Update in Lung Cancer 2006

Sarita Dubey[1] and Charles A. Powell[2]

[1]Division of Hematology and Oncology, University of California, San Francisco, California; and [2]Division of Pulmonary and Critical Care Medicine, Columbia University College of Physicians and Surgeons, New York, New York

LUNG CANCER RISK AND PREVENTION

It is clear that overall cancer mortality and lung cancer mortality in particular are correlated with prevalence of cigarette smoking. In the United States, recent declines in lung cancer death rates in men began in the mid- to late 1980s and parallel declines in smoking prevalence rates, and the mortality rate in women has plateaued (1). Smoking prevalence rates remain unacceptably high, at 21.6%, in the United States, however, and show signs of increasing in developing nations despite efforts to promote smoking prevention and improve strategies for successful smoking cessation. Seven smoking cessation pharmacologic agents are currently approved by the U.S. Food and Drug Administration. Of these, five are nicotine replacement therapies and one, bupropion SR, is hypothesized to aid smoking cessation by inhibition of dopamine reuptake (2).

Gonzalez and colleagues (3) and Jorenby and associates (4) report results of two phase III randomized controlled trials to determine continuous abstinence rates for 12 weeks of therapy with varenicline, which acts as an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist. These trials enrolled 1,025 and 1,027 patients, respectively, and reported 52-week abstinence rates of 21.9 and 23% for varenicline, which were significantly higher than for placebo and slightly higher than for buproprion. To determine if varenicline would prevent relapse in individuals who successfully stopped smoking at 12 weeks, Tonstad and coworkers (5) examined 52-week abstinence rates in patients treated with an additional 12 weeks of varenicline and reported significantly higher 52-week continuous abstinence rates compared with control. Varenicline represents a new pharmacologic class of smoking cessation aids that appears promising in clinical trials both for cessation and for relapse prevention.

Cigarette smoking causes lung cancer. Among lifetime smokers, 15% develop lung cancer. Approximately 10% of lung cancer cases arise in never-smokers (6). Risk is modified by exposure to secondhand smoke or to other lung carcinogens, such as radon, asbestos, or arsenic, and by unknown or known genetic susceptibility factors (7, 8) that modulate the injury response to exposure of the dozens of cigarette smoke carcinogens, such as acrolein (9). The contribution of exposure to low-dose ambient air pollution to lung cancer risk is controversial. Data supporting this association are provided by Laden and colleagues in an extended year follow-up report to the Harvard Six Cities cohort study (10). Lung cancer mortality was positively associated with exposure to fine particulate airborne matter smaller than 2.5 μm in diameter ($PM_{2.5}$). However, unlike cardiovascular mortality, lung cancer mortality did not decrease with pollution reduction. Overall, this study contributes to the existing evidence that exposure to airborne particulate pollution increases lung cancer mortality.

The importance of sex, race, ethnicity (11, 12), social status (13), and familial risk (14, 15) in lung cancer susceptibility and outcome is an active area of research. Lung cancer incidence rates have been increasing in women compared with men, suggesting that cancer susceptibility is higher in women. Although temporal trends in smoking prevalence may explain sex differences, other sex-related factors may be important. In a prospective cohort study of 16,925 participants in a lung cancer computed tomography (CT) screening trial, Henschke and associates (16) reported a point prevalence lung cancer rate of 2.1% in women and 1.2% in men. After controlling for age and smoking, the odds ratio for lung cancer risk in women was 1.7 (1.3–2.3). Although other studies support increased lung cancer susceptibility in women, large, well-controlled studies have generally not supported this finding (17, 18). As noted by Neugut and Jacobson, conflicting results of case-control and cohort susceptibility studies are more likely to be due to methodologic differences than to biological differences associated with sex (19). Henschke and colleagues also reported a difference in lung cancer survival, with an improved survival in women compared with men (odds ratio, 0.48; 95% confidence interval [CI], 0.25–0.89), adjusted for smoking, stage, cell type, and resection. Favorable lung cancer survival in women compared with men has been reported consistently; however, the biological basis for this association remains unclear.

SCREENING

Despite its position as the leading cause of cancer death in the United States, the incidence of lung cancer is less common than breast cancer in women and prostate cancer in men (1). However, the total number of deaths attributable to the three other most common cancers (breast, prostate, and colon) does not exceed the number of deaths attributable to lung cancer. The disparity in mortality is illustrated by the three-decade trend in 5-year survival rates. Prostate, breast, and colorectal carcinoma have all demonstrated significant improvements in 5-year survival over time, with survival rates that are currently 99, 89, and 64%, respectively. In contrast, the survival rate for lung cancer remains relatively flat and is currently 15%. There are several potential explanations for the disparity between lung cancer survival and that of the more common tumors. These explanations include late detection and histologic heterogeneity. Currently, more than 75% of new lung cancer diagnoses are in patients presenting with distant or regional metastatic disease. This rate is markedly higher than that of breast, colon, and

(*Received in original form February 5, 2007; accepted in final form February 5, 2007*)

Supported by the NIH (1RO1CA120174), the American Cancer Society (RSG-CNE-108857), the American Thoracic Society/Lungevity Foundation, and the Flight Attendants Medical Research Institute.

Correspondence and requests for reprints should be addressed to Charles A. Powell, M.D., Division of Pulmonary and Critical Care Medicine, Columbia University Medical Center, 630 West 168th Street, Box 91, New York, NY 10032. E-mail: cap6@columbia.edu

Am J Respir Crit Care Med Vol 175. pp 868–874, 2007
DOI: 10.1164/rccm.200702-190UP
Internet address: www.atsjournals.org

prostate cancer for which there are approved screening programs. In contrast, there is not an approved screening program for lung cancer. Encouraging recent reports suggest that screening with low-dose chest CT may provide clinical benefit; however, others suggest that overdiagnosis bias and low specificity may limit the overall utility of the procedure (20). The importance of overdiagnosis bias will be addressed by the ongoing randomized National Lung Screening Trial. Other recent studies have provided important information regarding the potential utility of low-dose CT scan screening and improved algorithms for management of nodules.

The International Early Lung Cancer Action program reported prevalence and follow-up results using low-dose CT in 31,567 asymptomatic individuals who were smokers or who were exposed to second-hand smoke or to occupation-related carcinogens (21). In line with previous studies, the cancer prevalence rate was 1.5%, with a predominance of adenocarcinoma (76%) and of clinical stage I tumors (85%). Interestingly, the prevalence of nodules was 13%, which was significantly lower than rates published previously by this group (22) and by others (23). This significant development promises to reduce the number of false positive studies. Nodule prevalence rates were likely influenced by modification of the definition of "positive" scans. In the current study, a nodule size cutoff of 5 mm was established for the scan to be read as positive, which is larger than the cut-off size used previously by this group and others. Although the probability of malignancy in small nodules is low, and despite the authors' assurance that no nodules less than 5 mm were ultimately found to be cancerous, it is plausible that some screen-detected nodules of less than 5 mm will be malignant, thus resulting in false negative studies. Continued evaluation of nodule work-up algorithms and examination of adjuvant tests to determine nodule malignancy will be important to optimize the clinical efficacy of CT screening. Examples of adjuvant testing include incorporation of computer-aided image diagnostic strategies (24) and genomics to identify cancer-specific gene signatures in specimens acquired by percutaneous biopsy (25, 26).

The safety of diagnostic percutaneous biopsy was examined by Wisnivesky and colleagues using 8,607 cases of stage I non–small cell lung cancer (NSCLC) in the Surveillance, Epidemiology, and End Results (SEER) registry and Medicare records (27). Lung cancer survival in patients who underwent biopsy was not different from those who did not. This study supports the safety of percutaneous biopsy as a strategy for evaluating indeterminate pulmonary nodules.

STAGING AND RESECTION FOR EARLY DISEASE

Advances in preoperative staging and thoracic surgical techniques have reduced invasive procedures related to lung cancer diagnosis and staging, and are also associated with reduced morbidity and complications. Yasufuku and colleagues prospectively examined the clinical utility of endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) for lung cancer staging (28). The sensitivity and specificity for mediastinal lymph node metastasis were 92.3 and 100%, respectively; these rates were significantly higher than those of CT and positron emission tomography. EBUS-TBNA is a promising technique, but the impressive diagnostic performance in this single-center, selected patient population study requires confirmation. The widespread implementation of video-assisted thoracoscopic techniques for lobectomy is associated with reduced patient length of stay, less postoperative pain (29), reduced blood loss, and equivalent long-term survival rates when compared with conventional surgical approaches in patients with stage IA disease (30). Although not yet specifically demonstrated, it is possible that video-assisted thoracoscopic lobectomy will reduce the incidence of lung cancer resection postoperative pneumonia, a "significant" complication with a reported incidence of 25% (31).

LUNG CARCINOGENESIS, INFLAMMATION, AND PROGRESSION

Recent lung cancer research has been directed at using molecular approaches to identify clinically relevant biological factors and pathways associated with histologic heterogeneity and progression for the purposes of facilitating early diagnosis, enhancing assessment of prognosis, and identifying novel therapeutic agents. Lucattelli and coworkers generated a neurokinin-1 receptor (NK-1R) knockout mouse to examine the role of this mediator of neurogenic inflammation in bleomycin-induced pulmonary fibrosis (32). Serendipitously, they observed adenocarcinoma in all bleomycin NK-1R knockout mice, but not in untreated animals, suggesting that the NK-1R pathway is required for DNA repair fidelity after injury. Ji and associates generated a conditional mouse with targeted expression of a mutant K-ras mutant allele in CC10-positive cells (33). In contrast to other K-ras mutant allele models (34, 35), the CC10 model was characterized by an exuberant inflammatory response composed of alveolar macrophages and neutrophils. This model, which demonstrated rapid progression and shortened survival, may provide potentially important insights into the role of inflammation in tumor progression. For example, Wislez and colleagues provided data that implicate chemokine receptor CXCR2 ligands in neoplastic progression in a related K-ras lung cancer model (36). These animal models provide information complementary to that obtained from genomic analysis of human tumors. Recent genomics studies, reviewed in Borczuk and Powell (37), support the role of inflammation pathways and provide additional insights into the importance of tumor differentiation in mediating lung adenocarcinoma progression.

EPIGENETICS

Three interrelated types of epigenetic information are DNA methylation, histone modification, and genomic imprinting (38). Alterations in DNA methylation and histone acetylation status are associated with aging and with environmental exposures, of which smoking and diet have been the best characterized (39). The preponderance of evidence in case-control studies and in animal studies strongly supports the association of cigarette smoking with DNA promoter hypermethylation, which is frequently detected in lung cells of smokers. Furthermore, these same genes are more frequently methylated in individuals with lung cancer compared with smoking control subjects, suggesting possible causation in the process of lung field carcinogenesis as indicated by clinical studies reported by Belinsky and associates and Machida and colleagues (40, 41).

Focus has been directed to environmental exposure effects on other epigenetic alterations, such as histone modification and DNA hypomethylation (42), the latter of which is relatively unstudied in lung cancer. New microarray-based methodologies for assessing global DNA methylation status, using single nucleotide polymorphism chips (MSNP) (43) and whole-genome tiling-array transcriptional profiling (44), will allow rapid analysis of genomewide losses and gains of DNA methylation, DNA copy number aberrations, and loss of heterozygosity using genomic DNA from human lung cancer tissues.

TREATMENT

For purposes of treatment, NSCLC can be divided into essentially three groups: early disease (surgery/adjuvant therapy),

locally advanced disease (combined chemotherapy and radiation), and advanced disease (systemic therapy). The most significant changes in management over the past 2 years have affected early and advanced disease.

Early Disease Adjuvant Therapy

The goal of adjuvant therapy after surgical resection is to reduce recurrence and increase cure rates. Adjuvant therapy has been an established modality in breast and colorectal cancers well before it became accepted in lung cancer.

Radiation therapy. After several early trials and a large meta-analysis, it has been accepted that postoperative radiation therapy (PORT) is detrimental in stage I and II (N0/N1) NSCLC. Despite decreasing local relapse in N2 disease, PORT has no survival advantage (45, 46). A recent meta-analysis of SEER data confirmed the detrimental effect in stage N0–N1, but surprisingly found improved overall survival for the stage N2 subgroup (hazard ratio [HR], 0.855; 95% CI, 0.76–0.95) (47). The difference in the results between the earlier studies and the recent analysis could be attributed to improved techniques in radiation delivery, linear accelerators, and three-dimensional planning. Thus, PORT should be considered for select patients with stage III disease with high risk for recurrence (i.e., multilevel N2 disease).

Chemotherapy. Early support for adjuvant chemotherapy arose in 1995 from a large meta-analysis of 14 trials that revealed a 5% increase in 5-year overall survival (OS) with cisplatin-based adjuvant chemotherapy (HR, 0.87; p = 0.08; 13% reduction in the risk of death) that was not statistically significant (48). However, the initial postmeta-analysis individual randomized controlled trials did not show a significant survival benefit (49–51). Subsequently, cisplatin-based randomized controlled trials have demonstrated a significant survival benefit of adjuvant chemotherapy in early NSCLC, with absolute survival improvements ranging from 5 to 15% (Table 1). In contrast to these trials, the Cancer and Leukemia Group B (CALGB) 9633 stage IB carboplatin-based trial failed to demonstrate a similar benefit (52, 53). The inclusion of stage IB–only patients, the use of carboplatin, and premature closure have been suggested as reasons for the negative results. Interestingly, in an unplanned subset analysis, adjuvant chemotherapy benefited patients with tumors 4 cm or larger (HR, 0.66; p = 0.04), but not those with tumors smaller than 4 cm (HR, 1.02; p = 0.51). Results of five large cisplatin-based studies [Italian/European Adjuvant Lung Cancer Project Italy (ALPI), British Big Lung Trial (BLT), International Adjuvant Lung Trial (IALT), JBR.10, and Adjuvant Navelbine International Trialist Association (ANITA)] were consolidated in the LACE (Lung Adjuvant Cisplatin Evaluation) meta-analysis (54). LACE showed adjuvant chemotherapy achieved a 5.3% absolute 5-year survival advantage (HR, 0.89; 95% CI, 0.82–0.96; p = 0.004). This study also highlighted certain key issues related to patient and drug selection that are discussed below.

Patient selection: stage. Although positive trials demonstrated the advantage of chemotherapy in stage II and IIIA disease, no clear advantage with adjuvant chemotherapy was seen in stage IB disease. The LACE meta-analysis confirmed this nonsignificant benefit in stage IB disease (HR, 0.92; 95% CI, 0.78–1.10), and suggested a detrimental effect of chemotherapy in stage IA disease (HR, 1.41; 95% CI, 0.96–2.09). The analysis confirmed the benefit of adjuvant chemotherapy in stages II and IIIA disease (HR, 0.83; 95% CI, 0.73–0.95). Taken together, LACE and the subset analysis of the CALGB 9633 study suggest that adjuvant chemotherapy should be considered and discussed with patients with large or high-risk stage IB tumors.

Patient selection: age. The median age at diagnosis of lung cancer is 70 years. Studies in the elderly with advanced disease indicate that performance status is more important than age in making treatment decisions. However, such information in the early disease setting was lacking until the retrospective analysis of JBR.10 (55). Among 155 patients who were 65 years and older, the 5-year OS was improved by 24% with chemotherapy (HR, 0.61; 95% CI, 0.38–0.98; p = 0.04). However, OS for those older than 75 years was worse than for the 66- to 74-year group with adjuvant chemotherapy (HR, 1.95; 95% CI, 1.11–3.41; p = 0.02).

Molecular predictors. Because lung cancer is a heterogeneous disease, patient outcomes and response to therapy are similarly heterogeneous and difficult to predict using conventional staging and morphology assessment. This is an important issue because, although adjuvant trials do not support routine administration of chemotherapy to all stage IA and IB patients for whom 5-year survival rates range from 60 to 85%, it is clear that some individual patients will benefit from such an approach. Recent studies suggest that gene expression signatures of resected tumors provide important information about the probability of postoperative recurrence and survival and that immunohistochemistry analysis may provide information about probability of drug response.

The lung "metagene" model, based on gene expression profiling of stage IA NSCLC (56), was found to be a better predictor of recurrence, with an accuracy of 72 to 90%, than a clinical model. Thus, the lung metagene may be a prognostic indicator of survival. Whether this molecular analysis will supplant conventional staging or provide supplemental information to that provided by clinical variables remains to be determined. Regardless, to ascertain its effect on decisions regarding administration

TABLE 1. RECENT POSITIVE ADJUVANT LUNG CANCER TRIALS

Study (reference)	No.	Stage	Chemotherapy Regimen	5-yr Survival (%)		p Value
				Control	Chemotherapy arm	
IALT (71)	1,867	I–IIIA	Cisplatin based Vin/VP/Vb/V	40	45	< 0.03
Japanese Lung Cancer Research group (72)	999	I	Uracil-tegafur	88	85	0.71
				90	89 (T1)	0.87
				74	85 (T2)	0.005
NCICTG (73)	482	IB/II	Cisplatin/Vin	54	69	0.03
ANITA trial (74)	840	IB–IIIA	Cisplatin/Vin	51	43	0.013
CALGB (53)	344	IB	Carboplatin/ paclitaxel	59	71 (4 yr)	0.028
				60	57 (5 yr)	0.32

Definition of abbreviations: ANITA = Adjuvant Navelbine International Trialist Association; CALGB = Cancer and Leukemia Group B; IALT = International Adjuvant Lung Trial; NCICTG = National Cancer Institute of Canada Trials Group; V = vindesine; Vb = vinblastine; Vin = vinorelbine; VP = etosposide.

of adjuvant chemotherapy, this model will need to be tested in a prospective fashion.

ERCC1 is a nucleoside excision repair enzyme, involved in repair of cisplatin-induced DNA adducts. In the IALT, cisplatin-based chemotherapy benefited those with ERCC1-negative tumors (HR, 0.65; 95% CI, 0.50–0.86; p = .002), whereas this benefit was lost in patients with ERCC1-positive tumors (HR, 1.14; 95% CI, 0.84–1.55; p = 0.40) (57). Thus, patients with ERCC1-positive tumors may not benefit from cisplatin-based adjuvant chemotherapy. The results of this retrospective study are significant and hypothesis generating, and should be pursued prospectively.

Adjuvant chemotherapy in lung cancer is now an established modality to improve cure rates in resected stage II and IIIA NSCLC. Chemotherapy should consist of cisplatin-based regimens unless contradicted by the patient's comorbid conditions. Adjuvant therapy should be offered to patients older than 65 years with good performance status. Further clarification is required concerning the management of patients with stage IB disease and those older than 75 years. Improved understanding of tumor biology and molecular predictors will further improve the benefit from adjuvant therapies.

Advanced Disease

Even though systemic chemotherapy is the mainstay of treatment for advanced NSCLC, its efficacy plateau has triggered the search for alternatives. Several critical pathways involved in tumor genesis have been identified together with the development of novel agents to target these pathways.

Epidermal growth factor inhibitors. Epidermal growth factor receptor (EGFR) is commonly overexpressed in NSCLC. Erlotinib, an EGFR tyrosine kinase inhibitor (TKI), was approved by the U.S. Food and Drug Administration based on BR.21, a randomized trial including patients with relapsed advanced-stage NSCLC. In this trial, patients receiving erlotinib had a median survival advantage of 2 months over those given placebo, with a 1-year survival of 31% (58).

Cetuximab is a chimeric antibody of EGFR. A recent phase II randomized study evaluated the role of cetuximab with carboplatin and paclitaxel in both concurrent and sequential designs (59). Preliminary outcomes were better with the concurrent arm; response rates and median survival were 37% and 10.5 months, respectively. This combination will be examined in a phase III study.

Angiogenesis inhibitors. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor, a primary mediator of angiogenesis that is commonly overexpressed in patients with lung cancer. A large phase III trial, Eastern Cooperative Oncology Group (ECOG) 4599, randomized patients with newly diagnosed nonsquamous NSCLC to standard-of-care carboplatin/paclitaxel, or to chemotherapy with bevacizumab (60). Squamous cell histology was excluded because of concern for increased hemorrhage that had been seen in earlier trials. The median survival of patients in the bevacizumab arm and the chemotherapy alone arm were 12.3 and 10.3 months, respectively (p = 0.003). The response rate and 1-year survivals were 35 and 51% in the experimental arm, and 15 and 44% in the chemotherapy-alone arm, respectively. As expected, the incidence of hemorrhage and hypertension was higher in the bevacizumab arm. There were 17 treatment-related deaths (2, chemotherapy; 15, experimental arm). Among the 15 deaths in patients randomized to bevacizumab, 7 were related to hemorrhage. Pulmonary hemorrhage was more common in patients with large cavitary tumors that were adjacent to large blood vessels and in patients with a prior history of hemoptysis. Response and adverse events data suggest the drug acts in part independently of angiogenesis inhibition; further research directed to bevacizumab's mechanisms of action will provide important information that will guide future trials. Thus, bevacizumab, in combination with chemotherapy, has demonstrated improved outcomes in advanced NSCLC and is now U.S. Food and Drug Administration–approved for use in first-line combination chemotherapy regimens for advanced-stage NSCLC. Patient selection is crucial to optimize safety. Those with history of thromboembolic disorders requiring anticoagulation, brain metastases, and prior hemoptysis are not eligible candidates.

Targeting one pathway can lead to resistance from compensatory mechanisms in other pathways, thus providing a rationale for combination regimens that target multiple pathways. The combination of erlotinib/bevacizumab was evaluated in a phase II trial with pretreated patients and compared with chemotherapy using docetaxel or pemetrexed as well as with the combination of chemotherapy/bevacizumab (61). OS was better in both the bevacizumab arms than the chemotherapy alone arms: 6-month survival rate, 62% (chemotherapy), versus 72% (chemotherapy/bevacizumab), versus 78% (erlotinib/bevacizumab). Erlotinib/bevacizumab is now being examined in a phase III trial in the same patient population. Combined inhibition can also be achieved with multitargeted TKIs, which are in various stages of investigation (Table 2).

Other targets. The ubiquitin–proteasome complex degrades several proteins, including those involved in cellular inflammatory response and tumor growth. The proteasome inhibitor bortezomib causes cell cycle arrest and apoptosis of tumor cells (62). Early results from a phase II combination study of bortezomib and cisplatin/gemcitabine (63) show a response rate of 21%, and median survival of 11 months. These promising findings are comparable to those found with other regimens used in newly diagnosed disease.

Up-regulation of the PI3K/Akt/mTOR pathway occurs in a variety of solid tumors. Preliminary results of a phase I trial of the mTOR inhibitor everolimus in combination with erlotinib are promising (64). However, overlapping toxicities, such as severe rash and stomatitis, have required modification of this study. Moving forward, identification of active combinations may be slowed by overlapping and unanticipated toxicity profiles.

Molecular predictors of response to TKIs. The overall response rate to TKIs in advanced disease is approximately 10%. Therefore, research has been directed toward development of diagnostic assays to predict response in individual patients. *EGFR* gene amplification by fluorescent *in situ* hybridization

TABLE 2. INHIBITORS OF ANGIOGENESIS

Drug	Target
Bevacizumab	Monoclonal antibody to VEGF
AE-941	Inhibits VEGF binding and MMPI
IMC-1C11	Monoclonal antibody to VEGFR 2
VEGF Trap/AVE-005	Fusion protein of VEGFR 1 and 2
Multitargeted Tyrosine Kinase Inhibitors	
PTK787	VEGFR 1,2,3, PDGFR, c-Kit
SU11248	VEGFR 1,2,3, PDGFR, Ret
AMG 706	VEGFR 1,2,3, PDGFR, Ret
GW786034	VEGFR 1,2,3, PDGFR, c-Kit
AZD2171	VEGFR 1,2,3, PDGFR
ZD6474	VEGFR 2, EGFR
Sorafenib	VEGFR 2, PDGFR, Raf

Definition of abbreviations: EGFR = epidermal growth factor receptor; MMPI = matrix metalloproteinase inhibitor; PDGFR = platelet-derived growth factor receptor; Ret = rearranged in transcription; VEGFR = vascular endothelial growth factor receptor

TABLE 3. EGFR GENE AMPLIFICATION–BASED MEDIAN SURVIVAL FROM THE ISEL TRIAL

	Gefitinib (*mo*)	Placebo (*mo*)	HR for Death, Gefitinib vs. Placebo
High gene copy number	8.3	4.5	0.61 (95% CI, 0.36–1.04) p = 0.06
Low gene copy number	4.3	6.2	HR, 1.16 (95% CI, 0.81–1.64) p = 0.417
HR for death high vs. low copy number	HR, 0.78 (95% CI, 0.54–1.13)	HR, 1.41 (95% CI, 0.84–2.35)	

Definition of abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; ISEL = IRESSA Survival Evaluation in Lung Cancer.

Data from Reference 69.

(FISH), EGFR expression by immunohistochemistry, and *EGFR* mutation analysis have been the most studied diagnostic techniques. The *EGFR* mutation (65, 66) is commonly found in exons 18–21 of the *EGFR* gene. The response to gefitinib, an EGFR-TKI, was higher in patients with the mutation than in those without (46 vs. 10%, p = 0.005) (67). The presence or absence of the mutation does not affect the survival of patients who receive gefitinib. On the other hand, in the Iressa NSCLC Trial Assessing Combination Treatment (INTACT) trials of chemotherapy with or without gefitinib, patients with mutation had a better survival than those without, regardless of their treatment regimens (HR, 0.48; 95% CI, 0.29–0.82), suggesting that the mutation may be a favorable prognostic indicator rather than a predictor of response to a particular therapy. Similarly, *EGFR* gene amplification was associated with higher survival regardless of gefitinib therapy (median survival > 20 mo in patients with amplification vs. 10.2 mo in those without amplification; HR, 0.46; 95% CI, 0.25–0.83). In contrast, two studies supported gene amplification as a predictor of outcome in response to treatment with EGFR-TK1. In BR.21, those with *EGFR* gene amplification had better survival with erlotinib compared with placebo (HR for death, 0.44; 95% CI, 0.23–0.82; p = 0.008) (68). Similar to BR.21, the IRESSA Survival Evaluation in Lung Cancer (ISEL) trial compared gefitinib and placebo and observed that the survival improvement from gefitinib in comparison with placebo was significantly higher in those with high gene copy number than those with low gene copy number (p = 0.045). The best survival was seen in patients who were FISH positive and received gefitinib, whereas patients who were FISH negative and received gefitinib had the worst survival (Table 3) (69). This analysis validated gene amplification as a predictor of outcome to treatment with EGFR-TKI rather than a prognostic indicator. High EGFR protein expression has been associated with increased response to gefitinib (8% high expression vs. 2% low expression) and erlotinib (11 vs. 4%). Similarly, the HR for death was lower for high expressers treated with gefitinib (HR, 0.77; 95% CI, 0.56–1.08; p = 0.126) or erlotinib (HR, 0.68; 95% CI, 0.49–0.95; p = 0.02). Interestingly, Kras mutation, unlike *EGFR* mutation, is more often detected in smokers and is associated with resistance to EGFR inhibitors (69, 70).

So what are the implications, at present, of our understanding of *EGFR* mutations? *EGFR* mutation predicts response to EGFR-TKIs, without an impact on survival. *EGFR* gene amplification predicts better response and better survival. At this time, there is no consensus on the predictive versus prognostic abilities of these markers. Differences in technologies and trial designs may have influenced these results. Extrapolation of these results suggests that patients who neither have gene amplification nor protein expression are less likely to benefit from treatment with such agents.

CONCLUSION

Advances in lung cancer therapy have led to modest improvements in survival of patients with early or advanced disease. Areas that need further research include early detection techniques and valid screening methodologies for patients at high risk for lung cancer. Drug resistance limits the efficacy of current therapeutic approaches. The adoption of multitargeted approaches has the potential to overcome such resistance and will be explored in ongoing trials of multitargeted agents and novel combinations. Prospective validation of predictive biomarkers in therapeutic trials is warranted to individualize treatment decisions based on tumor signatures.

Conflict of Interest Statement: Neither author has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43–66.
2. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, *et al.* A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685–691.
3. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR. Varenicline, an alpha4-beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:47–55.
4. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:56–63.
5. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006;296:64–71.
6. Spitz MR, Wei Q, Dong Q, Amos CI, Wu X. Genetic susceptibility to lung cancer: the role of DNA damage and repair. *Cancer Epidemiol Biomarkers Prev* 2003;12:689–698.
7. Ye Z, Song H, Higgins JP, Pharoah P, Danesh J. Five glutathione s-transferase gene variants in 23,452 cases of lung cancer and 30,397 controls: meta-analysis of 130 studies. *PLoS Med* 2006;3:e91.
8. Miller DP, Asomaning K, Liu G, Wain JC, Lynch TJ, Neuberg D, Su L, Christiani DC. An association between glutathione S-transferase P1 gene polymorphism and younger age at onset of lung carcinoma. *Cancer* 2006;107:1570–1577.
9. Feng Z, Hu W, Hu Y, Tang MS. Acrolein is a major cigarette-related lung cancer agent: preferential binding at p53 mutational hotspots and inhibition of DNA repair. *Proc Natl Acad Sci USA* 2006;103:15404–15409.
10. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med* 2006;173:667–672.
11. Haiman CA, Stram DO, Wilkens LR, Pike MC, Kolonel LN, Henderson BE, Le Marchand L. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med* 2006;354:333–342.
12. Howe HL, Wu X, Ries LA, Cokkinides V, Ahmed F, Jemal A, Miller B, Williams M, Ward E, Wingo PA, *et al.* Annual report to the nation on the status of cancer, 1975–2003, featuring cancer among US Hispanic/Latino populations. *Cancer* 2006;107:1711–1742.
13. Jha P, Peto R, Zatonski W, Boreham J, Jarvis MJ, Lopez AD. Social inequalities in male mortality, and in male mortality from smoking:

indirect estimation from national death rates in England and Wales, Poland, and North America. *Lancet* 2006;368:367–370.
14. Schwartz AG, Ruckdeschel JC. Familial lung cancer: genetic susceptibility and relationship to chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:16–22.
15. Nitadori J, Inoue M, Iwasaki M, Otani T, Sasazuki S, Nagai K, Tsugane S. Association between lung cancer incidence and family history of lung cancer: data from a large-scale population-based cohort study, the JPHC study. *Chest* 2006;130:968–975.
16. Henschke CI, Yip R, Miettinen OS. Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer. *JAMA* 2006;296:180–184.
17. Bain C, Feskanich D, Speizer FE, Thun M, Hertzmark E, Rosner BA, Colditz GA. Lung cancer rates in men and women with comparable histories of smoking. *J Natl Cancer Inst* 2004;96:826–834.
18. Vollset SE, Tverdal A, Gjessing HK. Smoking and deaths between 40 and 70 years of age in women and men. *Ann Intern Med* 2006;144:381–389.
19. Neugut AI, Jacobson JS. Women and lung cancer: gender equality at a crossroad? *JAMA* 2006;296:218–219.
20. Patz EF Jr. Lung cancer screening, overdiagnosis bias, and reevaluation of the Mayo Lung Project. *J Natl Cancer Inst* 2006;98:724–725.
21. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355:1763–1771.
22. Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, Libby DM, Pasmantier MW, Koizumi J, Altorki NK, *et al.* Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999;354:99–105.
23. Swensen SJ, Jett JR, Sloan JA, Midthun DE, Hartman TE, Sykes AM, Aughenbaugh GL, Zink FE, Hillman SL, Noetzel GR, *et al.* Screening for lung cancer with low-dose spiral computed tomography. *Am J Respir Crit Care Med* 2002;165:508–513.
24. Way TW, Hadjiiski LM, Sahiner B, Chan HP, Cascade PN, Kazerooni EA, Bogot N, Zhou C. Computer-aided diagnosis of pulmonary nodules on CT scans: segmentation and classification using 3D active contours. *Med Phys* 2006;33:2323–2337.
25. Gordon GJ, Deters LA, Nitz MD, Lieberman BC, Yeap BY, Bueno R. Differential diagnosis of solitary lung nodules with gene expression ratios. *J Thorac Cardiovasc Surg* 2006;132:621–627.
26. Borczuk AC, Shah L, Pearson GDN, Walter KL, Wang L, Austin JHM, Friedman RA, Powell CA. Molecular signatures in biopsy specimens of lung cancer. *Am J Respir Crit Care Med* 2004;170:167–174.
27. Wisnivesky JP, Henschke CI, Yankelevitz DF. Diagnostic percutaneous transthoracic needle biopsy does not affect survival in stage I lung cancer. *Am J Respir Crit Care Med* 2006;174:684–688.
28. Yasufuku K, Nakajima T, Motoori K, Sekine Y, Shibuya K, Hiroshima K, Fujisawa T. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. *Chest* 2006;130:710–718.
29. Onaitis MW, Petersen RP, Balderson SS, Toloza E, Burfeind WR, Harpole DH Jr, D'Amico TA. Thoracoscopic lobectomy is a safe and versatile procedure: experience with 500 consecutive patients. *Ann Surg* 2006;244:420–425.
30. Shigemura N, Akashi A, Funaki S, Nakagiri T, Inoue M, Sawabata N, Shiono H, Minami M, Takeuchi Y, Okumura M, *et al.* Long-term outcomes after a variety of video-assisted thoracoscopic lobectomy approaches for clinical stage IA lung cancer: a multi-institutional study. *J Thorac Cardiovasc Surg* 2006;132:507–512.
31. Schussler O, Alifano M, Dermine H, Strano S, Casetta A, Sepulveda S, Chafik A, Coignard S, Rabbat A, Regnard JF. Postoperative pneumonia after major lung resection. *Am J Respir Crit Care Med* 2006;173:1161–1169.
32. Lucattelli M, Fineschi S, Geppetti P, Gerard NP, Lungarella G. Neurokinin-1 receptor blockade and murine lung tumorigenesis. *Am J Respir Crit Care Med* 2006;174:674–683.
33. Ji H, Houghton AM, Mariani TJ, Perera S, Kim CB, Padera R, Tonon G, McNamara K, Marconcini LA, Hezel A, *et al.* K-ras activation generates an inflammatory response in lung tumors. *Oncogene* 2006;25:2105–2112.
34. Jackson EL, Willis N, Mercer K, Bronson RT, Crowley D, Montoya R, Jacks T, Tuveson DA. Analysis of lung tumor initiation and progression using conditional expression of oncogenic *K-ras. Genes Dev* 2001;15:3243–3248.
35. Fisher GH, Wellen SL, Klimstra D, Lenczowski JM, Tichelaar JW, Lizak MJ, Whitsett JA, Koretsky A, Varmus HE. Induction and apoptotic regression of lung adenocarcinomas by regulation of a *K-Ras* transgene in the presence of and absence of tumor suppressor genes. *Genes Dev* 2001;15:3249–3262.
36. Wislez M, Fujimoto N, Izzo JG, Hanna AE, Cody DD, Langley RR, Tang H, Burdick MD, Sato M, Minna JD, *et al.* High expression of ligands for chemokine receptor CXCR2 in alveolar epithelial neoplasia induced by oncogenic Kras. *Cancer Res* 2006;66:4198–4207.
37. Borczuk AC, Powell CA. Expression profiling and lung cancer development. *Proc Am Thorac Soc* 2007;4:127–132.
38. Feinberg AP, Tycko B. The history of cancer epigenetics. *Nat Rev Cancer* 2004;4:143–153.
39. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet* 2003;33:245–254.
40. Belinsky SA, Liechty KC, Gentry FD, Wolf HJ, Rogers J, Vu K, Haney J, Kennedy TC, Hirsch FR, Miller Y, *et al.* Promoter hypermethylation of multiple genes in sputum precedes lung cancer incidence in a high-risk cohort. *Cancer Res* 2006;66:3338–3344.
41. Machida EO, Brock MV, Hooker CM, Nakayama J, Ishida A, Amano J, Picchi MA, Belinsky SA, Herman JG, Taniguchi SI, *et al*. Hypermethylation of ASC/TMS1 is a sputum marker for late-stage lung cancer. *Cancer Res* 2006;66:6210–6218.
42. Suzuki K, Suzuki I, Leodolter A, Alonso S, Horiuchi S, Yamashita K, Perucho M. Global DNA demethylation in gastrointestinal cancer is age dependent and precedes genomic damage. *Cancer Cell* 2006;9:199–207.
43. Yuan E, Haghighi F, White S, Costa R, McMinn J, Chun K, Minden M, Tycko B. A single nucleotide polymorphism chip-based method for combined genetic and epigenetic profiling: validation in decitabine therapy and tumor/normal comparisons. *Cancer Res* 2006;66:3443–3451.
44. Zhang X, Yazaki J, Sundaresan A, Cokus S, Chan SW, Chen H, Henderson IR, Shinn P, Pellegrini M, Jacobsen SE, *et al.* Genome-wide high-resolution mapping and functional analysis of DNA methylation in arabidopsis. *Cell* 2006;126:1189–1201.
45. Stephens RJ, Girling DJ, Bleehen NM, Moghissi K, Yosef HM, Machin D. The role of post-operative radiotherapy in non-small-cell lung cancer: a multicentre randomised trial in patients with pathologically staged T1–2, N1–2, M0 disease. Medical Research Council Lung Cancer Working Party. *Br J Cancer* 1996;74:632–639.
46. PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet* 1998;352:257–263.
47. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* 2006;24:2998–3006.
48. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995;311:899–909.
49. Keller SM, Adak S, Wagner H, Herskovic A, Komaki R, Brooks BJ, Perry MC, Livingston RB, Johnson DH. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. *N Engl J Med* 2000;343:1217–1222.
50. Scagliotti GV, Fossati R, Torri V, Crino L, Giaccone G, Silvano G, Martelli M, Clerici M, Cognetti F, Tonato M. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 2003;95:1453–1461.
51. Waller D, Peake MD, Stephens RJ, Gower NH, Milroy R, Parmar MK, Rudd RM, Spiro SG. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *Eur J Cardiothorac Surg* 2004;26:173–182.
52. Strauss GM, Herndon J, Maddaus MA, Johnstone DW, Johnson EA, Watson DM, Sugarbaker DJ, Schilsky RL, Green MR. Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): report of Cancer and Leukemia Group B (CALGB). Protocol 9633. *J Clin Oncol* (Meeting Abstracts) 2004;22:7019.
53. Strauss GM, Herndon JE II, Maddaus MA, Johnstone DW, Johnson EA, Watson DM, Sugarbaker DJ, Schilsky RA, Vokes EE, Green MR. Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): update of Cancer and Leukemia Group B (CALGB) protocol 9633. *J Clin Oncol* (Meeting Abstracts) 2006;24:7007.
54. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Le Chevalier T. Lung Adjuvant Cisplatin Evaluation

(LACE): a pooled analysis of five randomized clinical trials including 4,584 patients. *J Clin Oncol* (Meeting Abstracts) 2006;24:7008.
55. Pepe C, Hasan B, Winton T, Seymour L, Pater J, Livingston R, Johnson D, Rigas J, Ding K, Shepherd F. Adjuvant chemotherapy in elderly patients: an analysis of National Cancer Institute of Canada Clinical Trials Group and Intergroup BR.10. *J Clin Oncol* (Meeting Abstracts) 2006;24:7009.
56. Potti A, Mukherjee S, Petersen R, Dressman HK, Bild A, Koontz J, Kratzke R, Watson MA, Kelley M, Ginsburg GS, *et al.* A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. *N Engl J Med* 2006;355:570–580.
57. Olaussen KA, Dunant A, Fouret P, Brambilla E, Andre F, Haddad V, Taranchon E, Filipits M, Pirker R, Popper HH, *et al.* DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med* 2006;355:983–991.
58. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, *et al*. The National Cancer Institute of Canada Clinical Trials. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–132.
59. Kelly K, Herbst RS, Crowley JJ, McCoy J, Atkins JN, Lara PN Jr, Dakhil SR, Albain KS, Kim ES, Gandara DR. Concurrent chemotherapy plus cetuximab or chemotherapy followed by cetuximab in advanced non-small cell lung cancer (NSCLC): a randomized phase II selectional trial SWOG 0342. *J Clin Oncol* (Meeting Abstracts) 2006;24:7015.
60. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–2550.
61. Fehrenbacher L, O'Neill V, Belani CP, Bonomi P, Hart L, Melnyk O, Sandler A, Ramies D, Herbst RS. A phase II, multicenter, randomized clinical trial to evaluate the efficacy and safety of bevacizumab in combination with either chemotherapy (docetaxel or pemetrexed) or erlotinib hydrochloride compared with chemotherapy alone for treatment of recurrent or refractory non-small cell lung cancer. *J Clin Oncol* (Meeting Abstracts) 2006;24:7062.
62. Borczuk AC, Cappellini GC, Kim HK, Hesdorffer M, Taub RN, Powell CA. Molecular profiling of malignant peritoneal mesothelioma identifies the ubiquitin-proteasome pathway as a therapeutic target in poor prognosis tumors. *Oncogene* 2007;26:610–617.
63. Davies AM, McCoy J, Lara PN Jr, Gumerlock PH, Crowley J, Gandara DR. Bortezomib + gemcitabine (Gem)/carboplatin (Carbo) results in encouraging survival in advanced non-small cell lung cancer (NSCLC): results of a phase II Southwest Oncology Group (SWOG) trial (S0339). *J Clin Oncol* (Meeting Abstracts) 2006;24:7017.
64. Papadimitrakopoulou V, Blumenschein G, Rollins M, Adjei AA, Dimitrijevic S, Kunz T, Discala L, Johnson BE. A phase I/II study investigating the combination of RAD001(R) (everolimus) and erlotinib (E) as 2nd/3rd line therapy in patients (pts)with advanced non-small cell lung cancer (NSCLC) previously treated with chemotherapy. *J Clin Oncol* 2006;24:17039.
65. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129–2139.
66. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497–1500.
67. Bell DW, Lynch TJ, Haserlat SM, Harris PL, Okimoto RA, Brannigan BW, Sgroi DC, Muir B, Riemenschneider MJ, Iacona RB, *et al.* Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. *J Clin Oncol* 2005;23:8081–8092.
68. Tsao M-S, Sakurada A, Cutz J-C, Zhu C-Q, Kamel-Reid S, Squire J, Lorimer I, Zhang T, Liu N, Daneshmand M, *et al*. Erlotinib in lung cancer: molecular and clinical predictors of outcome. *N Engl J Med* 2005;353:133–144.
69. Hirsch FR, Varella-Garcia M, Bunn PA Jr, Franklin WA, Dziadziuszko R, Thatcher N, Chang A, Parikh P, Pereira JR, Ciuleanu T, *et al.* Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* 2006;24:5034–5042.
70. Eberhard DA, Johnson BE, Amler LC, Goddard AD, Heldens SL, Herbst RS, Ince WL, Janne PA, Januario T, Johnson DH, *et al.* Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005;23:5900–5909.
71. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004; 350:351–360.
72. Kato H, Ichinose Y, Ohta M, Hata E, Tsubota N, Tada H, Watanabe Y, Wada H, Tsuboi M, Hamajima N, *et al.* A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004;350:1713–1721.
73. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, Cormier Y, Goss G, Inculet R, Vallieres E, *et al*. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005;352:2589–2597.
74. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzales-Larriba JL, Grodzki T, Pereira JR, Le Groumellec A, Lorusso V, *et al.* Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006;7:719–727.