# Tegafur-Uracil Plus Gemcitabine Combination Chemotherapy in Patients with Advanced Non-small Cell Lung Cancer Previously Treated with Platinum

*Takashi Seto, MD,*† Takeharu Yamanaka, PhD,‡ Makiko Nakano, MD,†§ Mayuko Ota, MD,† Riichiroh Maruyama, MD,* Tatsuro Okamoto, MD,* Hiroshi Wataya, MD,* Kazutsugu Uematsu, MD,†‖ Nobuhiko Seki, MD,†¶ Kenji Eguchi, MD,†¶ Hiroshi Semba, MD,# and Yukito Ichinose, MD**

**Background:** An open-label, single-arm prospective study was conducted to evaluate the efficacy and toxicity of the combination of gemcitabine and tegafur-uracil (UFT) in patients with advanced nonsmall-cell lung cancer (NSCLC) after the failure of previous platinum-containing regimens.

**Patients and Methods:** Patients with advanced NSCLC received 200 mg/m$^2$ of UFT twice daily from day 1 through 14 plus 900 mg/m$^2$ of gemcitabine per day via intravenous injection on days 8 and 15. This regimen was repeated every 3 or 4 weeks.

**Results:** A total of 40 patients were enrolled. Eleven patients (28%; 95% confidence interval [CI], 15–44%) achieved a partial response. The median progression-free survival, median overall survival, and 1-year survival rate were 4.0 months (95% CI, 3.3–6.7 months), 12.6 months (95% CI, 7.0–22.3 months), and 51% (95% CI, 33–66%), respectively. The most common grade 3 or 4 toxicity was neutropenia (38%; 95% CI, 23–54%) and the rate of grade 3 or 4 nonhematologic toxicity remained at less than 5%. A multivariate Cox model showed that adenocarcinoma, nonsmoking history, and good performance status predicted better survival.

**Conclusions:** Combination chemotherapy with UFT and gemcitabine showed a promising effectiveness and acceptable toxicity for patients with platinum-resistant NSCLC.

*Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan; †Division of Medical Oncology, Tokai University School of Medicine, Isehara, Japan; ‡Cancer Biostatistics Laboratory, Institute for Clinical Research, National Kyushu Cancer Center, Fukuoka, Japan; §Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo, Japan; ‖Division of Pulmonary Medicine, Saitama Medical Center, Kawagoe, Japan; ¶Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan; and #Division of Respiratory Diseases, Kumamoto Regional Medical Center, Kumamoto, Japan.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Takashi Seto, MD, Department of Thoracic Oncology, National Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka 811-1395, Japan. E-mail: tseto@nk-cc.go.jp



ISSN: 1556-0864/08/0306-0637

**Key Words:** Adenocarcinoma, Advanced nonsmall-cell lung cancer, Gemcitabine, Nonsmoking, Second-line chemotherapy, Tegafur-uracil.

(*J Thorac Oncol.* 2008;3: 637–642)

Systemic chemotherapy plays an important role in the treatment of non-small cell lung cancer (NSCLC), and in the past decade combination chemotherapy regimens including platinum have become the standard first-line treatments for advanced NSCLC.[1–7] Several meta-analyses, however, have found that these regimens confer only a limited survival benefit.[8] If a first-line therapy fails, single agents, including docetaxel,[9,10] pemetrexed,[11] and erlotinib,[12] can be administered. A response rate of more than 20% is sufficient to justify consideration of a regimen for second-line use, especially in patients with good performance status.

Gemcitabine is one of the most active new drugs against NSCLC. It has antitumor activity comparable to that of cisplatin with etoposide but produces less toxicity.[13–15] In vitro, gemcitabine shows significant activity against platinum-resistant cell lines[16] and the reported response rates of gemcitabine monotherapy in the second-line treatment is 6 to 21% with median survival time ranging from 4 to 7.9 months.[17–20] Tegafur-uracil (UFT) is an oral agent composed of a 1:4 molar ratio of tegafur, a prodrug that is converted to 5-fluorouracil (5-FU), and uracil, which elevates serum levels of 5-FU by inhibiting its enzymatic degradation. Although no data of single agent UFT is available in patients with advanced NSCLC, a recent randomized study in 984 patients with stage I adenocarcinoma has confirmed that postoperative adjuvant therapy with UFT increases overall survival.[21] Both gemcitabine and 5-FU are antimetabolites, but they inhibit DNA synthesis via different pathways. Gemcitabine most likely exerts its cytotoxic effects through phosphorylation by deoxycytidine kinase into gemcitabine triphosphate, which is then incorporated into DNA; in contrast, 5-FU inhibits DNA synthesis through the binding of its derivative, fluorodeoxy monophosphate, to thymidylate synthase. These different antitumor mechanisms suggest a potential synergism between

gemcitabine and 5-FU, which has been observed in vitro studies of various cancer cell lines.[22]

Our previous phase I study in 24 patients with advanced NSCLC reported that the combination of UFT and gemcitabine is both well-tolerated and effective. The most frequent toxicities of this regimen were hematologic. The objective response rates were 45% (5 of 11 patients) in chemonaïve patients and 23% (3 of 13 patients) in patients previously treated with a platinum-containing regimen. The most appropriate schedule and dosing were determined to be 200 mg/m$^2$ twice daily on days 1 through 14 with 900 mg/m$^2$ of gemcitabine on days 8 and 15.[23] This study was then followed by a phase II study in 44 chemonaïve patients with advanced NSCLC in which the above schedule of UFT and gemcitabine achieved a very high response rate of 41% (95% confidence interval [CI], 26–55%).[24] In the present study, we examined the efficacy and safety of this combination as second-line chemotherapy in patients with platinum-resistant NSCLC.

## PATIENTS AND METHODS

### Patient Eligibility

Patients were eligible for enrollment if they had histologically or cytologically confirmed stage IIIB or IV NSCLC; with measurable lesions; previously treated with one or more regimens, at least one of which is platinum-based regimens; an Eastern Cooperative Oncology Group performance status of zero to two; and a life expectancy of at least 3 months. The eligibility criteria regarding organ function were as follows: a leukocyte count of 4000 to 12,000/mm$^3$; a platelet count of 100,000/mm$^3$ or greater; a hemoglobin level of 9.0 g/dL or greater; a serum bilirubin level less than 1.5 mg/dL; serum levels of aspartate aminotransferase and alanine aminotransferase of twice the upper limit or less; a serum creatinine level of 1.5 mg/dL or less. For pretreatment tumor-staging, all patients underwent computed tomography of the thorax and upper abdomen. Metastatic brain tumors were evaluated by either magnetic resonance imaging or enhanced computed tomography, whereas metastases to bone were evaluated by either radioisotopic bone scan or FDG-PET. All imaging tests were required to be conducted within 4 weeks before patient registration. Any patients who had severe complications, concomitant other malignancies, pleural effusion necessitating treatment, or symptomatic cerebral involvement were excluded from the study. Patients were enrolled at least 4 weeks after their most recent previous treatment. Written informed consent was required before enrollment.

### Treatment Schedule

The present study used the same schedule in a previous phase II study for chemonaïve patients.[24] Patients received UFT (200 mg/m$^2$) twice daily orally before meals on days 1 through 21 plus gemcitabine (900 mg/m$^2$ on days 8 and 15) by intravenous infusion over 30 minutes. On the day the gemcitabine was to be administered, a complete blood count was obtained; gemcitabine was administered only if the leukocyte count was at least 2000/mm$^3$ and the platelet count was at least 70,000/mm$^3$. If these requirements were not met, administration of gemcitabine was postponed for a maximum of 4 days. The treatment regimen was repeated every 3 or 4 weeks and at least two cycles were scheduled to be administered unless disease progression or an unacceptable toxicity occurred. The next cycle was started only if the leukocyte count was at least 3000/mm$^3$ and if the other eligibility criteria regarding organ function were satisfied. The dose of gemcitabine was reduced to 800 mg/m$^2$ either if grade 4 hematotoxicities or grade 3 nonhematotoxicities occurred or if the administration of gemcitabine on day 15 was skipped in a previous cycle.

### Evaluation of Response and Toxicity

Objective tumor responses were based on findings of computed tomography and were evaluated with World Health Organization criteria. The response status of all patients considered to be showing a complete response or partial response (PR) was confirmed the extramural review meeting. Any adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria, version 2.0.

### Statistical Analysis

This study was designed as a multicenter study among three participating institutions. The primary end point was the objective response rate, defined as the percentage of patients with a best response of complete response or PR among all eligible patients, and its 95% CI was based on the exact binomial distribution. The sample size was determined as follows. Assuming that a response rate of 25% in eligible patients would indicate potential usefulness of the combination of UFT and gemcitabine, whereas a rate of 10% would be the lower limit of interest, and $\alpha = 0.05$ (one-side) and $\beta = 0.20$, the estimated required number of patients was 38.[25] In light of the possibility of patients becoming ineligible or providing no data for evaluation, we decided the sample size would be 40 registered patients. No interim analysis was planned. Secondary endpoints were toxicity, progression-free survival, and overall survival. The duration of progression-free survival or overall survival was measured from the date of registration to the date of event occurrence or last follow-up. Survival distribution was estimated with the method of Kaplan-Meier and confidence intervals were based on the Greenwood's formula. Pairs of survival curves were compared by the log-rank test.

An exploratory multivariate Cox model was applied to examine possible associations between baseline factors and overall survival. After screening out candidate factors by the log-rank test, a multivariate Cox model with a backward stepwise approach was performed to determine the final model that identifies independent prognostic factors. The proportional hazard assumption for each covariate was evaluated by the log-cumulative hazard plot and the Schoenfeld residuals.[26]

All *p*-values reported are two-tailed, and statistical analyses were performed with the SAS for Windows, version 9.1.

## RESULTS

The initial planned accrual period was 3 years. However, several studies in patients with previously treated NSCLC had been conducted concurrently with our study and the number of such studies was indeed more than

anticipated at the commencement of this study, resulting in a very slow accrual. Therefore, enrollment was extended and the planned cohort of 40 patients was registered from July 2000 through December 2005. All the patients met the eligibility criteria and received the study treatment. Thus, treatment delivery, efficacy and toxicity were evaluated in the 40 patients.

## Patient Characteristics

Patient characteristics are summarized in Table 1. Median age was 65 years (range, 45–80). Of the 40 patients, 26 (65%) were male, 15 (38%) had a performance status of 2, 30 (75%) had metastatic disease, and 30 (75%) had adenocarcinoma. Thirty-three (83%) had received cisplatin-containing regimens, 26 (65%) had received docetaxel or paclitaxel or both, 16 (40%) had received topoisomerase I or II inhibitors (irinotecan or amrubicin) and 8 (20%) had received epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). A total of 27 (68%) patients had received two or more regimens previously.

## Treatment Delivery

A total of 164 treatment cycles were administered to the 40 patients. The median number of administered cycles was 3 (range, 1–10). Thirty-seven (93%) patients completed 2 cycles of the protocol treatment, whereas 3 patients discontinued treatment before completing 2 cycles because of progression of tumor (1 patient), patient refusal (1 patient), or allergic reaction (1 patient). The administration of gemcitabine on day 15 was skipped in 10 (6%) of the 164 cycles. Doses were decreased to 800 mg/m$^2$ in 6 patients (15%).

**TABLE 1.** Patients Characteristics

| Characteristics | No. of Patients |
|---|---|
| Median age (range), yr | 65 (45–80) |
| Sex | |
| Male/female | 26/14 |
| Performance status | |
| 0/1/2 | 12/13/15 |
| Stage | |
| IIIB/IV | 10/30 |
| Tumor histologic type | |
| Adenocarcinoma/others | 30/10 |
| Smoking history | |
| No/yes | 15/25 |
| No. of previous chemotherapy regimens | |
| 1/2/3 | 13/22/5 |
| Response to previous chemotherapy | |
| Sensitive/resistant | 17/23 |
| Previously administered drugs | |
| Cisplatin/carboplatin/both | 25/7/8 |
| Paclitaxel/docetaxel/both | 8/15/3 |
| Vinorelbine | 13 |
| Irinotecan/amrubicin | 11/5 |
| Pemetrexed | 2 |
| EGFR-TKI | 8 |
| Previous surgery | 7 |
| Previous thoracic irradiation | 16 |

**TABLE 2.** Hematologic and Nonhematologic Toxicities in 40 Patients

| | Grade | | |
|---|---|---|---|
| Toxicity | 3 | 4 | Total (%) |
| Leukopenia | 12 | 2 | 14 (35) |
| Neutropenia | 7 | 8 | 15 (38) |
| Anemia | 9 | 1 | 10 (25) |
| Thrombocytopenia | 9 | 0 | 9 (23) |
| AST/ALT increased[a] | 2 | 0 | 2 (5) |
| Anorexia | 2 | 0 | 2 (5) |
| Diarrhea | 1 | 0 | 1 (3) |
| Pneumonitis | 1 | 0 | 1 (3) |

[a] ALT/AST, alanine aminotransferase/aspartate aminotransferase.

## Toxicity

The main toxicities were hematologic (Table 2). Grade 3 or 4 neutropenia was observed in 38% of the patients and grade 4 in 20%. Grade 4 anemia was observed in 1 patient, but grade 4 thrombocytopenia did not occur. For nonhematotoxicity, there were 4 cases with grade 3 (2 for anorexia, 1 for diarrhea, and 1 for pneumonitis) whereas no patient experienced grade 4 events.

## Tumor Response

Of the 40 patients, 11 showed a PR, resulting in an objective response rate of 28% (95% CI, 15–44%). Twenty-two patients (55%) showed no change, 5 (13%) had progressive disease, and 2 were not evaluable.

## Progression-Free and Overall Survival

Median progression-free survival and overall survival were 4.0 months (95% CI, 3.3–6.7 months) and 12.6 months (7.0–22.3 months), respectively (Fig. 1). Thirty of the 40 patients were confirmed to have died. The remaining 10 patients were lost to follow-up, with a median follow-up time of 9.0 months (range, 1.8–55.9 months). The overall survival rates at 6, 12, and 24 months were 66% (95% CI, 48–78%), 51% (33–66%), and 23% (10–39%), respectively.

To investigate the association between the baseline characteristics and overall survival, a planned exploratory analysis was performed. Table 3 shows the result of univariate analysis with the log-rank test for each variable. Characteristics significantly correlated with overall survival were the following five features: sex, performance status, tumor histologic type, smoking history, and response to previous chemotherapy (Fig. 2). To identify independent prognostic factors that were associated with survival, the Cox regression with backward elimination technique at 5% significance level was employed among these five significant factors. This resulted in three factors being retained in the final model: performance status, tumor histologic type and smoking history (Table 4). Namely, good performance status, adenocarcinoma, and nonsmoking history could independently predicted better survival outcome. Although adenocarcinoma

 

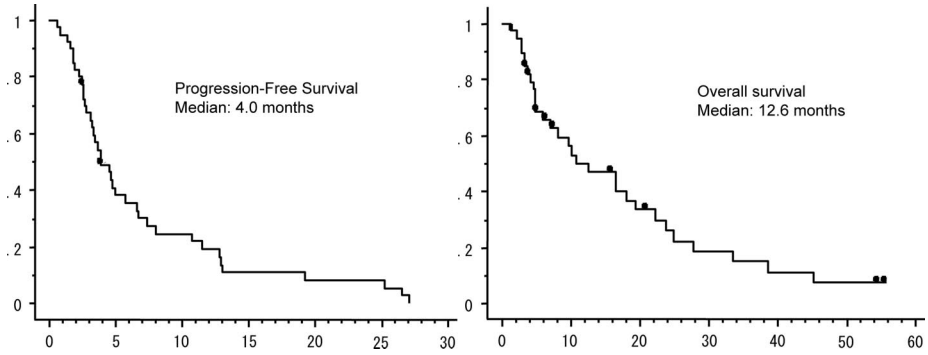


**FIGURE 1.** Kaplan-Meier curves for progression-free survival and overall survival.

**TABLE 3.** Association of Baseline Characteristics with Overall Survival (Univariate Analysis [Log-Rank test])

| | *p* |
|---|---|
| Age (>65 vs ≤65) | 0.4630 |
| Sex (female vs male) | 0.0339* |
| Performance status (2 vs 0/1) | <0.0001* |
| Stage (IV vs IIIB) | 0.8791 |
| Histologic type (adenocarcinoma vs others) | <0.0001* |
| Smoking history (no vs yes) | 0.0001* |
| Number of previous chemotherapy (1 vs 2/3) | 0.6767 |
| Response to previous chemotherapy (sensitive vs refractory) | 0.0348* |

*Statistically significant at 5% level.

**TABLE 4.** Association of Baseline Characteristics with Overall Survival (Multivariate Cox Analysis after the Backward Stepwise Selection)

| | HR | 95% CI of HR | *p* |
|---|---|---|---|
| Performance status (2 vs 0/1) | 3.823 | (1.53–9.53) | 0.0040 |
| Histologic type (adenocarcinoma vs others) | 0.104 | (0.03–0.36) | 0.0004 |
| Smoking history (no vs yes) | 0.371 | (0.16–0.87) | 0.0257 |

HR, hazard ratio; CI, confidence interval.

and nonsmoking history may be predictive factors of EGFR-TKI efficacy according to recent studies and indeed several patients received it after failure of UFT/gemcitabine, the same result holds in light of the possible effect of post EGFR-TKI use (Table 5).

## DISCUSSION

To date, three phase III trials to develop second-line chemotherapies have been performed in patients with advanced NSCLC.[8–10] Because of the results of these studies, docetaxel or pemetrexed are now considered the most effective single agents for chemotherapy after the failure of the first-line platinum-based regimens. On the hand, several single-arm phase II studies have found that combination regimens have possible benefits on survival outcome in the

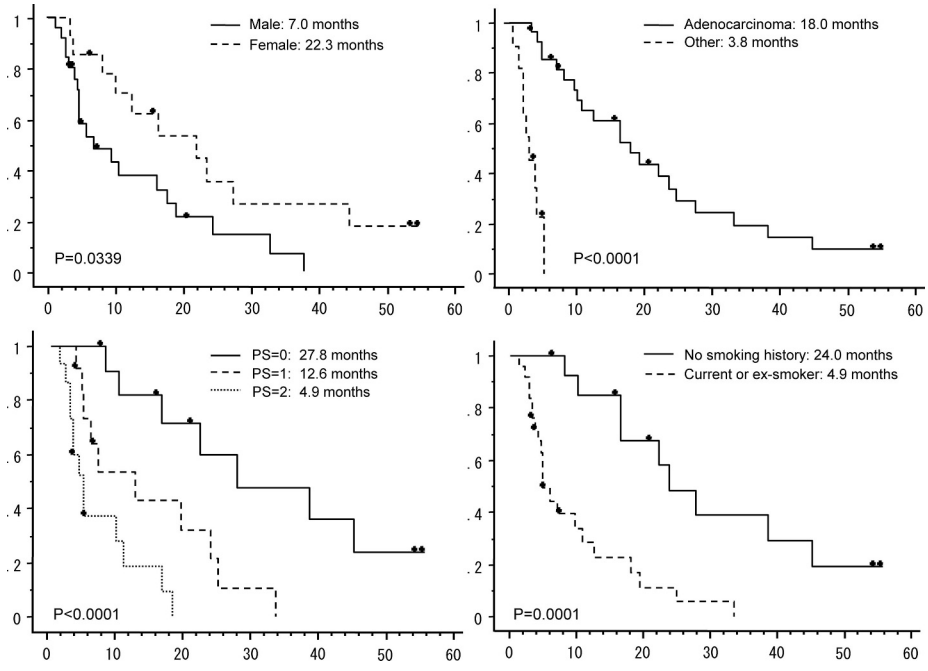


**FIGURE 2.** Kaplan-Meier curves for overall survival according to four factors including sex, performance status, tumor histologic type, and smoking history.

**TABLE 5.** Association of Baseline Characteristics with Overall Survival (Multivariate Analysis Adjusted with "EGFR-TKI Use" as a Time-Dependent Covariate)

| | HR | 95% CI of HR | *p* |
|---|---|---|---|
| Performance status (2 vs 0/1) | 3.741 | (1.50–9.34) | 0.0047 |
| Histologic type (adenocarcinoma vs others) | 0.103 | (0.03–0.36) | 0.0004 |
| Smoking history (no vs yes) | 0.363 | (0.15–0.86) | 0.0227 |
| EGFR-TKI-use after failure (yes vs no) | 0.713 | (0.18–2.82) | 0.6296 |

HR, hazard ratio; CI, confidence interval.

second-line treatment of advanced NSCLC. Although four randomized trials (one phase III and three phase II studies) of second-line therapy have compared some of such the experimental combination regimens with a standard single agent,[27–30] all failed to demonstrate a survival benefit over single agents. One important reason for the negative results was frequent severe toxicities in the combination regimens, which easily led to poor compliance of the treatment. Therefore, the development of combinations with lesser toxicity would be a necessary improvement over standard single-agent therapies for previously treated patients with NSCLC. In this regard, particularly notable was that the incidence of adverse effects of our protocol regimen was much lower than that of other second-line combination treatments. The antitumor activity shown by UFT and gemcitabine was satisfactory with a high response rate of 28%. Furthermore, its efficacy is quite comparable to that of other combinations examined in previous studies. Thus, given its favorable toxicity, the combination of UFT and gemcitabine warrants further phase III evaluation with the standard control arm of docetaxel or pemetrexed monotherapy.

We obtained an impressive result when compared with the recent Taiwanese study on the same combination with the reported response rate of 15.6%.[31] The difference may be because their daily dose of UFT was half of ours. In addition, gemcitabine was infused on days 1 and 8 in their regimen whereas on days 8 and 15 in ours. The preclinical data indicated that prior 5-FU followed by gemcitabine can yield higher response rate than gemcitabine followed by 5-FU.[22]

An exploratory analysis by multivariate Cox model showed that good performance status, adenocarcinoma and nonsmoking history can predict increased survival. Although these factors are recognized as key factors for a good response and survival prolongation with EGFR-TKI[32,33] and several patients in our study were treated with EGFR-TKI after the failure of UFT and gemcitabine, our analysis concluded that the survival benefits associated with adenocarcinoma and nonsmoking history are not biased by EGFR-TKI use. It is unclear whether these are prognostic factors for survival or predictive factors for efficacy of UFT/gemcitabine, but at least it is of value to recognize that these factors may have possible prognostic effect regardless of the EGFR-TKIs; the percentages of patients with adenocarcinoma and nonsmoking history should be carefully considered when interpreting the results of clinical trials.

In conclusion, following the earlier trial of UFT and gemcitabine in chemonaïve patients, the present study has demonstrated that the same combination is also promising as a second-line treatment in patients with NSCLC previously treated with platinum-containing regimens. Good performance status, adenocarcinoma, and nonsmoking history are associated with longer survival. Further study of this second-line chemotherapy in advanced NSCLC is highly warranted.

## ACKNOWLEDGMENTS

*We thank Ms. Yumiko Ohsima, Izumi Wasada, Fumiko Inoue, and Mika Nagamatsu for their kind help in the preparation of this manuscript.*

## REFERENCES

1. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ* 1995;311:899–909.
2. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003;21:3016–3024.
3. Kelly K, Crowley J, Bunn PA Jr, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: a Southwest Oncology Group trial. *J Clin Oncol* 2001;19:3210–3218.
4. Ohe Y, Ohashi Y, Kubota K, et al. 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* 2007; 18:317–323.
5. 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: 2542–2550.
6. Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* 2002;20:4285–4291.
7. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
8. Hotta K, Matsuo K, Ueoka H, et al. Meta-analysis of randomized clinical trials comparing Cisplatin to Carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2004;22:3852–3859.
9. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 non-small cell lung cancer study group. *J Clin Oncol* 2000;18:2354–2362.
10. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18:2095–2103.
11. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589–1597.
12. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353: 123–132.
13. Manegold C, Bergman B, Chemaissani A, et al. Single-agent gemcitabine versus cisplatin-etoposide: early results of a randomised phase II study in locally advanced or metastatic non-small-cell lung cancer. *Ann Oncol* 1997;8:525–529.
14. Perng RP, Chen YM, Ming-Liu J, et al. Gemcitabine versus the combination of cisplatin and etoposide in patients with inoperable non-small-cell lung cancer in a phase II randomized study. *J Clin Oncol* 1997;15: 2097–2102.
15. Vansteenkiste JF, Vandebroek JE, Nackaerts KL, et al. Clinical-benefit response in advanced non-small-cell lung cancer: a multicentre prospective randomised phase III study of single agent gemcitabine versus cisplatin-vindesine. *Ann Oncol* 2001;12:1221–1230.
16. Ruiz van Haperen VW, Veerman G, Eriksson S, et al. Development and

 

molecular characterization of a 2′,2′-difluorodeoxycytidine-resistant variant of the human ovarian carcinoma cell line A2780. *Cancer Res* 1994;54:4138–4143.
17. Crino L, Mosconi AM, Scagliotti G, et al. Gemcitabine as second-line treatment for advanced non-small-cell lung cancer: a phase II trial. *J Clin Oncol* 1999;17:2081–2085.
18. Gridelli C, Perrone F, Gallo C, et al. Single-agent gemcitabine as second-line treatment in patients with advanced non small cell lung cancer (NSCLC): a phase II trial. *Anticancer Res* 1999;19:4535–4538.
19. Sculier JP, Lafitte JJ, Berghmans T, et al. A phase II trial testing gemcitabine as second-line chemotherapy for non small cell lung cancer. The European lung cancer working party. *Lung Cancer* 2000;29:67–73.
20. van Putten JW, Baas P, Codrington H, et al. Activity of single-agent gemcitabine as second-line treatment after previous chemotherapy or radiotherapy in advanced non-small-cell lung cancer. *Lung Cancer* 2001;33:289–298.
21. Kato H, Ichinose Y, Ohta M, et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004;350:1713–1721.
22. Hagag N, Hentschel P, Madajewicz S. Biochemical modulation of 5 fluorouracil/folinic acid by gemzar in colon cancer cells. *Proc Am Assoc Cancer Res* 1999;40:339.
23. Seto T, Yoh K, Asoh H, et al. A phase I study of combination chemotherapy with gemcitabine and oral UFT for advanced non-small cell lung cancer. *Br J Cancer* 2002;86:1701–1704.
24. Ichinose Y, Seto T, Semba H, et al. UFT plus gemcitabine combination chemotherapy in patients with advanced non-small-cell lung cancer: a multi-institutional phase II trial. *Br J Cancer* 2005;93:770–773.
25. Fleiss JL. Statistical Methods for Rates and Proportions, 2nd Ed. New York: John Wiley & Sons, 1981.
26. Collett D. Modelling Survival Data in Medical Research, 2nd Ed. New York: Chapman & Hall/CRC, 1999.
27. Georgoulias V, Kouroussis C, Agelidou A, et al. Irinotecan plus gemcitabine vs irinotecan for the second-line treatment of patients with advanced non-small-cell lung cancer pretreated with docetaxel and cisplatin: a multicentre, randomised, phase II study. *Br J Cancer* 2004; 91:482–488.
28. Pectasides D, Pectasides M, Farmakis D, et al. Comparison of docetaxel and docetaxel-irinotecan combination as second-line chemotherapy in advanced non-small-cell lung cancer: a randomized phase II trial. *Ann Oncol* 2005;16:294–299.
29. Takeda K, Negoro S, Tamura T, et al. Docetaxel (D) versus docetaxel plus gemcitabine (DG) for second-line treatment of non-small cell lung cancer (NSCLC): results of a JCOG randomized trial (JCOG0104). *Proc Am Soc Clin Oncol* 2004;22:abstr #7034.
30. Wachters FM, Groen HJ, Biesma B, et al. A randomised phase II trial of docetaxel vs docetaxel and irinotecan in patients with stage IIIb–IV non-small-cell lung cancer who failed first-line treatment. *Br J Cancer* 2005;92:15–20.
31. Chen YM, Perng RP, Tsai CM, et al. A phase II trial of gemcitabine plus UFUR combination chemotherapy in non-small-cell lung cancer patients failing previous chemotherapy. *Lung Cancer* 2006;52:333–338.
32. Ando M, Okamoto I, Yamamoto N, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol* 2006;24:2549–2556.
33. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;366: 1527–1537.