Adjuvant Chemotherapy for Resected Non–Small-Cell Lung Cancer

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Because of the high rate of distant disease recurrence, the 5-year survival of patients who have undergone complete surgical resection of localized non–small-cell lung cancer (NSCLC) is approximately 50%. Initial results from early studies of adjuvant postoperative chemotherapy reported an adverse effect of alkylating agent and older chemotherapy regimens on survival. Cisplatin-based combinations were the first to show a survival advantage. A 1995 meta-analysis of these studies suggested a 13% reduction in the hazard ratio for death (HR = 0.87), leading to a 5% survival benefit at 5 years. Still, these trials involved limited numbers of patients (N = 1,394), and the results failed to reach statistical significance (P = .08). Of the five largest subsequent randomized trials of platinum-based adjuvant therapy, three showed a significant survival advantage. Although it is impossible to determine the reasons for the differing outcomes of these studies, several key features distinguish them, and the data suggest that medically fit patients with resected stage IB or II NSCLC should be offered chemotherapy with a platinum/new drug combination.

Surgery is potentially curative and represents the most appropriate treatment modality for medically fit patients who present with localized non-small-cell lung cancer (NSCLC; stage I, II, and IIIA without N2 involvement). Despite complete surgical resection, however, recurrence rates remain unsatisfactorily high. The majority of patients who relapse do so with distant metastatic disease, highlighting the need for effective systemic adjuvant therapy. Until recently, convincing evidence for the benefit of postoperative adjuvant chemotherapy has been lacking. However, recent studies have demonstrated the value of modern platinum-based chemotherapy and also of uracil/tegafur (UFT) in defined populations of patients with resected NSCLC. The overall 5-year survival of patients following resection of NSCLC is only about 50%. The major determinant for survival is the stage of the tumor, reflecting the importance of tumor size and particularly lymph node involvement. In American Joint Committee on Cancer (AJCC) pathologic stage I cancer survival is approximately 64.6%, while in stage II disease survival falls to 41.2%.[1] Survival is highest in pathologic stage IA disease (pIA), with 5-year survival rates of 69% to 83% depending on the surgical series. In contrast, the 5-year survival for pIIIA is only about 23%.[2] Other factors that influence survival include histologic subtype (improved survival in squamous cell carcinoma vs adenocarcinoma), involvement of multiple lymph nodes, involvement of multiple levels of N2 disease, and the presence of extranodal extension. Molecular markers such as Ras, p53, and EGFR, although thought to be important, have not consistently been shown to be of prognostic significance. Rationale for Adjuvant Therapy The majority of deaths occur as a result of recurrent disease. Analysis of the pattern of failure in patients who relapse following primary resection of NSCLC reveals that local recurrence occurring in isolation accounts for only about one-quarter of relapses (Table 1).[3-10] Distant recurrence alone or in combination with local recurrence occurs considerably more frequently. The brain is the most frequent site of recurrent metastatic disease, followed by bone and the contralateral lung. These data draw attention to the importance of unrecognized micrometastatic disease present at the time of operation. It is of concern that sensitive immunohistochemical techniques (using antibody to cytokeratin 18) have demonstrated the presence of micrometastatic disease in the bone marrow of as many as 28% to 60% of patients undergoing surgical resection thought not to have evidence of extrathoracic disease after conventional staging.[11-13]
The rationale for adjuvant systemic therapy is that postoperative chemotherapy can eliminate residual sites of micrometastatic disease following surgical resection of the primary tumor and prevent the subsequent emergence of incurable clinical disease. It is based on the observation in experimental models that there is an inverse relationship between tumor burden and potential curability by drugs.[14,15] This may be mediated by factors such as the increased proportion of actively dividing cells in micrometastatic deposits, reduced opportunities for the emergence of drug resistance, and improved access of drug to tumor cells. Support for this concept is provided by the demonstrated effectiveness of adjuvant chemotherapy in breast cancer, colorectal cancer, and a growing list of other tumor types including early-stage ovarian cancer and soft-tissue sarcomas of the extremities. In NSCLC, early trials of postoperative adjuvant chemotherapy revealed a detrimental effect of alkylating agent and older chemotherapy regimens on survival.[16] Subsequent studies performed with cisplatin-based combinations were the first to suggest a survival advantage. The magnitude of the survival benefit in these early studies, when seen, was small and often counterbalanced by the toxicities of the agents used. However, recent studies using more effective and less toxic modern platinum-based combinations have provided convincing evidence for the value of adjuvant chemotherapy for NSCLC. These studies and those evaluating a parallel strategy of postoperative adjuvant therapy with UFT treatment are discussed below.

Platinum-Based Adjuvant Chemotherapy

Trials of adjuvant cisplatin-based chemotherapy for completely resected NSCLC commenced in the 1970s. Several of these early trials evaluated cisplatin in combination with cyclophosphamide and doxorubicin, a combination widely used in patients with advanced disease at that time. These included the Lung Cancer Study Group (LCSG) trial 772[17] in which 141 patients with resected stage II or III NSCLC were randomized to CAP chemotherapy (six cycles of monthly cyclophosphamide at 400 mg/m², doxorubicin [Adriamycin] at 40 mg/m², and cisplatin [Platinol] at 40 mg/m²) or intrapleural BCG (TheraCys, TICE BCG) and 6 months of oral levamisole (Ergamisol). Although the recurrence rate was significantly reduced in patients receiving CAP, the improvement in median survival failed to reach statistical significance. Another LCSG study (LCSG 791) randomized 172 patients to postoperative CAP plus thoracic radiotherapy or to thoracic radiotherapy alone.[18] Again improvements were observed in median survival which did not reach statistical significance (20 vs 13 months, \(P = .113\)). A third LCSG study (LCSG 801) randomized 269 patients with resected T1, N1 or T2, N0 NSCLC to four cycles of CAP chemotherapy or no treatment.[19] No difference in time to recurrence or median survival was found with CAP chemotherapy. A small Finnish study[20] found a beneficial effect on 5- and 10-year survival of six cycles of postoperative CAP chemotherapy compared with no treatment in 110 patients. However, after adjustment for an imbalance in randomization (more patients underwent pneumonectomies in the observation arm and thus had potentially less favorable disease), the results lost significance. Other randomized trials
evaluated postoperative cisplatin and vindesine (alone[21] or followed by UFT[22]) or cisplatin in combination with doxorubicin followed by UFT.[23] Many of these studies suffered from difficulties in accruing patients, heterogeneity in patient populations, and difficulties in delivering full doses of chemotherapy. All failed to demonstrate an unequivocal survival advantage for adjuvant platinum-containing chemotherapy. **Meta-analysis**

Recognition of the difficulties in detecting small but potentially real survival benefits in individual trials with limited sample size led to a metaanalysis using updated individual patient data conducted by the Non-Small Cell Lung Cancer Collaborative Group reported in 1995.[16] The meta-analysis incorporated data from 52 randomized trials encompassing 9,387 patients. Included were eight trials (1,394 patients, 614 deaths) that evaluated the role of cisplatin-based combination chemotherapy following surgery. These trials used cisplatin in a range of doses (50 to 240 mg/m$^2$ total dose) and in various combinations with doxorubicin, cyclophosphamide, and vindesine. A 13% reduction in the risk of death was observed in favor of chemotherapy plus surgery compared with surgery alone, which translated to an absolute benefit from chemotherapy of 5% at 5 years (Figure 1).[8] However, the result fell short of statistical significance with 95% confidence intervals (CIs) ranging from a detriment of 1% to a benefit of 10% for adjuvant chemotherapy (hazard ratio [HR] = 0.87; $P = .08$). This contrasted with the clear benefit of chemotherapy for patients with advanced disease where a 27% reduction in the risk of death was demonstrated (HR = 0.73; $P < .0001$).
Figure 1: Meta-analysis of Adjuvant Chemotherapy Studies in Non–Small-Cell Lung Cancer—A 1998 meta-analysis of early postoperative studies of cisplatin-based chemotherapy from the Non-Small Cell Lung Cancer Collaborative Group. (A) Forrest plot, where individual trials are represented by squares, the center of which denotes the hazard ratio for that trial, with horizontal bars indicating 95% and 99% confidence intervals. The size of the square is directly proportional to the amount of information in the trial. The diamond denotes the overall hazard ratio when the results of all trials are combined (0.87; P = .08). (B) Survival in trials of surgery vs surgery plus platinum chemotherapy. HR = haz-
Trials

In spite of the lack of statistical significance, the suggestion of activity of adjuvant cisplatin-based chemotherapy evident in meta-analysis encouraged the initiation of a large number of randomized studies of postoperative adjuvant chemotherapy, many of which have been recently reported (Table 2).[24-31] The two largest studies and arguably the only studies sufficiently powered to detect an improvement in survival of the size suggested by the meta-analysis were the Adjuvant Lung Project Italy (ALPI) and the International Adjuvant Lung Trial (IALT) study. These two randomized trials provided apparently contradictory results.

**ALPI Trial** - The ALPI study randomized 1,209 patients with resected stage I (42%), II (31%), or IIIA (27%) NSCLC to receive chemotherapy with three postoperative cycles of the triplet combination MVP (mitomycin at 8 mg/m² on day 1, vindesine at 3 mg/m² on days 1 and 8, and cisplatin at 100 mg/m² on day 1 every 3 weeks) or no chemotherapy. Postoperative radiotherapy was permitted at the discretion of the participating centers and was given to about 65% of patients in the MVP arm and 82% of the patients in the control arm. Results were reported on 1,088 patients (13 patients were ineligible, and 108 patients from one center were excluded because of concerns about data integrity). After median follow-up of 64.5 months no significant difference in overall survival was observed (HR = 0.96, 95% CI = 0.81-1.13; P = .589). Progression- free survival favored chemotherapy, but was not statistically significant (HR = 0.89, 95% CI = 0.76-1.03; P = .128). Only 69% received the planned three cycles of MVP chemotherapy.
IALT Trial

The IALT was a large international study that evaluated the effect of adjuvant chemotherapy with cisplatin plus a vinca alkaloid or etoposide compared with no adjuvant therapy in patients with resected NSCLC. A total of 1,867 patients with completely resected stage I-III NSCLC were recruited by 148 centers in 33 countries. The study utilized an open choice design to facilitate accrual. Each participating center could determine the pathologic stages of disease to include, the dose of cisplatin given per cycle, the drug that was combined with cisplatin, and the postoperative radiotherapy policy. The chemotherapy options included 3 or 4 cycles of cisplatin (with doses ranging from 80 to 120 mg/m²) in combination with etoposide (49.3%), vinorelbine (26.8%), vinblastine (11.0%), or vindesine (5.8%). A total of 73.8% of patients received at least 240 mg/m² of cisplatin. In the chemotherapy group 7.8% did not receive any chemotherapy. Seven patients (0.8%) died from chemotherapy related toxicity. Postoperative radiotherapy was given to slightly more patients in the control group (27.7%) than in the chemotherapy group (22.9%). In contrast to the ALPI study, after a median follow-up of 56 months in the IALT study both overall and disease- free survival were found to be significantly improved in the group receiving chemotherapy. An absolute improvement in 2-year survival of 3.6% (70.3% vs 66.7%) and 5-year survival of 4.1% (44.5% vs 40.4%) was seen in the chemotherapy group (HR = 0.86, 95% CI = 0.76-0.98; P < .003). Disease-free survival was also improved in the chemotherapy arm (P < .003) with an absolute difference in deaths or recurrence of 5.1% at 5 years. Subset analyses showed the greatest improvement in overall survival in patients with resected stage III disease.

Discrepancies Between ALPI and IALT Trials

There are several possible explanations for the discrepancy between the positive IALT study and the negative ALPI trial. A mitomycincontaining triplet combination (MVP) was used in the ALPI trial, while in the IALT trial several cisplatin-based doublet combinations were used. Recent randomized studies have shown that two-drug regimens are less toxic and possibly more efficacious than three-drug regimens such as MVP.[32-35] The negative impact of toxic chemotherapy is likely to be of particular importance in the population of NSCLC patients who frequently suffer from multiple comorbidities and is likely to negate any beneficial effect on survival. Consistent with this is the excess of early deaths (< 12 months from randomization) seen in the chemotherapy arm of the ALPI study (90 patients in the MVP arm and 69 patients in the control arm). Furthermore, improved delivery of chemotherapy was possible in IALT (74%) compared with the ALPI study (69%), although a subset analysis from ALPI did not suggest that this was sufficient to explain the negative result of the study. A further contributory factor is likely to be the use of postoperative thoracic radiotherapy (PORT). A recent update of the PORT meta-analysis[ 36] based on the results of 10 randomized controlled trials and 2,232 individuals continued to show, as did the 1998 meta-analysis,[37] that there was a detrimental effect of surgery followed by postoperative radiotherapy, with an 18% increased relative risk of death (HR = 1.18; P = .02). Postoperative radiotherapy, which is likely to contribute additive toxicity to adjuvant chemotherapy, was used in more patients in the ALPI study than in the IALT study.

Big Lung Trial

In addition to the IALT and ALPI studies several other adjuvant studies have been performed, often in small or heterogeneous patient populations. The Big Lung Trial (BLT) was a large European multicenter randomized trial designed to evaluate the value of cisplatin- based chemotherapy in a heterogeneous group of patients with NSCLC. A total of 1,394 patients were enrolled, of which 381 who had been treated with surgery (with or without radiotherapy) were randomized to receive chemotherapy (n = 192) or no chemotherapy (n = 189).[26] Chemotherapy consisted of three 3-weekly cycles of either CV (cisplatin, vindesine), MIC (mitomycin, ifosfamide, cisplatin), MVP (mitomycin, vinblastine, cisplatin), or NP (vinorelbine, cisplatin). In total, 52 patients (14%) received radiotherapy. No survival benefit was observed for the use of adjuvant chemotherapy (HR = 1.02; P = .9). Significant toxicity was observed (28% grade 3 or 4 toxicity), including six treatment related deaths. Interestingly, despite the lack of benefit in the surgical setting, the BLT trial demonstrated an improved survival in the setting of advanced disease using the same cisplatin- based combination regimens.[38] Again, it is likely that the toxicity of the chemotherapy and the use of postoperative radiotherapy contributed to the negative results in the postoperative setting.
Other Trials

and Meta-analyses

Several other small trials, each with a sample size of less than 150 randomized patients, have also been recently reported. Two trials—a Chinese study of cisplatin/cyclophosphamide/vincristine/doxorubicin/lomustine (CeeNu) followed by tegafur in stage I-III NSCLC[27] and a Japanese study of cisplatin/vindesine in pN2 NSCLC[28]—also failed to show evidence of benefit. In contrast, a study of 66 patients with stage IB disease randomized to postoperative chemotherapy with six cycles of cisplatin and etoposide or observation[29] reported an improvement in 5-year survival (63% in the adjuvant group and 45% in the control group, \( P = .04 \)). Abstracted data from the studies above have been incorporated into two recent meta-analyses. Hotta et al[39] performed a meta-analysis of eight
recent trials,\cite{24-29,40,41} including 3,825 patients and more than 1,900 events, and found a summary hazard ratio of 0.891 (95% CI = 0.815-0.975; \(P = .012\)) in favor of adjuvant cisplatin-based chemotherapy compared with surgery alone. Sedrakyan et al\cite{42} updated the 1995 meta-analysis with the results of four recent studies of cisplatin-based adjuvant chemotherapy,\cite{24-26,29} including 3,402 patients and 1,769 events, and found an updated summary hazard ratio of 0.89 (95% CI = 0.82-0.96; \(P = .003\)). Despite the limitations of these metaanalyses, which did not use updated individual patient data,\cite{43} they showed the magnitude of the beneficial effect of chemotherapy to be similar to that observed in the original meta-analysis (HR = 0.87), albeit with narrowed confidence intervals and improved statistical significance. **NCIC-CTG JBR10 and CALGB 9633**

Two randomized studies of postoperative adjuvant treatment presented at the 2004 annual meeting of the American Society of Clinical Oncology have spurred interest in this strategy. These studies, the National Cancer Institute of Canada (NCIC) Clinical Trials Group study JBR10 and the Cancer and Leukemia Group B (CALGB) trial 9633, used new third-generation platinum combinations in more defined patient populations with early-stage disease and reported markedly improved reductions in the risk of death when compared with earlier studies (Figure 2).

**CALGB 9633**-In CALGB 9633 patients with completely resected stage IB (T2, N0) tumors were randomized to receive postoperative treatment with four cycles of carboplatin (area under the concentration-time curve [AUC] of 6) in combination with paclitaxel (200 mg/m\(^2\)) every 3 weeks or observation alone. This study was closed in November 2003 prior to reaching its accrual goal of 384 patients following a planned interim analysis which found that the level of significance for the improvement in survival due to chemotherapy exceeded the prespecified stopping boundary. Results were reported for 344 enrolled patients after a median followup of 36 months\cite{36}; 85% of patients received all four planned cycles. Grade 3 or 4 neutropenia was seen in 36% but there were no treatment-related deaths. The overall survival at 4 years was 71% in the carboplatin/paclitaxel group compared with 59% in the control group (HR = 0.62; \(P = .028\)). Lung cancer mortality was reduced approximately 50% in those receiving adjuvant chemotherapy (11% vs 19.9%; HR = 0.51; \(P = .018\)). No difference in deaths due to other causes was seen.
Further Considerations—Several reasons have been proposed to explain the vastly improved survival due to chemotherapy seen in JBR10 (15% at 5 years) and CALGB 9633 (12% at 4 years) compared to the approximately 5% benefit seen in the 1995 meta-analysis and in IALT. Firstly, these studies used modern chemotherapy combinations incorporating new agents which are better tolerated and known to have improved activity in advanced disease compared with older agents. This is likely to favorably influence the balance between early mortality due to treatment toxicity and the beneficial effect on survival due to activity against micrometastatic disease of the chemotherapy. Secondly, neither of these studies allowed for the use of postoperative thoracic radiotherapy. Finally, both studies included defined subsets of patients, stage IB in CALGB 9633, or IB and II (excluding T3, N0) in JBR10 rather than the heterogenous populations included in earlier studies.

**UFT-Based Adjuvant Chemotherapy** A series of Japanese trials have evaluated the effects of long-term administration of the oral agent UFT following surgery.[45] UFT is a combination of tegafur (ftorafur) plus uracil administered orally in a 1:4 molar ratio. Tegafur is a fluorouracil (5-FU) derivative that is well absorbed orally and is converted to 5-FU by cytochrome P-450 in the liver. Concomitant administration of uracil inhibits degradation of 5-FU, allowing for more sustained tissue concentrations of the active drug. In the postoperative adjuvant setting randomized studies have been reported of UFT given either alone for 6 months to 2 years or given in combination with cisplatin-based chemotherapy (summarized in Table 3).[22,23,40,41,46-49] **WJSG-2nd Study** The West Japan Study Group-2nd study (WJSG-2nd Study) randomized 323 patients with NSCLC (stage I-III) to postoperative treatment with cisplatin at 50 mg/m² for one cycle and vindesine at 2 to 3 mg/m² for three cycles followed by 1 year of UFT at 400 mg/kg/d (CV-UFT group), 1 year of UFT (UFT group), or observation alone (control group).[22] Greater toxicity was observed in the CV-UFT group compared with the UFT group, and a slightly lower, though not significantly different, total dose of UFT was administered in the CV-UFT group compared with the UFT group (102 ± 59.8 g vs 116.4 ± 57.2 g). The 5-year survival rates were 60.6% for the CV-UFT group and 64.1% for the UFT group compared with 49.0% for the control group. The difference was statistically significant compared to the control group for both the CV-UFT group (P = .037) and the UFT group (P = .009).

**Other Trials**
Several other trials have evaluated cisplatin-based chemotherapy followed by UFT. A study conducted by the Study Group for Adjuvant Chemotherapy for Lung Cancer (SGALC) randomized patients with resected stage I-III NSCLC to cisplatin (66 mg/m² * 1), doxorubicin (26 mg/m² * 1) and UFT (8 mg/kg/d) for 6 months or observation.[23] Although on initial analysis there was no difference in survival, after reanalysis for an imbalance in pN stage, the adjusted survival rate and disease-free survival rate for the chemotherapy-UFT group was improved compared with the control group (P = .044 and P = .036, respectively). Wada et al.[46] reported the results of surgery alone or surgery followed by postoperative treatment with PVM and UFT (cisplatin at 80 mg/m²/day 1, vindesine at 2-3 mg/m² day 1 and/or 8, and mitomycin at 8 mg/m² day 1 followed by 400 mg/d of UFT for 1 year) in 225 eligible patients with stage I or II NSCLC. No significant difference in 5-year survival was seen (71.1% vs 76.8%, P = .39). Two other smaller studies (containing 100 or fewer patients)[40,41] reported no improvement with the adjuvant combination chemotherapy-UFT over observation alone. Following up the results of the WJSG-2nd Study, the same group narrowed its focus to patients with pathologic stage I NSCLC (WJSG-4th Study).[49] Here 332 patients were randomized to the surgery alone (control group) or treatment with UFT at 400 mg/m² for 1 year after surgery (UFT group). Although the 5- and 8-year survival rates for the UFT group were 82.2% and 73.0%, and those for the control group were 75.9% and 61.2%, respectively, no statistically significant improvement in survival was achieved by UFT administration (P = .105). Similar results were seen in the North East Japan Study Group.[47] Here 221 patients with resected stage I/II NSCLC were assigned to 2 years of treatment with UFT or observation. Five-year overall survival rates for the UFT and control groups were similar at 79% and 75%, respectively (P = .7013). **Japan Lung Cancer Research Group Trial**
In the largest adjuvant UFT study performed, the Japan Lung Cancer Research Group evaluated 2 years of postoperative treatment with UFT (250 mg/m² of tegafur) compared to placebo in 979 eligible patients with completely resected pathologic stage I adenocarcinoma of the lung.[48] The rate of compliance was 74% at 1 year and 61% at 2 years. Grade 3 toxicity was only seen in 10 out of the 482 patients receiving UFT and no grade 4 toxicity was observed. After a median follow-up of 72 months, overall 5-year survival was modestly improved in patients receiving UFT compared with placebo: 88% compared with 85% (P = .04). However, no benefit was seen in patients with T1, N0...
tumors (HR = 0.97; \( P = .87 \)). Meta-analysis
A meta-analysis has been performed incorporating individual patient data from the four published studies above and two unpublished studies in which patients had been treated with single-agent UFT or observation.[50] Adjuvant chemotherapy with UFT was found to significantly improve overall survival. The 5-year overall survival rates were 81.8% for the UFT arm and 77.2% for the surgery alone arm (HR = 0.77, 95% CI = 0.63-0.94; \( P = .011 \)) and 7-year overall survival rates were 76.5% for the UFT arm and 69.5% for the surgery alone arm (HR = 0.74, 95% CI = 0.61-0.88; \( P = .001 \)).

Further Considerations
Intriguingly, the overall response rate of UFT given alone in advanced NSCLC is only 6% to 8%.[45] The reason why UFT is effective in the adjuvant setting despite its modest direct antitumor effect remains unclear. The prolonged duration of administration and possible antiangiogenic activity have been suggested to be important. Importantly, the magnitude of the benefit of UFT, while comparable with that seen in the 1995 metaanalysis of cisplatin-based adjuvant chemotherapy, is less than that observed with the modern regimens used in CALGB 9633 and NCIC JBR10. Studies of adjuvant UFT outside Japan have not been reported, and UFT is not available in the United States.

Studies With Other Agents
Several other agents have been evaluated as postoperative adjuvant treatments for NSCLC. The 1995 meta-analysis clearly demonstrated a detriment for the use of alkylating agent chemotherapy with a 15% increase in the risk of death (HR = 1.15; \( P = .005 \)).[16] Bestatin is a compound derived from the bacterium Streptomyces olivoreticuli. Through inhibition of aminopeptidase N/CD13 it inhibits tumor angiogenesis and invasion and is also reported to have direct antitumor and immunostimulatory properties. Initial studies with bestatin as adjuvant therapy in NSCLC failed to demonstrate any survival advantage.[51,52] However, activity of bestatin was suggested in squamous cell lung cancer.[51,53] Ichinose et al therefore randomized 400 patients following resection of a stage I squamous cell carcinoma of the lung to receive oral bestatin (30 mg daily) or placebo.[54] The treatment was well tolerated with few adverse events. The 5-year survival was 81% in the bestatin group and 74% in the placebo group (\( P = .033 \)). Similarly the 5-year cancer-free survival rate was 71% in the bestatin group and 62% in the placebo group (\( P = .017 \)). Recurrence or a second primary cancer as the first treatment failure after operation was documented in 29% of the patients in the bestatin group and 37% of those in the placebo group (\( P = .066 \)). These encouraging data remain to be confirmed by other randomized studies with this agent. Given the activity of inhibitors of the EGFR such as erlotinib (Tarceva) and gefitinib (Iressa) in advanced NSCLC, a study of adjuvant gefitinib is under way. NCIC BR19 is a randomized study of 2 years of adjuvant gefitinib in patients with completely resected primary stage IB, II, or IIIA NSCLC conducted by the NCIC together with the Eastern Cooperative Oncology Group and the Southwest Oncology Group. The planned accrual for the study is 1,242 patients (621 per treatment arm). Following the positive results of IALT, platinum-based adjuvant chemotherapy prior to gefitinib is
permitted (study schema is shown in Figure 3).

### Table 4

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<th>Study</th>
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<th>5-Year Survival</th>
<th>P Value</th>
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<td>355</td>
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<td>44%^b</td>
<td>.15</td>
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*Postoperative thoracic radiation (RT) was given to patients with pT3 or pN2 disease or those who did not receive complete resection.

^b4-yr survival.

CEP = cyclophosphamide, etoposide, cisplatin; EP = etoposide, cisplatin; MIC = mitomycin 6 mg/m², ifosfamide 3 g/m², cisplatin 50 mg/m²; MIP = mitomycin 6 mg/m² day 1, ifosfamide 1.5 g/m² days 1–3, cisplatin 30 mg/m² days 1–3; NS = not specified.

### Table 5

| Trial | Location | Patient Eligibility
<table>
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<td>I and II</td>
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<td>Spain and Europe</td>
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</table>

### Ongoing Studies or Recently Closed Trials of Neoadjuvant Chemotherapy

**Chemotherapy Regimen**: PCa, GC, MIP, MVP, PCa, GC, PCa x 4 → surgery, PCa x 2 → surgery, GC x 4 → surgery, GC x 2 → surgery, Surgery alone

**Accrual Goal**: 660 (356)º, 700 (256)º, 600 (501), 520 (420), 624

*Clinical stage.

ºAccrual to date in parentheses.

ºTrial closed.

ChEST = Italian Chemotherapy in Early Stages Trial; GC = gemcitabine, cisplatin; MIP = mitomycin, ifosfamide, cisplatin; MVP = mitomycin, vinblastine, cisplatin; NATCH = Neoadjuvant Taxol Carboplatin Hope; PCa = paclitaxel/carboplatin; SWOG = Southwest Oncology Group.
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**Adjuvant Chemotherapy**

The use of preoperative neoadjuvant (or induction) chemotherapy has a number of theoretical advantages over adjuvant postoperative chemotherapy, namely, improved patient compliance,[55] early control of micrometastatic disease, and reduction in the size of the primary tumor prior to surgery (including pathologic complete response). On the other hand, this approach does not allow for accurate surgical staging, it delays surgery with a small but measurable risk of disease progression (approximately 3% to 5%),[56] and may be associated with increased operative mortality. Several randomized studies of neoadjuvant chemotherapy have been reported (Table 4).[57-62] While three of these studies suggested improvement in survival with neoadjuvant treatment in stage IIIA disease,[57-59] this benefit was not observed in a fourth study.[60] Limited inferences can be drawn about the comparative value of adjuvant vs neoadjuvant chemotherapy on the basis of the available randomized data. Only a small number of patients (approximately 600) have been included in the randomized studies of neoadjuvant chemotherapy reported to date, in contrast to the more than 6,000 patients in the reported studies of postoperative treatment. Only one reported study has examined the effects of neoadjuvant chemotherapy in early-stage disease.[60] In addition, three of the four studies used two to three cycles of postoperative chemotherapy as well as preoperative chemotherapy in responding patients, and none of these studies used the modern regimens used in CALGB 9633 or JBR10. A number of studies of ongoing or recently completed trials should, however, clarify the role of neoadjuvant chemotherapy (Table 5).

These include the SWOG 9900 study, which closed in July 2004 due to the results of CALGB 9633 or JBR10 showing that surgery alone was an inferior therapy. At the time of closure 356 of 600 planned patients were enrolled. In this study, patients with clinical stage IB, II, and selected IIIA (T3, N1) NSCLC were randomized to surgery alone or surgery plus preoperative paclitaxel and carboplatin. The Italian Chemotherapy in Early Stages Trial (ChEST), which evaluated three cycles of preoperative cisplatin and gemcitabine (Gemzar) in a similar patient population (resectable stage IB, II, and selected IIIA [T3, N1]) NSCLC was also closed early after reaching an accrual of 256 patients. The British MRC-LU22 study, performed in collaboration with the Dutch Chest Physician Association and the European Organisation for Research and Treatment of Cancer, is evaluating preoperative chemotherapy with a choice of six different platinum-based regimens in patients with resectable NSCLC of any stage and is approaching its accrual goal of 600 patients. Two trials of particular interest in the comparison of neoadjuvant to adjuvant chemotherapy are the Spanish Neoadjuvant Taxol Carboplatin Hope (NATCH) trial and the French IFCT (Intergroupe Francophone de Cancrologie Thoracique)-0002 neoadjuvant study. The NATCH trial provides a direct comparison of preoperative and postoperative chemotherapy. A planned total of 600 patients with stage IA (> 2.5 cm), IB, II, and IIIA (T3 N1) NSCLC are to be randomized to chemotherapy with three cycles of carboplatin and paclitaxel given before surgery or after surgery, or to surgery alone. The French study is a four-arm trial that compares four cycles of preoperative chemotherapy with two cycles of preoperative chemotherapy and two cycles of postoperative chemotherapy using two different chemotherapy regimens. **Postoperative Adjuvant Chemoradiation**

Six trials included in the 1995 meta-analysis evaluated the effects of cisplatin-based chemotherapy plus postoperative radiotherapy in comparison to postoperative radiotherapy alone. Although a 6% reduction in the risk of death was seen favoring chemotherapy, suggesting a 2% absolute benefit at both 2 and 5 years, this difference was not statistically significant (HR = 0.93; *P* = .46).[16] Two more recently performed randomized studies have also failed to demonstrate an advantage of postoperative chemoradiation. The ECOG randomized 488 patients with resected stage II or IIIA NSCLC to postoperative radiotherapy alone or radiotherapy given with four cycles of cisplatin and etoposide.[63] No difference was seen in either overall survival (*P* = .56) or intrathoracic recurrence rate (*P* = .84). A French study from the Groupe d’Etude et de Traitement des Cancers Bronchiques randomized 267 patients with stage I to III NSCLC to postoperative radiotherapy (60 Gy) or three courses of postoperative COPAC (cyclophosphamide, doxorubicin [Adriamycin], cisplatin, vincristine [Oncovin], lomustine [CeeNu]) followed by radiotherapy.[64] Again, no significant differences in overall survival (*P* = .47) or disease-free survival (*P* = .68) were seen. Significantly, as discussed above for postoperative thoracic radiation, the control arm for these studies has not been shown to improve survival.[36,37] **Toward Individualized Adjuvant Chemotherapy for NSCLC**

At present there is no way to prospectively identify particular patients who will derive benefit from adjuvant chemotherapy, and thus avoid the toxicity of chemotherapy in the majority of patients who are already cured by surgery alone or who will relapse despite treatment. Although a variety of molecular markers have been implicated in the prognosis of NSCLC, including k-ras, p53, and p16, none has proved to have sufficient sensitivity or specificity to be of use for this purpose. In breast cancer, gene expression assays have been shown to be of benefit in addition to conventional staging, histologic, and immunohistochemical data for
selecting patients for adjuvant therapy. Preliminary studies suggest that genomic and proteomic analyses have potential to provide prognostic information that may be useful in selecting patients for adjuvant therapy in NSCLC. Appropriate molecular analyses of tumors may also enable the selection of the right therapy for particular patients. Recently, a number of genetic alterations in tumors responsible for sensitivity or resistance to a number of agents used in NSCLC have become evident. For example, EGFR mutations analysis and increased EGFR copy number detected by fluorescence in situ hybridization predict sensitivity to gefitinib and erlotinib, high levels of excision repair cross-complementing gene 1 (ERCC1) and ribonucleotide reductase subunit M1 (RRM1) mRNA correlate with resistance to cisplatin and gemcitabine chemotherapy, and beta-tubulin mutations are associated with resistance to taxane-based chemotherapy. Conclusions

The 5-year survival improvement of 5% as a result of postoperative adjuvant cisplatin-based chemotherapy suggested by the 1995 metaanalysis is significantly improved by the use of more active and less toxic third-generation platinum doublet regimens in defined subsets of patients with completely resected NSCLC. The magnitude of the survival benefit of adjuvant chemotherapy in NSCLC seen with the new chemotherapy regimens appears comparable to that achieved in breast cancer and colon cancer. On this basis, patients with resected stage IB or II NSCLC who are of reasonable performance status should be offered adjuvant chemotherapy with a modern platinum-based regimen such as carboplatin and paclitaxel or cisplatin and vinorelbine. At this point there is no evidence that survival is improved by adjuvant chemotherapy in patients with stage IA disease, but the results in stage IB and II disease suggest that these patients should be considered for future trials. The role of adjuvant chemotherapy in stage IIIA disease is uncertain; neoadjuvant chemotherapy or chemoradiation followed by surgery may be reasonable options in these patients. Postoperative adjuvant UFT also appears to be beneficial for patients with resected NSCLC, with the exception of patients with T1, N0 tumors. However, the relevance of these results outside Japan and the comparative benefits of UFT compared to modern platinum regimens have not been established. These studies clearly establish a place for adjuvant chemotherapy in patients with resected NSCLC. Ongoing studies will determine if preoperative or neoadjuvant chemotherapy will provide similar or improved results compared with postoperative adjuvant chemotherapy. Finally, and perhaps most challenging of all, it remains to establish reliable molecular methods that take advantage of the tumor tissue obtained at surgery to select those patients that will benefit from adjuvant chemotherapy and facilitate the selection of the appropriate regimen in these patients. Note Added in Proof: Results of the ANITA trial (Adjuvant Navelbine International Trialist Association) were reported at the 2005 ASCO annual meeting. In this phase III study, 840 patients with completely resected stage IB-IIIA NSCLC were randomized to postoperative treatment with cisplatin/vinorelbine (cisplatin at 100 mg/m² on day 1 every 4 weeks plus vinorelbine at 30 mg/m²/wk) or observation alone. After 70 months follow-up, the median survival was significantly greater in the group receiving adjuvant cisplatin/vinorelbine than in the observation group (65.8 vs 43.7 months; \( P = .0131 \); hazard ratio = .79 [0.66-.95]). Subgroup analysis by stage showed benefit in stage II and IIIA but no apparent benefit in stage IB NSCLC.

Disclosures:
Dr. Bunn has acted as a consultant for ImClone/Bristol-Myers Squibb, AstraZeneca, and OSI/Genentech. Dr. Mitchell has acted as a consultant for Aventis.

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