^2 days 1-3 I.V., and bevacizumab 15 mg/m^2 day 1 was administered for 4 cycles with maintenance bevacizumab given thereafter until PD or unacceptable toxicity. The primary endpoint was to detect an improvement in 6-month PFS from 16% to 33% in 66 patients. Updated survival analysis reported at the 2008 ILCC showed a 6-month PFS of 35% and a 1-year OS rate of 37%.[26] Median PFS and OS were 4.7 months and 11.1 months, respectively. Of the evaluable patients, there were no grade 3/4 hemorrhagic events, despite the known predisposition for SCLC to be centrally located. In another nonrandomized phase II study, CALGB 3036, 72 patients with previously untreated ES-SCLC received a maximum of 6 cycles of cisplatin 30 mg/m^2 days 1 and 8 I.V., irinotecan 65 mg/m^2 days 1 and 8 I.V., and bevacizumab 15 mg/m^2 day 1 without maintenance therapy. The regimen was feasible, and the 1-year PFS and OS rates were 18.3% and 48.9% (median PFS, 7.1 months; median OS, 11.7 months), respectively.[27] VEGF and PDGF levels showed no correlation with response, PFS, or OS. Overall, these studies are forming the rationale for the industry to evaluate bevacizumab in the phase III setting.

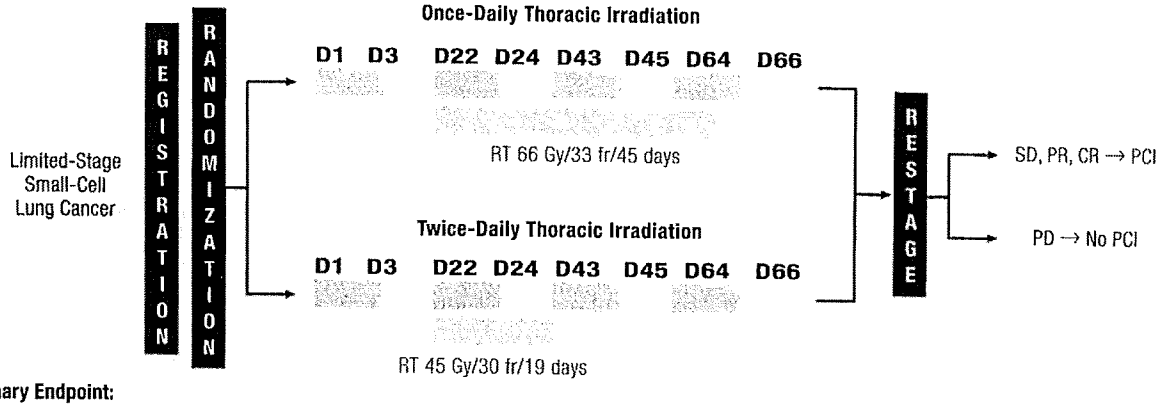
The Hedgehog (Hh) pathway is an essential embryonic signaling cascade implicated as an oncogenic catalyst in a variety of malignancies. There is evidence supporting persistent activation of the Hh pathway in SCLC, and in cell lines treated with a potent Hh inhibitor, cyclopamine, significant growth inhibition has been observed.[28,29] GDC-0449 is an orally bioavailable synthetic inhibitor of Hh signal transduction and has shown safety and clinical benefit in a phase I clinical trial for patients with advanced solid tumors.[30] Similarly, inhibition of the insulin-like growth factor (IGF) pathway is a promising new target with therapeutic efficacy in a variety of tumor models. This pathway is thought to mediate chemotherapy resistance as well as resistance to certain novel agents in SCLC.[31,32] Cixutumumab (IMC-A12), a MoAb targeting the IGF type 1 receptor (IGF-1R), is in clinical development. ECOG is proposing an ECOG 1508 three-armed, randomized phase II trial to determine "proof of activity." Patients with ES-SCLC will be randomized to receive (1) cisplatin/etoposide alone, (2) cisplatin/etoposide plus GDC-0449, or (3) cisplatin/etoposide plus cixutumumab for a total of four 21-day cycles. PFS is the planned primary endpoint, and the statistical design will include 74 patients per arm to have 85% power to detect a 33% reduction in the HR for PFS, corresponding to a 50% improvement in median PFS from 5.0 months to 7.5 months. Extensive correlative analysis will be integrated within this trial, with particular emphasis on Hh ligand and IGF-1R expression.

European Organization for the Research and Treatment of Cancer

The EORTC extends over multiple European countries and is a key contributor to clinical lung cancer research. Building upon the Intergroup 0096 study in LS-SCLC, the CONVERT (Concurrent ONce-daily VErsus Radiotherapy Twice-daily) trial hypothesizes that increasing the total dose of once-daily thoracic irradiation will improve efficacy and negate the benefit of twice-daily fractionation, thus making the once-daily regimen more practical and logistically easier to deliver. The CONVERT trial is a 2-arm, multicenter, randomized phase III Intergroup trial comparing a once-daily with a twice-daily schedule, given concurrently with cisplatin and etoposide (Figure 2). The radiation therapy regimen put forth by the Intergroup 0096 trial (45 Gy, twice-daily fractionation over 3 weeks) will be compared with 66 Gy, once-daily fractionation over 6.5 weeks. Unlike in the CALGB 30610 trial, thoracic irradiation will commence with the second cycle of chemotherapy. The primary endpoint will be OS, and the goal for accrual is 532 patients within a 4-year time span. The study is currently open in a number of EORTC member institutions.

Amrubicin is a novel cytotoxic agent being evaluated for the treatment of patients with ES-SCLC. It is a completely synthetic 9-amino-anthracycline that is converted to its ^{13}C alcohol metabolite amrubicinol, which has greater antitumor activity than its parent molecule, in stark contrast to the traditional anthracycline derivatives, doxorubicinol and daunorubicinol.[31] Moreover, amrubicin has been found to be less cardiotoxic than doxorubicin in animal models.[33] In a study of patients with refractory and sensitive relapsed SCLC, amrubicin has shown activity as a single agent. The overall response rate (ORR) was approximately 50% in each group, and the median PFS, median OS, and 1-year survival times in the refractory and sensitive groups were 2.6 months and 4.4 months, 10.3 months and 11.6 months, and 40% and 46%, respectively.[34] EORTC 08062 is a phase II trial equally randomizing chemotherapy-naive patients with ES-SCLC to 1 of 3 treatment arms: arm 1, amrubicin 45 mg/m^2 on days 1-3; arm 2, amrubicin 40 mg/m^2 on days 1-3 plus cisplatin 60 mg/m^2 on day 1; and arm 3, cisplatin 75

Figure 2 Treatment Schema: Phase III CONVERT Trial



[a]Maximum of 6 cycles of cisplatin/etoposide.
Abbreviations: CONVERT = Concurrent ONce-daily VErsus Radiotherapy Twice-daily; CR = complete response; D = day; fr = fractions; OS = overall survival; PCI = prophylactic cranial irradiation, PD = progressive disease; PFS = progression-free survival; PR = partial response; RT = radiation therapy; SD = stable disease

Table 1 Japan Clinical Oncology Group Research Portfolio of Ongoing and Proposed Clinical Trials in Small-Cell Lung Cancer

Protocol Number	Phase	Population	Reference Arm	Experimental Arm	Accrual Target, N	Primary Endpoint
JCOG 0202	III	Treatment-naive LS-SCLC	Cisplatin/etoposide + RT → Cisplatin/etoposide	Cisplatin/etoposide + RT → Cisplatin/irinotecan	250	Overall survival
JCOG 0509	III	Treatment-naive ES-SCLC	Cisplatin/irinotecan	Cisplatin/amrubicin	282	Overall survival
JCOG 0605	III	Relapsed SCLC: sensitive	Nogitecan	Cisplatin/etoposide/irinotecan	180	Overall survival
[a]PC 705	II	Relapsed SCLC: refractory	–	Amrubicin	80	Response rate

[a]Proposed clinical trial in development.
Abbreviations: ES-SCLC = extensive-stage small-cell lung cancer; JCOG = Japan Clinical Oncology Group; LS-SCLC = limited-stage small-cell lung cancer; PC = protocol concept; RT = radiation therapy; SCLC = small-cell lung cancer

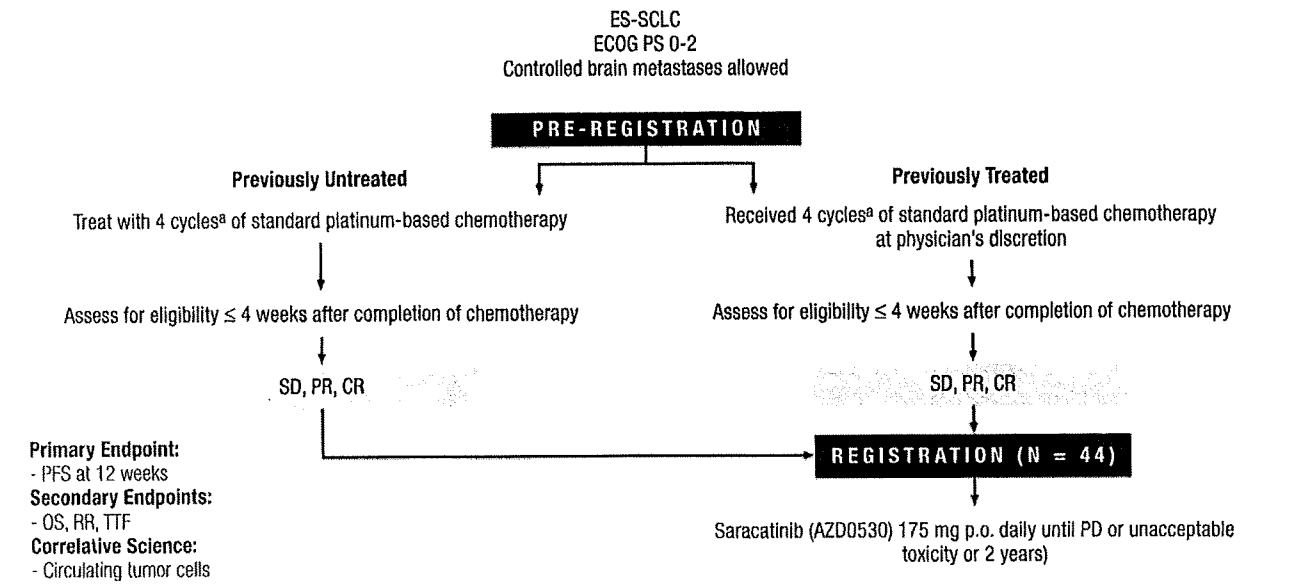
mg/m^2 on day 1 plus etoposide 100 mg/m^2 I.V. on day 1 followed by oral etoposide 200 mg/m^2 on days 2 and 3. In all arms, treatment is repeated every 21 days in the absence of progressive disease or unacceptable toxicity. Patients are stratified based on institution, sex, and performance status. The primary endpoint is RR, with secondary endpoints examining PFS, OS, and toxicity. Amrubicin is already approved in Japan and is currently being investigated in the United States in a multinational, randomized phase III trial for patients with SCLC who do not respond to first-line therapy. Considerable hope exists for this agent, but its role will need to be more clearly defined.

Finally, a proposal is in place for a phase II EORTC 08061 trial treating patients with chemotherapy-naive or sensitive relapsed ES-SCLC. Sunitinib will be given as a single oral agent (150-mg loading dose followed by 37.5 mg daily) until progressive disease. Disease control rate at 4 weeks after the start of treatment will be the primary endpoint.

Japan Clinical Oncology Group

Although there are a number of cooperative oncology groups in Japan, JCOG and the North Japan Lung Cancer Study Group (NJLCSG) are particularly active in SCLC research efforts. JCOG draws from its 190 participating institutions to enroll patients into its trials. In SCLC, there are 3 ongoing phase III trials, in addition to 1 phase II protocol in development that is evaluating amrubicin in the relapsed/refractory setting (Table 1). However, the featured trial at the 2008 ILCC was NJLCSG 0402, a randomized phase II trial comparing amrubicin with topotecan in previously treated SCLC. Sixty patients, stratified according to performance status and type of relapse (chemotherapy sensitive or refractory), were randomly assigned to receive amrubicin 40 mg/m^2 days 1-3 or topotecan 1 mg/m^2 days 1-5 for a minimum of three 21-day cycles. The primary endpoint of ORR was 38% for the amrubicin arm and 21% in the topotecan arm.[35] In sensitive relapse, the ORRs for amrubicin and topotecan were 53% and 21%, and in refractory relapse, 17% and 0%, respectively. There were no significant advantages of either therapy in median PFS and OS. Neutropenia was severe for those treated with amrubicin, with 79% of the patients experiencing grade 4 neutropenia and 14% of the patients experiencing febrile neutropenia. Moreover, 1 treatment-related death was observed resulting from sepsis. Encouragingly, amrubicin has activity, particularly in chemotherapy-refractory relapse, which is

Figure 3 NCCTG 0621 Treatment Schema: Phase II Trial of Saracatinib (AZD0530) in Extensive-Stage Small-Cell Lung Cancer



[a]1 cycle = 21 days
Abbreviations: CR = complete response; ECOG = Eastern Cooperative Oncology Group; ES-SCLC = extensive-stage small-cell lung cancer; NCCTG = North Central Cancer Treatment Group; OS = overall survival; PD = progressive disease; PFS = progression-free survival; p.o. = orally; PS = performance status; RR = response rate; SD = stable disease; TTF = time to treatment failure

notoriously difficult to treat. Results are limited by the small sample size but still warrant further evaluation in larger-scale trials.

North Central Cancer Treatment Group

The NCCTG is a regional cooperative network based in the Mayo Clinic in Minnesota with a number of centers scattered across the United States, Canada, and Puerto Rico. The NCCTG customarily focuses on phase II clinical trial designs with novel therapeutic agents and also participates in Intergroup protocols such as the ongoing CALGB 30610 trial described earlier. The NCCTG research portfolio recently featured a phase II NCCTG 0621 trial evaluating a novel oral c-SRC inhibitor, saracatinib (AZD0530), administered daily in nonprogressing patients with ES-SCLC who received a maximum of 4 cycles of standard platinum-based chemotherapy (Figure 3). The trial was designed for a primary endpoint of 12-week PFS, and secondary endpoints included RR, OS, and time to treatment failure. Incorporated within the study is an intriguing analysis of the effects of saracatinib treatment on the levels of circulating tumor cells (CTCs) as well as correlative science attempting to determine potential predictive markers of response in CTCs. Complete analysis of the results are eagerly anticipated.

National Cancer Institute of Canada Clinical Trials Group

The NCIC-CTG is the only adult cooperative oncology group based in Canada with a national membership supporting a spectrum of clinical trials ranging from phase I testing of novel therapeutic agents to the conduct of large, randomized, controlled phase III trials. The importance of its contributions to the treatment of lung cancer is well recognized. Historically, the NCIC-CTG has been an active participant of SCLC trials initiated by other cooperative groups. NCIC-CTG BR.28, also known as the previously described CONVERT trial, is one such effort that has recently opened to accrual in NCIC-CTG member institutions.

Radiation Therapy Oncology Group

In lung cancer, RTOG research endeavors are intended to decipher the optimal methods of using radiation therapy in a consistently effective and safe manner. Besides being a key collaborator in the CALGB 30610 trial, designated as RTOG 0538 within the group, RTOG has been instrumental in discerning the best method of delivering PCI in LS-SCLC. RTOG 0212, closed to accrual in February 2008, was designed to determine the optimal dose of PCI after a meta-analysis suggested a reduced incidence of brain metastases with higher PCI doses. Patients with LS-SCLC who were complete responders to primary treatment were randomized to receive standard (25-Gy/10-fraction/12 days) or higher PCI doses (36-Gy) administered using either conventional (18 fractions/24 days) or accelerated hyperfractionated radiation therapy (24 twice-daily fractions/16 days). This phase II/III trial had significant contributions from CALBG, ECOG, EORTC, and SWOG, with results presented at the 2008 American Society of Clinical Oncology meeting. A total of 720 patients were enrolled, and although there was a nonsignificant trend for reduced 2-year brain metastases incidence with high-dose PCI compared with standard-dose PCI (24% vs. 30%; $P = .13$), there was a significantly marked increase in chest relapse (48% vs. 40%; $P = .02$) and mortality (2-year OS 37% with high-dose PCI vs. 42% with standard-dose PCI; $P = .03$).[36] Thus, the prevailing PCI dose of 25 Gy remains the standard of care for LS-SCLC.

Intergroup 0096 showed a survival benefit using an accelerated fractionation schedule compared with daily radiation therapy. RTOG 0239, a phase II trial, evaluated an innovative radiation therapy design where once-daily radiation therapy along with concurrent chemotherapy was given followed by a hyperfractionated schedule, a concomitant boost, in LS-SCLC (61.2 Gy/34 fractions). This schedule was found to be tolerable but was associated with a high incidence of myelosuppression.[37] RTOG 0623 is a phase II trial designed to overcome this adverse event by incorporating filgrastim with concurrent chemoradiation therapy and pegfilgrastim, with adjuvant cisplatin/etoposide chemotherapy in patients with LS-SCLC. Historically, hematopoietic growth factors have not been recommended during combined modality chemoradiation therapy based on early theoretical concerns that growth factors might release progenitor cells and expose them to the damaging effects of radiation therapy, but significant improvements in supportive care and delivery of radiation therapy could make these concerns less applicable. The primary endpoint of RTOG 0623 is to evaluate the safety and efficacy of filgrastim in reducing grade ≥ 3 neutropenia when given with concurrent chemoradiation. Unfortunately, this trial is accruing poorly and is expected to close soon.

Southwest Oncology Group

The premier effort of the SWOG research portfolio in SCLC is the recently reported S0124 phase III trial, a study in which CALGB, ECOG, and NCCTG also participated as part of the Intergroup.[38] This protocol duplicated the treatment regimen of a small phase III study conducted by JCOG (JCOG 9511) demonstrating the superiority of the cisplatin/irinotecan combination over cisplatin/etoposide in patients with chemotherapy-naive ES-SCLC with respect to RR, PFS, and OS.[39] After an interim analysis, the trial was closed to further accrual, with only 154 patients entered. Because of its small sample size and possible effects from pharmacogenomic differences between Japanese and North American populations, further confirmatory studies were prompted.

In a comparative North American and Australian phase III trial directed by the Hoosier Oncology Group, 331 patients were randomized to receive a modified dose schedule of cisplatin/irinotecan or cisplatin/etoposide.[40] The modified treatment regimens were intended to improve delivery, reduce toxicity, and be more consistent with the dosages and schedules administered in the United States.[31] In this trial, there were no differences in outcome between cisplatin/irinotecan and cisplatin/etoposide. Because of the differing dose schedules, questions remained regarding the validity of cisplatin/irinotecan as an optimal regimen for ES-SCLC.

The Southwest Oncology Group sought to conduct a confirmatory, appropriately powered trial (S0124) by designing a similar study to JCOG 9511 by using identical cisplatin/irinotecan and cisplatin/etoposide treatment doses and schedules, thereby determining whether the results were reproducible and relevant to a Western population.[38] Correlative studies were incorporated to seek out the possible role of population-related pharmacogenomic variability in irinotecan metabolism due to genetic polymorphisms. Over a 4-year time span, 671 patients were randomized to receive a maximum of 4 cycles of either cisplatin 60 mg/m^2 on day 1 plus irinotecan 60 mg/m^2 on days 1, 8, and 15 every 28-days or cisplatin 30 mg/m^2 on day 1 plus etoposide 100 mg/m^2 on days 1-3 every 21-days. Patients were stratified based on performance status, number of metastatic sites, weight loss, and lactate dehydrogenase levels. The primary endpoint was OS. Cisplatin/irinotecan efficacy outcomes were similar to cisplatin/etoposide, with an ORR of 60% versus 57%, median PFS of 5.8 months versus 5.2 months (P = .07), and a median OS of 9.9 months versus 9.1 months (P = .71), respectively.[38]

Evaluation of the adverse events between the S0124 and JCOG9511 trials demonstrated a significantly higher hematologic toxicity in Japanese patients compared with North American patients with either treatment regimen ($P \leq .02$), but the incidence of nonhematologic toxicities did not differ significantly. Of those enrolled in the S0124 trial, 142 patient samples were analyzed for pharmacogenetic variability of select genes in irinotecan metabolism performed on genomic DNA from peripheral blood mononuclear cells. Intriguingly, significant correlations for genetic polymorphisms and hematologic and gastrointestinal toxicities were found.[38]

Thus, S0124 did not confirm the results of JCOG9511 in a Western population. The putative mechanisms underlying the differences in efficacy and toxicity are hypothesized to be related to allelic variants of genes involved in irinotecan metabolism. SWOG has confirmed that in North America, platinum/etoposide remains the standard of care for previously untreated ES-SCLC.

The Southwest Oncology Group also recently reported S0435, a phase II study investigating the role of sorafenib in ES-SCLC.[41] Sorafenib, an oral multikinase inhibitor with effects on tumor proliferation and angiogenesis, is FDA-approved for the treatment of advanced renal cell and hepatocellular carcinoma. Patients with ES-SCLC treated with only 1 previous platinum-based chemotherapy regimen were stratified according to platinum sensitivity and treated with sorafenib 400 mg orally twice daily on a continuous basis for a 28-day cycle. Of 80 evaluable patients, 3 patients with platinum-sensitive disease had a partial response (PR; 8%), whereas only 1 patient with platinum-resistant disease had a PR (2%). The stable-disease rates were similar between both groups (32% and 31%, respectively). Median PFS was 2 months for both strata, and OS was 7 months for platinum-sensitive patients and 5 months for platinum-resistant patients. Given these results and the general tolerability of sorafenib, further study of this agent in SCLC is warranted.

Conclusion

Through their capacity to offer a wide range of scientific and patient resources, multi-institutional cooperative groups have a vital responsibility to ensure that significant strides in SCLC research continue to be made. As many SCLC trials have traditionally been underpowered, the importance of large collaborative research efforts to maximize accrual cannot be overemphasized. In addition, the trend to incorporate translational science studies into each trial offers an avenue to discern the underlying mechanisms of SCLC chemotherapy resistance and to perhaps develop future prognostic and predictive biomarker profiles. However, considerable work remains in order to overcome 2 decades of stagnant gains in SCLC management. The focus has shifted to first optimizing the delivery

of known effective treatments, such as thoracic irradiation in LS-SCLC, before expanding upon the paradigm so that therapeutic advances are built on a solid foundation. Moreover, novel targeted agents will certainly be added to the SCLC treatment armamentarium, ideally based on strong preclinical rationale and an appropriate "druggable" target, but to date, no targeted therapy has been approved for patients with SCLC. Indeed, the ongoing and planned research endeavors of the cooperative group system are essential to ensure that the future progress for SCLC management remains encouraging.

Disclosures

Dr. Gandara has served on the Board of Directors or held other leadership positions with Response Genetics, Inc.; has received research funding from Abbott Laboratories, Bristol-Myers Squibb Company, and Eli Lilly and Company; has served as a paid consultant or been on an Advisory Board for AstraZeneca, Bayer Pharmaceuticals Corporation, Genentech, Inc., Pfizer Inc., Response Genetics, Inc., and sanofi-aventis U.S.; and is a member of the Speaker's Bureau for Eli Lilly and Company.

Dr. Saijo has held stock or equity ownership in Takeda Pharmaceuticals.

Dr. Baas has served as a paid consultant or been on an Advisory Board for Hospira; Merck & Co., Inc.; Pfizer Inc.

Dr. Vokes has received research funding from Bristol-Myers Squibb Company, Pfizer Inc., and Roche Pharmaceuticals; has served as a paid consultant or been on an Advisory Board for Bristol-Myers Squibb Company, Eli Lilly and Company, Genentech, Inc., ImClone Systems Incorporated, and OSI Pharmaceuticals; and is a member of the Speaker's Bureau for Genentech, Inc.

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References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008; 58:71-96.
2. Davies AM, Evans WK, Mackay JA, et al. Treatment of recurrent small cell lung cancer. *Hematol Oncol Clin North Am* 2004; 18:387-416.
3. Wakelee H, Langer C, Vokes E, et al. Cooperative group research efforts in lung cancer: focus on early-stage non-small-cell lung cancer. *Clin Lung Cancer* 2008; 9:9-15.
4. Sundstrom S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol* 2002; 20:4665-72.
5. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992; 327:1618-24.
6. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol* 1992; 10:890-5.
7. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1993; 11:336-44.
8. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. *J Clin Oncol* 2004; 22:4837-45.
9. Turrisi AT III, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999; 340:265-71.
10. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999; 341:476-84.
11. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007; 357:664-72.
12. von Pawel J, von Roemeling R, Gatzemeier U, et al. Tirapazamine plus cisplatin versus cisplatin in advanced non-small-cell lung cancer: A report of the international CATAPULT I study group. Cisplatin and Tirapazamine in Subjects with Advanced Previously Untreated Non-Small-Cell Lung Tumors. *J Clin Oncol* 2000; 18:1351-9.
13. Lally BE, Urbanic JJ, Blackstock AW, et al. Small cell lung cancer: have we made any progress over the last 25 years? *Oncologist* 2007; 12:1096-104.
14. Perry MC, Eaton WL, Propert KJ, et al. Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. *N Engl J Med* 1987; 316:912-8.
15. Choi NC, Herndon JE II, Rosenman J, et al. Phase I study to determine the maximum-tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily radiation schedules with concurrent chemotherapy for limited-stage small-cell lung cancer. *J Clin Oncol* 1998; 16:3528-36.
16. Bogart JA, Herndon JE II, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys* 2004; 59:460-8.
17. Komaki R, Swann RS, Ettinger DS, et al. Phase I study of thoracic radiation dose escalation with concurrent chemotherapy for patients with limited small-cell lung cancer: Report of Radiation Therapy Oncology Group (RTOG) protocol 97-12. *Int J Radiat Oncol Biol Phys* 2005; 62:342-50.
18. Gandara DR, Lara PN Jr, Natale R, et al. Progress in small-cell lung cancer: the lowest common denominator. *J Clin Oncol* 2008; 26:4236-8.
19. Schiller JH, Adak S, Cella D, et al. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593--a phase III trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2001; 19:2114-22.
20. Niell HB, Herndon JE II, Miller AA, et al. Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. *J Clin Oncol* 2005; 23:3752-9.
21. Giaccone G, Debruyne C, Felip E, et al. Phase III study of adjuvant vaccination with Bec2/bacille Calmette-Guerin in responding patients with limited-disease small-cell lung cancer (European Organisation for Research and Treatment of Cancer 08971-08971B; Silva Study). *J Clin Oncol* 2005; 23:6854-64.
22. Pujol JL, Breton JL, Gervais R, et al. Phase III double-blind, placebo-controlled study of thalidomide in extensive-disease small-cell lung cancer after response to chemotherapy: an intergroup study FNCLCC cleo04 IFCT 00-01. *J Clin Oncol* 2007; 25:3945-51.
23. Rudin CM, Salgia R, Wang X, et al. Randomized phase II Study of carboplatin and etoposide with or without the bcl-2 antisense oligonucleotide oblimersen for extensive-stage small-cell lung cancer: CALGB 30103. *J Clin Oncol* 2008; 26:870-6.
24. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; 355:2542-50.
25. Dowell J, Amirkhan RH, Lai WS, et al. Survival in small cell lung cancer (SCLC) is independent of vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX-2) expression. *Proc Am Soc Clin Oncol* 2003; 22: (Abstract 2451).
26. Sandler A, Szwaric S, Dowlati A, et al. A phase II study of cisplatin (P) plus etoposide (E) plus bevacizumab (B) for previously untreated extensive stage small cell lung cancer (SCLC) (E3501): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2007; 25(18 suppl):400s (Abstract 7564).
27. Ready N, Dudek AZ, Wang XF, et al. CALGB 30306: a phase II study of cisplatin (C), irinotecan (I) and bevacizumab (B) for untreated extensive stage small cell lung cancer (ES-SCLC). *J Clin Oncol* 2007; 25(18 suppl):400s (Abstract 7563).
28. Watkins DN, Berman DM, Burkholder SG, et al. Hedgehog signalling within airway epithelial progenitors and in small-cell lung cancer. *Nature* 2003; 422:313-7.
29. Subramanian J, Govindan R. Small cell, big problem! Stem cells, root cause? *Clin Lung Cancer* 2008; 9:252-3.
30. LoRusso PM, Rudin CM, Borad MJ, et al. A first-in-human, first-in-class, phase (ph) 1 study of systemic Hedgehog (Hh) pathway antagonist, GDC-0449, in patients (pts) with advanced solid tumors. *J Clin Oncol* 2008; 26(15 suppl):157s (Abstract 3516).
31. Sher T, Dy GK, Adjei AA. Small cell lung cancer. *Mayo Clin Proc* 2008; 83:355-67.
32. Tsurutani J, West KA, Sayyah J, et al. Inhibition of the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin pathway but not the MEK/ERK pathway attenuates laminin-mediated small cell lung cancer cellular survival and resistance to imatinib mesylate or chemotherapy. *Cancer Res* 2005; 65:8423-32.
33. Suzuki T, Minamide S, Iwasaki T, et al. Cardiotoxicity of a new anthracycline derivative (SM-5887) following intravenous administration to rabbits: comparative study with doxorubicin. *Invest New Drugs* 1997; 15:219-25.
34. Onoda S, Masuda N, Seto T, et al. Phase II trial of amrubicin for treatment of refractory or relapsed small-cell lung cancer: Thoracic Oncology Research Group Study 0301. *J Clin Oncol* 2006; 24:5448-53.
35. Inoue A, Sugawara S, Yamazaki K, et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. *J Clin Oncol* 2008; 26:5401-6.

36. Le Péchoux C, Hatton M, Kobierska A, et al. Randomized trial of standard dose to a higher dose prophylactic cranial irradiation (PCI) in limited-stage small cell cancer (SCLC) complete responders (CR): primary endpoint analysis (PCI99-01, IFCT 99-01, EORTC 22003-08004, RTOG 0212). *J Clin Oncol* 2008; 26(15 suppl):400s (Abstract LBA7514).
37. Komaki R, Moughan J, Ettinger D, et al. Toxicities in a phase II study of accelerated high dose thoracic radiation therapy (TRT) with concurrent chemotherapy for limited small cell lung cancer (LSCLC) (RTOG 0239). *J Clin Oncol* 2007; 25(18 suppl):438s (Abstract 7717).
38. Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S024.
39. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002; 346:85-91.
40. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006; 24:2038-43.
41. Gitlitz BJ, Glisson BS, Moon J, et al. Sorafenib in patients with platinum (plat) treated extensive stage small cell lung cancer (E-SCLC): A SWOG (S0435) phase II trial. *J Clin Oncol* 26(15 suppl):433s (Abstract 8039).

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

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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

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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 × 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.