VOLUME 25 · NUMBER 33 · NOVEMBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Phase III Trial of Two Versus Four Additional Cycles in Patients Who Are Nonprogressive After Two Cycles of Platinum-Based Chemotherapy in Non–Small-Cell Lung Cancer

*Joon Oh Park, Sang-We Kim, Jin Seok Ahn, Cheolwon Suh, Jung Shin Lee, Joung Soon Jang, Eun Kyung Cho, Sung Hyun Yang, Jin-Hyuk Choi, Dae Seog Heo, Suk Young Park, Sang Won Shin, Myung Ju Ahn, Jong Seok Lee, Young Ho Yun, Jae-Won Lee, and Keunchil Park*

From the Samsung Medical Center, Sungkyunkwan University School of Medicine; the Asan Medical Center, College of Medicine, University of Ulsan; the Korea Cancer Center Hospital; the Seoul National University Hospital; the Korea University Medical Center; the Hanyang University Hospital; the Chung-Ang University, College of Medicine; and the Korea University, Seoul; the Ajou University Hospital, Suwon; the Gyeongsang National University, Chinju; the Gachon University Gil Medical Center, Inchon; the Daejeon St Mary's Hospital, Daejeon; the Seoul National University Bundang Hospital, Sungnam; and the National Cancer Center, Goyang, Republic of Korea.

Submitted January 20, 2007; accepted July 19, 2007.

Joon Oh Park and Sang-We Kim contributed equally to the work as first authors.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Keunchil Park, MD, PhD, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-Dong, Gangnam-Gu, Seoul, Republic of Korea 135-710; e-mail: kpark@smc.samsung.co.kr.



0732-183X/07/2533-5233/$20.00

DOI: 10.1200/JCO.2007.10.8134



## ABSTRACT

### Purpose
This trial was conducted to determine the optimal duration of chemotherapy in Korean patients with advanced non–small-cell lung cancer (NSCLC).

### Patients and Methods
Patients with stages IIIB to IV NSCLC who had not progressed after two cycles of chemotherapy were randomly assigned to receive either four (arm A) or two (arm B) more cycles of third-generation, platinum-doublet treatment.

### Results
Of the 452 enrolled patients, 314 were randomly assigned to the groups. One-year survival rates were 59.0% in arm A and 62.4% in arm B, and the difference of 3.4% (95% CI, −8.0 to 4.8) met the predefined criteria for noninferiority. The median time to progression (TTP), however, was 6.2 months (95% CI, 5.7 to 6.7 months) in arm A and 4.6 months (95% CI, 4.4 to 4.8 months) in arm B, the difference of which is statistically significant ($P = .001$). The frequencies of hematologic and nonhematologic toxicities were similar in the two arms.

### Conclusion
This study confirms the noninferiority of overall survival with four cycles compared with six cycles of chemotherapy for the first-line treatment of advanced NSCLC and supports the current American Society of Clinical Oncology guidelines. Notably, patients receiving six cycles of chemotherapy compared with four cycles showed a favorable TTP, suggesting that further investigation of the new strategies of maintenance therapy with less toxic agents after three to four cycles of induction chemotherapy might be warranted to improve survival, with consideration of both ethnicity and pharmacogenomic signatures.

*J Clin Oncol 25:5233-5239. © 2007 by American Society of Clinical Oncology*

## INTRODUCTION

Lung cancer is the second most common cancer in Korea and is the leading cause of cancer deaths, accounting for 20% of all cancer deaths.[1] Several meta-analyses have reported moderate gains in survival and quality of life (QOL) when platinum-based chemotherapy is used.[2-4]

The optimal duration of first-line chemotherapy has long been debated. Until now, only two phase III trials have been published that addressed this issue in patients with advanced non–small-cell lung cancer (NSCLC).[5,6] Both trials showed no significant differences in survival or QOL between groups undergoing short- or long-duration chemotherapy, whereas relatively higher incidences of cumulative toxicity were observed in patients treated with a longer duration of chemotherapy. Based on these trials, the American Society of Clinical Oncology guidelines recommend that initial chemotherapy should be stopped at four cycles of a platinum doublet in patients who are not responding to treatment and that no more than six cycles should be given, even to patients who have responded to treatment.[7]

Although it is not yet clear whether race/ethnicity by itself is important in determining the prognosis of advanced NSCLC,[8-10] it has been proposed that there are racial disparities in treatment outcomes.[11-14] It is well known that Asian ethnicity is considered one of the predictive markers for a good response and for longer survival in patients with NSCLC who are treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) such as gefitinib and erlotinib.[15,16] It has also

been suggested that potential differences exist between white and Asian patients in the efficacy and tolerability of chemotherapy.[11-14] However, race/ethnicity has not been cited as a potential prognostic factor in previous trials. To address this issue, we conducted a prospective, phase III trial using third-generation platinum doublets to define the optimal duration of chemotherapy in Korean patients with advanced NSCLC.

## PATIENTS AND METHODS

### Patient Selection

Chemotherapy-naive patients with histologically proven, stage IIIB with malignant effusion or stage IV NSCLC were eligible. Prior radiotherapy was allowed if completed 4 weeks before entry. Patients with documented brain metastases were excluded. Patients were required to have a Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2 and adequate organ function, defined as an absolute neutrophil count of $\geq$ 1,500/mm$^3$, platelets $\geq$ 100,000/mm$^3$, creatinine $\leq 2\times$ the upper limit of normal (ULN) and creatinine clearance $\geq$ 60 mL/min, bilirubin $\leq 1.5\times$ ULN, AST $\leq 2.5\times$ ULN, and no clinically significant baseline peripheral neuropathy. All patients were required to participate in the QOL component of the study and to give written informed consent. This trial was reviewed by the protocol review committee of the Korean Cancer Study Group and the institutional review board of each institute.

### Treatment and Response Evaluation

Eligible patients were initially treated with two cycles of cisplatin 70 mg/m$^2$ on day 1 plus either a taxane (paclitaxel 175 mg/m$^2$ or docetaxel 75 mg/m$^2$) on day 1 or gemcitabine 1,000 mg/m$^2$ on days 1 and 8 every 3 weeks. Patients without progression after two cycles of chemotherapy were randomly assigned to receive either four (arm A, six-cycle group) or two (arm B, four-cycle group) more cycles of the same regimen (Fig 1). Treatment was continued until the maximum of four or six cycles was completed, depending on random assignment, unless disease progression or unacceptable toxicity occurred or unless the patient refused further chemotherapy. Relative dose intensity was calculated by the ratio of the received dose divided by the scheduled dose to the actual duration of treatment divided by the scheduled duration.

Evaluation was performed every two cycles. Objective tumor responses were assessed according to World Health Organization criteria. After completing six cycles of therapy in arm A, the patients were followed monthly and were evaluated by computed tomography scans every 3 months or when clinically indicated. Patient follow-up and evaluation were performed at the same time points in arm B. Second-line chemotherapy was considered at the discretion of the treating oncologist after documentation of progression. All enrolled patients were included in the intent-to-treat analysis of efficacy. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.

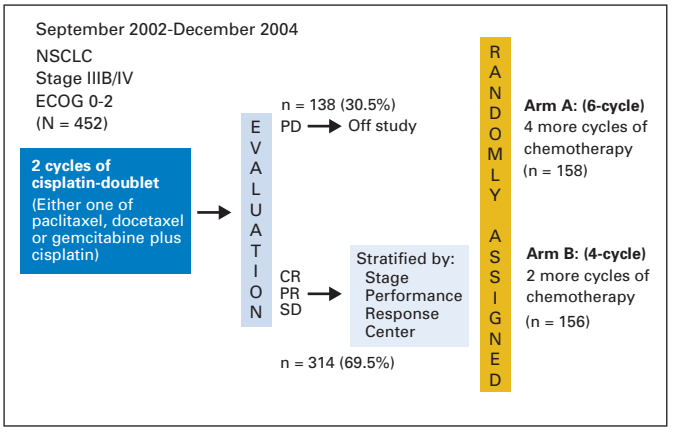


**Fig 1.** Study schema. NSCLC, non–small-cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease.

### QOL Analysis

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and the lung cancer–specific module QLQ-LC13 were used to compare the impact of the treatment duration on the QOL.[17] For all analyses, the time-by-treatment interaction was examined to determine whether QOL changes over time were differentially affected by the treatment arm. QOL data were prospectively collected from all patients before treatment at baseline, on the first day of the third and fifth cycles during chemotherapy, and at 3 weeks and at 3 months after the completion of chemotherapy for patients randomly assigned to the six-cycle or four-cycle groups.

### Random Assignment

The Korean Cancer Study Group Clinical Trial Center was the coordinating center for this trial. Random assignment was carried out using the permuted block design, with a block size of four at the end of the second cycle, to exclude patients who progressed during the first two cycles of therapy. At random assignment, patients were stratified according to center, PS (0 to 1 *v* 2), response to two cycles of chemotherapy (partial response [PR] *v* stable disease) and stage (IIIB *v* IV) to minimize any imbalance between the groups.

### Statistical Design

The primary end point of the trial was the overall survival (OS), and secondary end points included the response rate, time to progression (TTP), toxicity, and QOL analysis. In the decision analysis of sample size, an exponential survival distribution was assumed. This study was designed to demonstrate noninferiority in OS for four cycles, using a noninferiority margin of 15% for a 1-year survival rate. Given a $P$ value of .05 with a one-tailed test, a power of .80, an accrual period of 18 months, and a follow-up period of 18 months after the last patient was accrued, the total number of observed deaths required was 152 in both arms. Therefore, the total sample size required was 218 patients (109 patients/arm). A 10% nonassessable rate and a 40% rate of disease progression rate after two cycles of chemotherapy were assumed, resulting in an accrual goal of 452 patients. The survival curves were estimated using the Kaplan-Meier method and were compared using the log-rank test. Subgroup analysis was performed using the Cox proportional hazards model. To test the proportional hazards assumption of the Cox model, time-varying covariates were applied to the patient demographic covariates that were associated with survival. The statistical significance of two-way interactions between the patient demographic covariates and the assigned treatment was also studied. We scored the QLQ-C30 and QLQ-LC13 items according to the EORTC scoring manual. We linearly transformed the QLQ-C30 and QLQ-LC13 data to yield scores from 0 to 100; a higher score represented a better level of functioning or worse level of symptoms. In the QOL analysis, the mean change of the QOL score was calculated separately for two time periods (from baseline to the completion of four cycles and from the completion of four cycles to 3 months later) to represent the effect of courses with respect to the changes in their QOL scores. Analysis of covariance with repeated measures was conducted to compare the differences in the mean change of the QOL score at the slope between the two arms. Complete cases of QOL were used in the analysis. Sensitivity analyses using analysis of complete cases, last observation carried forward, imputation of mean and worst scores per time point, and multiple imputations with the Markov Chain Monte Carlo method were performed to check the robustness of the main results.

## RESULTS

### Patient Characteristics

A total of 452 patients were enrolled between September 2002 and December 2004 from 15 centers in Korea. After two cycles of

**Table 1.** Patient Characteristics

| Characteristic | All Patients (N = 452) | After Random Assignment: Arm A (n = 158) No. of Patients | Arm A % | Arm B (n = 156) No. of Patients | Arm B % |
|---|---|---|---|---|---|
| Sex | | | | | |
| Male | 312 | 110 | — | 99 | — |
| Female | 140 | 48 | — | 57 | — |
| Age, years | | | | | |
| Median | 58 | 60 | — | 56 | — |
| Range | 26-81 | 32-80 | — | 26-81 | — |
| ECOG PS | | | | | |
| 0-1 | 416 | 147 | 93.0 | 148 | 94.5 |
| 2 | 36 | 11 | 7.0 | 8 | 5.5 |
| Stage | | | | | |
| IIIB | 79 | 24 | 15.2 | 33 | 21.2 |
| IV | 373 | 134 | 84.8 | 123 | 78.8 |
| Histology | | | | | |
| Squamous | 126 | 56 | 35.5 | 41 | 26.3 |
| Adenocarcinoma | 269 | 89 | 56.3 | 94 | 60.2 |
| Others | 57 | 13 | 8.2 | 21 | 13.5 |
| Regimen | | | | | |
| TP | 105 | 47 | 29.7 | 32 | 20.5 |
| DP | 82 | 25 | 15.8 | 27 | 17.3 |
| GP | 265 | 86 | 54.5 | 97 | 62.2 |

NOTE. No characteristic comparisons within each group were statistically significant.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; TP, paclitaxel/cisplatin; DP, docetaxel/cisplatin; GP, gemcitabine/cisplatin.

chemotherapy, 138 patients (30.5%) progressed and 314 patients (69.5%) were randomly assigned (Fig 1). Most patients were male (69.0%), had stage IV disease (82.5%), had a good PS (0 to 1; 92.0%), and had nonsquamous histology (72.1%). Gemcitabine plus cisplatin was the most commonly used regimen. The demographics between arms A and B were well balanced (Table 1).

### *Treatment Summary and Response Rate*

Of the 158 patients randomly assigned to arm A, 74.1% (n = 117) completed five or more cycles, and 91.2% (n = 144) completed four or more cycles (median, six; range, two to six cycles; Table 2). Ninety-two percent (n = 144) of the 156 patients randomly assigned to arm B

**Table 2.** Patients Treated in Each Cycle

| | Arm A (n = 158) No. of Patients | Arm A % | Arm B (n = 156) No. of Patients | Arm B % | *P* |
|---|---|---|---|---|---|
| No. of cycles | | | | | |
| Median | 6 | — | 4 | — | .001 |
| Range | 2-6 | — | 2-4 | — | |
| No. of cycles completed | | | | | |
| 2 | 1 | 0.6 | 2 | 1.3 | — |
| 3 | 13 | 8.2 | 10 | 6.4 | — |
| 4 | 27 | 17.1 | 144 | 92.3 | — |
| 5 | 9 | 5.7 | — | — | — |
| 6 | 108 | 68.4 | — | — | — |

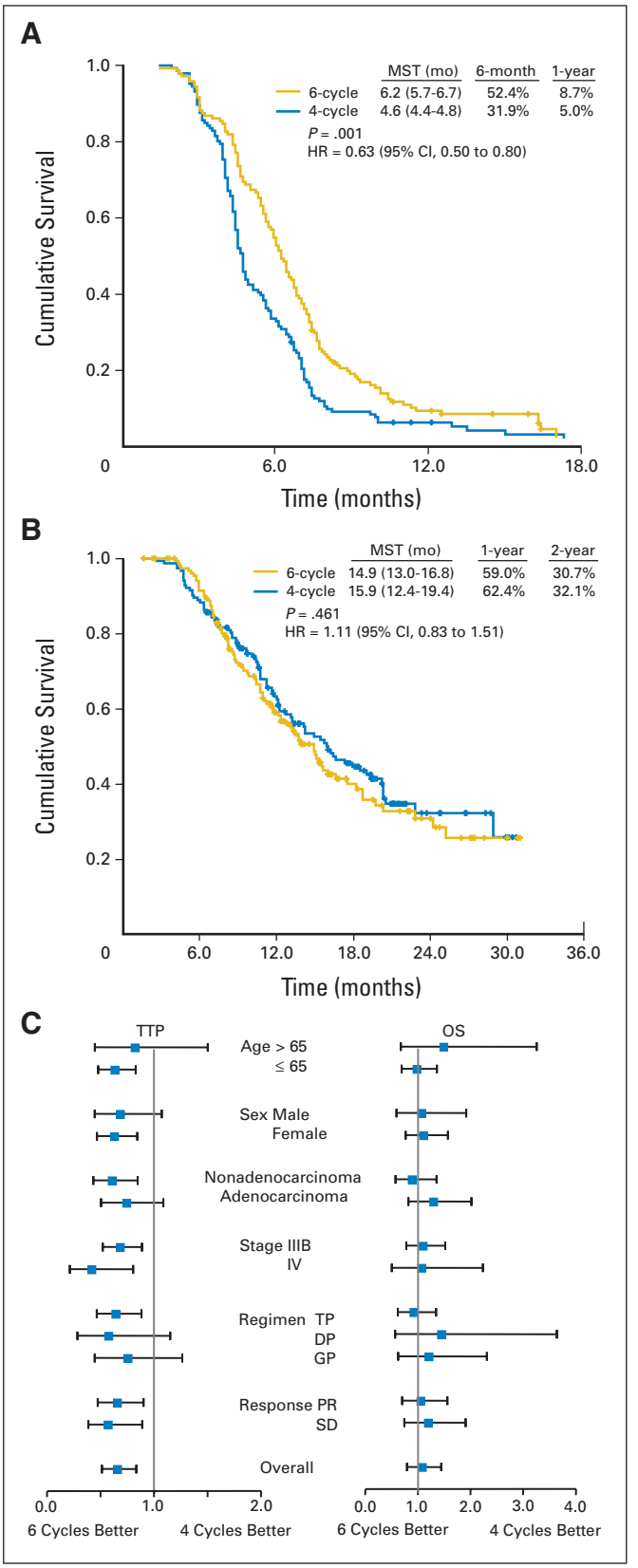


**Fig 2.** Survival by treatment arm: The insert shows the median survival times (MSTs) and the 1- and 2-year survival rates with 95% CIs. (A) time to progression (TTP); (B) overall survival (OS); (C) hazard ratios (HRs) for TTP and OS in both groups according to prognostic factors. TP, paclitaxel/cisplatin; DP, docetaxel/cisplatin; GP, gemcitabine/cisplatin; PR, partial response; SD, stable disease.

completed four planned cycles of treatment (median, four; range, two to four cycles). Overall, more than 90% of patients received at least four cycles of chemotherapy across both arms. The most common reason in both arms for not receiving the planned cycles of chemotherapy was disease progression. The relative dose intensity was greater than 90% in both groups. The overall objective response rate at random assignment was 29.5% in all patients enrolled (Appendix Table A1, online only). The responses at random assignment did not differ between the two groups (42.4% *v* 42.6%). Of the 158 patients randomly assigned to arm A, 75 (47.5%) achieved a PR (95% CI, 39.5 to 55.6). Of the 156 patients randomly assigned to arm B, 64 (41.6%) achieved a PR (95% CI, 33.2 to 49.2) at the completion of the planned first-line treatment (Appendix Table A1).

### Survival

All randomly assigned patients were included in the intent-to-treat analysis for survival. The median follow-up was 12.2 months (range, 2.3 to 31.5 months). The difference in the 1-year survival rate between the groups was 3.4% (95% CI, −8.0 to 14.8) and met the predefined criteria for noninferiority. Median OS was 14.9 months (95% CI, 13.0 to 16.8) for arm A and 15.9 months (95% CI, 12.4 to 19.4) for arm B ($P = .461$). No statistically significant difference in OS was seen between the groups (Appendix Table A2, online only). However, the median TTP was 6.2 months (95% CI, 5.7 to 6.7) in arm A and 4.6 months (95% CI, 4.4 to 4.8) in arm B, which was statistically significant ($P = .001$; Fig 2). However, the TTP benefit was not translated into a survival benefit in arm A. We evaluated the interactions between prognostic factors, and, on subgroup analysis, none of the clinical parameters had a significantly different effect on OS and TTP between the two groups (Fig 2).

### Toxicity

Worst toxicities were scored according to the National Cancer Institute Common Toxicity Criteria version 2.0 (Table 3). The overall rates of toxicity in this study were similar in both arms, and there was no evidence of cumulative toxicity, such as neurotoxicity, in the six-cycle arm. The overall rates of grade 3 to 4 toxicities were lower than those of previous trials. There were no life-threatening toxicities.

### Second- or Third-Line Chemotherapy

The proportion of patients receiving second-line chemotherapy and the reasons for not receiving second-line therapy are summarized in Table 4 and in Appendix Table A3 (online only). Ninety-nine (62.7%) of 158 patients in arm A and 116 (74.4%) of 156 patients in arm B received second-line chemotherapy, and these values were significantly different ($P = .026$). Single-agent docetaxel was commonly used as the second-line chemotherapy in both arms. The alternative second-line chemotherapies administered included single-agent gemcitabine, gefitinib, pemetrexed, and others. Approximately 40% of patients in both groups received third-line chemotherapy, mostly gefitinib.

### QOL Analysis

The QOL data were prospectively collected for 311 patients, using the EORTC QLQ-C30 and QLQ-LC13 at baseline and throughout. Of the QOL data, 77.1% were available for complete analysis. The most common reasons for incomplete data were progression, inability to answer, and follow-up failure. There were no differences in the baseline QOL subscales between the two arms (Appendix Figs A1 and A2, online only). As anticipated, no QOL subscale was significantly different between two arms until the completion of four cycles. However, from the completion of four

**Table 3.** Hematologic and Nonhematologic Toxicities

| | All Patients (N = 452) | | | | Arm A (n = 158) | | | | Arm B (n = 156) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | G1-2 | | G3-4 | | G1-2 | | G3-4 | | G1-2 | | G3-4 | |
| Toxicity | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| Hematologic toxicity | | | | | | | | | | | | |
| Neutropenia | 144 | 31.9 | 48 | 10.6 | 69 | 43.7 | 20 | 12.7 | 50 | 32.1 | 15 | 9.6 |
| Febrile neutropenia | — | — | 25 | 5.5 | — | — | 13 | 8.2 | — | — | 5 | 3.2 |
| Thrombocytopenia | 43 | 9.5 | 8 | 1.8 | 20 | 12.7 | 4 | 2.5 | 16 | 10.3 | 1 | 0.6 |
| Anemia | 346 | 76.5 | 24 | 5.3 | 123 | 77.8 | 15 | 9.5 | 134 | 85.9 | 6 | 0.6 |
| Nonhematologic toxicity | | | | | | | | | | | | |
| Alopecia | 219 | 48.5 | 3 | 0.7 | 94 | 59.5 | 1 | 0.6 | 82 | 52.6 | 1 | 0.6 |
| Anorexia | 121 | 26.8 | 7 | 1.5 | 55 | 34.8 | 4 | 2.5 | 34 | 21.8 | 3 | 1.9 |
| Fatigue | 122 | 27.0 | 0 | 0 | 57 | 36.5 | 0 | 0.0 | 31 | 19.9 | 0 | 0.0 |
| Myalgia | 67 | 14.8 | 1 | 0.2 | 30 | 19.0 | 0 | 0.0 | 22 | 14.1 | 1 | 0.6 |
| Hypersensitivity | 55 | 12.2 | 5 | 1.1 | 23 | 14.6 | 2 | 1.3 | 22 | 14.1 | 0 | 0 |
| Stomatitis | 92 | 20.4 | 0 | 0 | 37 | 23.4 | 0 | 0.0 | 30 | 19.2 | 0 | 0.0 |
| Nausea | 259 | 57.3 | 10 | 2.2 | 102 | 64.6 | 4 | 2.5 | 97 | 62.2 | 3 | 1.9 |
| Vomiting | 157 | 34.7 | 13 | 2.9 | 63 | 39.9 | 3 | 1.9 | 59 | 37.8 | 5 | 3.2 |
| Constipation | 90 | 19.9 | 5 | 1.1 | 32 | 20.3 | 2 | 1.3 | 32 | 20.5 | 3 | 1.9 |
| Diarrhea | 85 | 18.8 | 12 | 2.7 | 36 | 22.8 | 3 | 1.9 | 33 | 21.2 | 5 | 3.2 |
| Peripheral neuropathy | 139 | 30.8 | 7 | 1.5 | 63 | 39.9 | 3 | 1.9 | 50 | 32.1 | 3 | 1.9 |
| Renal toxicity | 30 | 6.6 | 4 | 0.9 | 15 | 9.5 | 1 | 0.6 | 5 | 3.2 | 0 | 0 |

Abbreviations: G1-2, grades 1 to 2; G3-4, grades 3 to 4.

**Table 4.** Summary of Second-Line and Third-Line Chemotherapy

| Chemotherapy | Arm A (n = 158) No. of Patients | Arm A % | Arm B (n = 156) No. of Patients | Arm B % | P |
|---|---|---|---|---|---|
| Second-line chemotherapy | | | | | |
| Yes | 99 | 62.7 | 116 | 74.4 | .026 |
| No | 59 | 37.3 | 40 | 25.6 | |
| Second-line regimens | | | | | |
| Docetaxel | 33 | 33.3 | 50 | 43.1 | — |
| Gemcitabine | 23 | 23.2 | 18 | 15.5 | — |
| Gefitinib | 7 | 7.1 | 10 | 8.6 | — |
| Gemcitabine/vinorelbine | 9 | 9.1 | 9 | 7.8 | — |
| Gemcitabine/cisplatin | 8 | 8.1 | 12 | 10.3 | — |
| Docetaxel/cisplatin | 6 | 6.1 | 5 | 4.3 | — |
| Paclitaxel/cisplatin | 2 | 2.0 | 1 | 0.9 | — |
| Paclitaxel | 1 | 1.0 | 2 | 1.7 | — |
| Pemetrexed | 2 | 2.0 | 6 | 5.2 | — |
| Other | 8 | 8.1 | 3 | 2.6 | — |
| Third-line chemotherapy | | | | | |
| Yes | 60 | 38.0 | 70 | 44.9 | NS |
| No | 98 | 62.0 | 86 | 55.1 | |
| Third-line regimens | | | | | |
| Docetaxel | 7 | 11.7 | 6 | 8.6 | — |
| Gemcitabine | 0 | 0 | 1 | 1.4 | — |
| Gefitinib | 51 | 85.0 | 55 | 78.6 | — |
| Gemcitabine/navelbine | 1 | 1.7 | 2 | 2.9 | — |
| Gemcitabine/cisplatin | 1 | 1.7 | 1 | 1.4 | — |
| Other | 1 | 1.7 | 5 | 4.3 | — |

Abbreviation: NS, not significant.

cycles to 3 months later, the patients in arm B showed significant improvement in role-functioning compared with arm A ($P < .05$). Furthermore, patients in arm B experienced less nausea/vomiting, sore mouth, and dyspnea ($P < .05$) than arm A. The sensitivity analysis using complete case and the replacement using multiple imputations with the Markov Chain Monte Carlo method showed comparable results. Imputation of the mean or worse score and of the last observation carried forward did not alter the conclusions.

## DISCUSSION

In this study, we could not find an OS difference between the groups, although we found a significantly better TTP in the six-cycle group. The main reason why the TTP benefit did not translate into the survival benefit probably involved the dilution effect of the second-line chemotherapy.[18-20] As noted, 62.7% of the six-cycle group and 74.4% of the four-cycle group received the second-line chemotherapy, respectively ($P = .026$). Toxicities or declining PS seem to be the reasons why fewer patients in arm A received second-line treatment and why there was no difference in OS despite the improved TTP in arm A. To minimize the possible influence of the salvage treatment after progression, tailoring the second-line treatment based on the first-line chemotherapy was recommended but not mandated. However, new agents, such as pemetrexed and gefitinib, for the second-line treatment became available during the trial, and some patients received them at the discretion of the treating oncologist and the patient. Remarkably, more than half of the patients received gefitinib as salvage treatments. Because it is well known that EGFR TKIs are more effective in Asian patients,[16,21,22] the potential survival impact of salvage therapy may be an important confounding factor that influenced OS after disease progression in the present study.

Importantly, the present study has several different aspects in terms of the design and the characteristics of the target patient population compared with previous trials. The first difference concerns the eligibility of the patients for random assignment to further chemotherapy. In previous studies, patients were randomly assigned from the beginning of chemotherapy, whereas only patients whose disease had not progressed after two cycles of chemotherapy were randomly assigned to further two versus four cycles of chemotherapy in our study. It is likely to enrich the more homogeneous patient population, is expected to minimize the dilution effect, and may keep the patients' accrual practical and feasible. Secondly, most of the patients in each arm received their planned cycles and doses. Approximately 75% of patients in longer-treated arm of our study completed five or more cycles of chemotherapy, whereas only approximately 30% to 40% of patients completed the cycles in previous studies.[5,6] Even though direct comparison with the previous trials is not possible because of the different designs, one of the plausible explanations of the differences might be related to ethnicity. It has been strongly suggested that ethnic variations in genetic polymorphisms of genes related to drug activity and metabolism are associated with differential effects on toxicity and outcomes.[23,24] Therefore, the role of genetic polymorphisms in defining the optimal duration of chemotherapy is worthy of further investigation, and tailoring the optimal duration of chemotherapy to the genetic background of the patient should be considered. Thirdly, we wanted to test if the commonly used third-generation regimens would make any difference for the optimal duration of first-line chemotherapy, because the regimens have not been well evaluated in the previous trials. The median OS and TTP in all enrolled patients (N = 452) were 11.5 months (95% CI, 10.5 to 12.5) and 4.7 months (95% CI, 4.3 to 5.1), respectively. These are better than those of Western studies and are similar to a recent Japanese study.[14,25] The survival of randomly assigned groups (n = 314) was even more promising. Although the study design of randomizing only nonprogressors had affected the outcomes, extensive usage of gefitinib for a salvage treatment might also have an impact on the outcomes. Lastly, to the best of our knowledge, this study is the first and largest phase III, randomly assigned trial to address the issue of the optimal duration of first-line chemotherapy for advanced NSCLC in Asia, a region that has been relatively underrepresented in previous studies. Recently, Murthy et al[26] raised the issue of race-, sex-, and age-based disparities in the participants of clinical trials. In that report, special populations, such as racial or ethnic minorities, women, and the elderly, were less likely to be enrolled in a cancer trial. Therefore, the development of trials that are targeted and appropriate to the needs of a special population, like our current trial, should be encouraged to increase the generalizability of that trial.

The present study also showed a favorable QOL after four cycles of chemotherapy in shorter-treatment group, which is consistent with previous phase III trials in Western populations.[5,6,27] The use of a first-line treatment of shorter duration that results in equivalent survival will reduce the risk of any cumulative toxicity that may negatively affect an individual patient's QOL and outcome. The present study, however, gives an insight into a new therapeutic strategy. In contrast to

previous Western trials, our study showed better TTP in patients with longer durations of chemotherapy. Until now, neither trial addressed the more specific question of whether patients who are responding to chemotherapy and tolerating chemotherapy well benefit from treatment beyond three to four cycles.[7] Also, the potential benefit of switching stable or responding patients to an alternative chemotherapy, perhaps with different profiles of adverse effects to avoid cumulative toxicity after three to four cycles, has not been well studied. Given that recently introduced EGFR TKIs are well tolerated and more effective in the Asian patients, they are good candidates for maintenance after induction cytotoxic chemotherapy, especially in the Asian region or in a specific subgroup of patients who are likely to respond, which might improve the outcomes of this difficult-to-treat disease. This new strategy of maintenance treatment with molecularly targeted agents after cytotoxic chemotherapy is now under development in Korea.

In conclusion, the present study argues against the current common practice in Asia, including Korea, of giving chemotherapy until progression or toxicity, but it supports the current American Society of Clinical Oncology guideline. Improved TTP with more cycles of chemotherapy, however, raises an interesting issue of maintenance therapy after the initial three to four cycles of cytotoxic chemotherapy. With the availability of effective and less toxic EGFR TKIs in the Asia-Pacific region, future trials for advanced NSCLC that integrate molecularly targeted agents as maintenance should be actively investigated and compared with the current standard recommendation while taking into account this paradigm, preferably with consideration of both ethnicity and pharmacogenomic signatures.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Joon Oh Park, Sang-We Kim, Myung Ju Ahn, Young Ho Yun, Keunchil Park
**Administrative support:** Joon Oh Park, Jin Seok Ahn, Myung Ju Ahn, Keunchil Park
**Provision of study materials or patients:** Joon Oh Park, Sang-We Kim, Jin Seok Ahn, Cheolwon Suh, Jung Shin Lee, Joung Soon Jang, Eun Kyung Cho, Sung Hyun Yang, Jin-Hyuck Choi, Dae Seog Heo, Suk Young Park, Sang Won Shin, Myung Ju Ahn, Jong Seok Lee, Keunchil Park
**Collection and assembly of data:** Joon Oh Park, Sang-We Kim, Jin Seok Ahn, Cheolwon Suh, Jung Shin Lee, Joung Soon Jang, Eun Kyung Cho, Sung Hyun Yang, Jin-Hyuck Choi, Dae Seog Heo, Suk Young Park, Sang Won Shin, Myung Ju Ahn, Jong Seok Lee, Keunchil Park
**Data analysis and interpretation:** Joon Oh Park, Sang-We Kim, Jin Seok Ahn, Myung Ju Ahn, Young Ho Yun, Jae-Won Lee, Keunchil Park
**Manuscript writing:** Joon Oh Park, Sang-We Kim, Jin Seok Ahn, Myung Ju Ahn, Young Ho Yun, Keunchil Park
**Final approval of manuscript:** Joon Oh Park, Sang-We Kim, Jin Seok Ahn, Jin-Hyuck Choi, Myung Ju Ahn, Jae-Won Lee, Keunchil Park

## REFERENCES


**1.** Shin HR, Jung KW, Won YJ, et al: 2002 Annual report of the Korea Central Cancer Registry: Based on registered data from 139 hospitals. Cancer Res Treat 36:103-114, 2004

**2.** 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 311:899-909, 1995

**3.** Grilli R, Oxman AD, Julian JA: Chemotherapy for advanced non–small-cell lung cancer: How much benefit is enough? J Clin Oncol 11:1866-1872, 1993

**4.** D'Addario G, Pintilie M, Leighl NB, et al: platinum-based versus non-platinum-based chemotherapy in advanced non–small-cell lung cancer: A meta-analysis of the published literature. J Clin Oncol 23:2926-2936, 2005

**5.** Smith IE, O'Brien MER, Talbot DC, et al: Duration of chemotherapy in advanced non–small-cell lung cancer: A randomized trial of three versus six courses of mitomycin, vinblastine, and cisplatin. J Clin Oncol 19:1336-1343, 2001

**6.** Socinski MA, Schell MJ, Peterman A, et al: Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non–small-cell lung cancer. J Clin Oncol 20:1335-1343, 2002

**7.** Pfister DG, Johnson DH, Azzoli CG, et al: American Society of Clinical Oncology treatment of unresectable non–small-cell lung cancer guideline: Update 2003. J Clin Oncol 22:330-353, 2004

**8.** Blackstock AW, Herndon JE II, Paskett ED, et al: Outcomes among African American/Non–African American patients with advanced non–small-cell lung carcinoma: Report from the Cancer and Leukemia Group B. J Natl Cancer Inst 94:284-290, 2002

**9.** Blackstock AW, Herndon JE II, Paskett ED, et al: Similar outcomes between African American and Non–African American patients with extensive-stage small-cell lung carcinoma: Report from the Cancer and Leukemia Group B. J Clin Oncol 24:407-412, 2006

**10.** Mulligan CR, Meram AD, Proctor CD, et al: Unlimited access to care: Effect on racial disparity and prognostic factors in lung cancer. Cancer Epidemiol Biomarkers Prev 15:25-31, 2006

**11.** Millward MJ, Boyer MJ, Lehnert M, et al: Docetaxel and carboplatin is an active regimen in advanced non–small-cell lung cancer: A phase II study in Caucasian and Asian patients. Ann Oncol 14:449-454, 2003

**12.** Crowley J, Furuse K, Kawahara M, et al: Second Japan-SWOG common arm analysis of paclitaxel/carboplatin in advanced stage non–small-cell lung cancer (NSCLC): A model for testing population-related pharmacogenomics. J Clin Oncol 24:376, 2006 (suppl; abstr 7050)

**13.** Kim JH, Kim SY, Jung KH, et al: Randomized phase II study of gemcitabine plus cisplatin versus etoposide plus cisplatin for the treatment of locally advanced or metastatic non–small cell lung cancer: Korean Cancer Study Group experience. Lung Cancer 52:75-81, 2006

**14.** 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 18:317-323, 2007

**15.** Bell DW, Lynch TJ, Haserlat SM, 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 23:8081-8092, 2005

**16.** Janne PA, Engelman JA, Johnson BE: Epidermal growth factor receptor mutations in non–small-cell lung cancer: Implications for treatment and tumor biology. J Clin Oncol 23:3227-3234, 2005

**17.** Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-376, 1993

**18.** 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 18:2095-2103, 2000

**19.** 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. J Clin Oncol 18:2354-2362, 2000

**20.** 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 22:1589-1597, 2004

**21.** Park J, Park BB, Kim JY, et al: Gefitinib (ZD1839) monotherapy as a salvage regimen for previously treated advanced non–small cell lung cancer. Clin Cancer Res 10:4383-4388, 2004

**22.** 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 366:1527-1537, 2005

**23.** Gurubhagavatula S, Liu G, Park S, et al: XPD and XRCC1 genetic polymorphisms are prognostic factors in advanced non–small-cell lung cancer patients treated with platinum chemotherapy. J Clin Oncol 22:2594-2601, 2004

**24.** King CR, Yu J, Freimuth RR, et al: Interethnic variability of ERCC2 polymorphisms. Pharmacogenomics J 5:54-59, 2004

**25.** Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. N Engl J Med 346:92-98, 2002

**26.** Murthy VH, Krumholz HM, Gross CP: Participation in cancer clinical trials: Race-, sex-, and age-based disparities. JAMA 291:2720-2726, 2004

**27.** Westeel V, Quoix E, Moro-Sibilot D, et al: Randomized study of maintenance vinorelbine in responders with advanced non–small-cell lung cancer. J Natl Cancer Inst 97:499-506, 2005

## *Acknowledgment*

We thank all participating investigators and coordinators and are particularly indebted to Ms. Sun-Young Yun, a coordinator of Korean Cancer Study Group Clinical Trial Center, for her coordination of the trial.

## *Appendix*

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).