# Maintenance Chemotherapy for Non-Small-Cell Lung Cancer

Young Hak Kim and Michiaki Mishima

Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University,

54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

**For reprints and all correspondence:** Young Hak Kim

Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University,

54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

Phone: +81-75-751-3830; Fax: +81-75-751-4643; E-mail: ekim@kuhp.kyoto-u.ac.jp

**Running title:** Maintenance Chemotherapy for Non-Small-Cell Lung Cancer

**Key words:** non-small-cell lung cancer, chemotherapy, maintenance, continuation, switch

## Abstract

Currently, platinum-based combination chemotherapy is the standard first-line chemotherapy for non-small-cell lung cancer (NSCLC). Historically, platinum-based chemotherapy has been recommended for up to six cycles even for responders, and second-line chemotherapy has been considered when disease progression is confirmed. In spite of extensive investigations into maintenance chemotherapy, no positive data have been obtained; however, the results of recent clinical trials suggest both the safety and efficacy of maintenance chemotherapy in patients with NSCLC, although it is still controversial. In this review, we summarize the major clinical trials of maintenance chemotherapy in patients with NSCLC, and discuss its clinical validity and present future perspectives.

## Introduction

Lung cancer is the leading cause of cancer-related death in many industrialized countries. Platinum-based combination chemotherapy has been shown to improve the survival and quality of life of patients with advanced non-small-cell lung cancer (NSCLC); however, chemotherapy for advanced NSCLC has been of limited benefit, and seems to have reached a plateau.[1, 2] Historically, platinum-based chemotherapy has been recommended up to four to six cycles, and a 'watch and wait' strategy until disease progression has been considered a reasonable therapeutic strategy.

Maintenance chemotherapy is a promising treatment strategy to improve survival and has been extensively investigated; however, no positive results have been obtained. Recently, effective second-line chemotherapy, such as docetaxel, pemetrexed, gefitinib, and erlotinib, has been developed.[3-7] Nevertheless, it is said that only about 50% of NSCLC patients in clinical trials go on to receive second-line chemotherapy.[8] This fact prompted the exploration of a maintenance strategy, and some positive results have been reported recently.

Maintenance chemotherapy is defined as the prolongation of treatment duration with the administration of additional drugs at the end of a defined number of initial chemotherapy cycles after achieving tumor control, and has been extensively

investigated in patients with NSCLC. It consists of drugs included in the induction regimen or other non-cross-resistant agents. Although the terminology is still confusing, according to the recent literature, when drugs included in the induction regimen are used it is called ‘continuation maintenance’, and when other non-cross-resistant agents are used it is called ‘switch maintenance’ or ‘early second-line’.[9, 10]

In this review, we summarized recent major clinical trials of maintenance chemotherapy in patients with NSCLC.

## Duration of first-line chemotherapy

Platinum-based combination chemotherapy is the standard first-line regimen for NSCLC; however, the duration of the platinum regimen has been a matter of debate. Current major guidelines recommend that platinum-based chemotherapy should be administered for no more than six cycles.[11-13] Randomized trials on which these guidelines are based are summarized in Table 1.

Smith et al. conducted a phase III trial comparing three and six cycles of mitomycin, vinblastine, and cisplatin (MVP) in 308 patients. Seventy-three percent of patients randomized to six cycles completed three cycles and 31 % six cycles, while 72% of patients randomized to three cycles completed treatment. Median time to

disease progression (TTP) was 5 months for both arms, and median survival time (MST) was 6 months in the 3-cycle arm and 7 months in the 6-cycle arm, respectively ($p$=0.2). Quality-of-life (QOL) parameters were almost identical between the two arms; however, patients randomized to six cycles experienced significantly more fatigue ($p$=0.03).[14]

Socinski et al. performed a phase III trial in which 230 patients were randomized to either four cycles of carboplatin and paclitaxel (CP) or CP until disease progression. The median number of treatment cycles was four in both arms. There were no significant differences in MST between the two arms ($p$=0.63). TTP was not reported in the study. There were no differences in toxicities, except for neuropathy; however, the QOL of both treatment arms was not significantly different.[15]

In the trial conducted by von Plessen et al., three and six cycles of carboplatin and vinorelbine were compared in 297 patients. Survival data and QOL were not significantly different between the two arms. The authors concluded that more than three cycles of chemotherapy confers no survival or consistent QOL benefits in advanced NSCLC.[16]

In the recent trial conducted by Park et al., patients with stages IIIB or IV NSCLC who had not progressed after two cycles of cisplatin-based chemotherapy were

randomly assigned to receive either four (6-cycle arm) or two (4-cycle arm) more cycles of chemotherapy. There were no significant differences in MST (14.9 months vs. 15.9 months, $p$=0.461); however, median TTP was significantly longer in the 6-cycle arm (6.2 months vs. 4.6 months, $p$=0.001). Patients in the 4-cycle arm showed significant improvement in role-functioning from the completion of four cycles to 3 months later, and also experienced less nausea/vomiting, sore mouth, and dyspnea than the 6-cycle arm. In addition, patients in the 6-cycle arm significantly less frequently received second-line chemotherapy than the 4-cycle arm (62.7% vs. 74.4%, $p$=0.026), which may explain why the difference in TTP did not translate into overall survival (OS). The authors speculated that toxicities or a declining performance status (PS) might have led to the lower frequency of the use of second-line chemotherapy in the 6-cycle arm.[17] Nevertheless, their results suggested that further investigation of maintenance chemotherapy with less toxic agents is warranted.

## Cytotoxic agents

### Continuation maintenance (summarized in Table 2)

#### *Paclitaxel*

Belani et al. conducted a phase III trial in which patients whose disease did not progress

after initial chemotherapy with carboplatin and paclitaxel were randomly assigned to either weekly paclitaxel (n=65) or observation (n=65). Median TTP and MST were 38 weeks and 75 weeks in the paclitaxel arm, and 29 weeks and 60 weeks in the observation arm, respectively. As a result, the efficacy of maintenance paclitaxel was not indicated.[18]

***Gemcitabine***

In the trial conducted by Brodowicz et al., patients achieving an objective response or disease stabilization following initial chemotherapy with cisplatin and gemcitabine were randomized to the maintenance gemcitabine arm (n=138) or best supportive care (BSC) arm (n=68). Median TTP throughout the study period was 6.6 and 5.0 months for the gemcitabine and BSC arms, respectively ($p < 0.001$), while values in the maintenance period were 3.6 and 2.0 months ($p < 0.001$). MST throughout the study was 13.0 months for the gemcitabine arm and 11.0 months for the BSC arm ($p=0.195$). The toxicity profile was mild, with neutropenia being the most common grade 3/4 toxicity.[19]

In the 2010 American Society of Clinical Oncology (ASCO) annual meeting, Belani et al. presented the results of a phase III trial evaluating the efficacy of gemcitabine as maintenance therapy. In the trial, patients with wet stage IIIB/IV

NSCLC were initially treated with carboplatin and gemcitabine every 3 weeks for 4 cycles. Subsequently, patients with CR/PR or SD were randomized 1:1 to receive maintenance gemcitabine every 3 weeks with BSC or BSC alone until disease progression. Following 4 cycles of carboplatin and gemcitabine, 255 non-progressive patients were randomized to receive gemcitabine + BSC (n=128) or BSC alone (n=127). The median progression-free survival (PFS) was 3.9 months for gemcitabine and 3.8 months for BSC arms. MST was 8.0 months for gemcitabine and 9.3 months for BSC. The differences in survival between the two arms were not statistically significant (HR=0.97 [95% CI: 0.72, 1.30], *p*=0.84). Maintenance therapy was well tolerated despite a higher incidence of grade 3/4 toxicity (anemia 9.4% vs. 2.4%; neutropenia 13.3% vs. 1.6%; thrombocytopenia 9.4% vs. 1.4%; and fatigue 3.9% vs. 1.6%). The author concluded that it was a negative study, mentioning that nearly two thirds of patients had a performance status (PS) of 2 and that less than 20% of patients received post-study treatment.[20]

In the same meeting, Perol et al. presented the results of an interesting phase III trial, in which stage IIIB/IV patients with PS of 0-1 whose tumors did not progress following four cycles of cisplatin-gemcitabine were randomized to observation (n=155), or to receive either gemcitabine (n=154) or erlotinib (n=155) as maintenance therapy

until disease progression. Second-line chemotherapy was pre-defined as pemetrexed. Median PFS was 1.9 months in the observation arm, 3.8 months in the gemcitabine arm, and 2.9 months in the erlotinib arm, respectively. The difference between the observation arm and gemcitabine arm ($p < 0.0001$) or erlotinib arm ($p=0.002$) was significant. OS was not significantly different; however, the OS data were immature and there was a tendency in favor of maintenance chemotherapy. In addition, both drugs had manageable toxicities in the maintenance setting.[21] Final results are awaited.

**Switch maintenance (summarized in Table 3)**

***Vinorelbine***

In a phase III trial conducted by Westeel et al., 573 patients with stage IIIB and IV NSCLC were initially treated with mitomycin, ifosfamide, and cisplatin (MIC). Those with stage IIIB disease received two cycles of MIC followed by thoracic radiation, and those with wet IIIB and IV disease received four cycles of MIC. Of 227 patients who responded to initial treatment, 181 were randomized to either maintenance chemotherapy with weekly vinorelbine for 6 months (n=91) or observation (n=90). One- and 2-year survival rates were 42.2% and 20.1% in the vinorelbine arm and 50.6% and 20.2% in the observation arm, respectively ($p=0.48$). The hazard ratio of survival after adjustment for

stage in the vinorelbine arm relative to the observation arm was 1.08 (95% CI: 0.79, 1.47, $p$=0.65). There was also no difference between the two arms in PFS ($p$=0.32). The main toxicity was hematologic, and it was more frequently observed in patients who had received induction chemoradiation than in patients who had received induction chemotherapy. [22]

***Docetaxel***

Fidias et al. conducted a phase III trial in which patients with wet IIIB or IV NSCLC were enrolled. In the trial, patients were initially treated with four cycles of chemotherapy with carboplatin and gemcitabine, and those who did not have progression were randomly assigned to either immediate or delayed docetaxel. In the immediate group, docetaxel was initiated from day 21 up to day 35 after the start of cycle 4 of initial chemotherapy. In the delayed group, in contrast, docetaxel was given only at the time of documented progression. After four cycles of initial chemotherapy, 309 of 566 patients were deemed non-PD and were randomized to either immediate or delayed docetaxel. Of the patients randomized to immediate docetaxel, 94.8% of patients received at least one treatment cycle, whereas only 62.8% of patients randomized to the delayed arm ever received docetaxel. The most common reasons for not receiving docetaxel in the delayed arm

were disease progression, patient or investigator decision, and death. Median PFS was significantly better in the immediate arm than the delayed arm (5.7 vs 2.7 months, $p$=0.0001). OS was also better in the immediate arm; however, the difference was not significant (12.3 vs 9.7 months, $p$=0.0853). When the survival of patients who actually received docetaxel in the delayed arm was compared with that of treated patients in the immediate arm, OS was identical (12.5 months for both groups). There were no differences in toxicity or QOL between the two arms.[23]

***Pemetrexed***

More recently, pemetrexed has been examined as maintenance chemotherapy. In the trial conducted by Ciuleanu et al., patients who had not progressed on four cycles of platinum-based chemotherapy were randomly assigned in a 2:1 ratio to either maintenance pemetrexed (n=441) or placebo (n=222). Median PFS was 4.3 months in the pemetrexed arm and 2.6 months in the placebo arm ($p$＜0.0001). OS was also significantly favored in the pemetrexed arm (13.4 vs 10.6 months, $p$=0.012). Subgroup analysis revealed that the survival benefit of maintenance pemetrexed was seen in patients with non-squamous histology but not in patients with squamous histology. Median PFS was 4.4 months in the pemetrexed arm and 1.8 months in the placebo arm,

for non-squamous histology ($p < 0.0001$), whereas 2.4 months in the pemetrexed arm and 2.5 months in the placebo arm for squamous histology ($p=0.896$). MST was 15.5 months in the pemetrexed arm and 10.3 months in the placebo arm for non-squamous histology ($p < 0.0001$), whereas 9.9 months in the pemetrexed arm and 10.8 months in the placebo arm for squamous histology ($p=0.678$). Pemetrexed toxicities were generally mild, and no treatment-related deaths were observed. For post-study treatment, only 18% of patients received pemetrexed in the placebo arm.[24] There is a criticism that this study did not show that the timing of subsequent therapy is crucial, but only showed that pemetrexed can significantly improve the survival of patients who receive the agent.[25]

## Molecular-targeted agents

### Continuation maintenance (summarized in Table 4)

#### *Bevacizumab*

There have been two large randomized phase III trial of bevacizumab for NSCLC, one of which was conducted by the Eastern Cooperative Oncology Group (ECOG), E4599. In this trial, patients with stage IIIB/IV, non-squamous histology were randomly assigned to either chemotherapy with carboplatin and paclitaxel alone (n=444) or

carboplatin and paclitaxel plus bevacizumab 15mg/kg (n=434). Chemotherapy was repeated for up to six cycles unless there was evidence of disease progression. Patients in the bevacizumab arm were administered bevacizumab concurrently with chemotherapy and continued to receive bevacizumab monotherapy every 3 weeks until disease progression or intolerable toxicities. Both PFS and OS were significantly better in the bevacizumab arm (6.2 vs 4.5 months, HR 0.66 [95% CI 0.57, 0.77], $p<0.001$ for PFS; 12.3 vs 10.3 months, HR 0.79 [95% CI 0.67, 0.92], $p=0.003$ for OS).[26]

In the other trial (AVAstin In Lung cancer: AVAiL) conducted in Europe, patients with non-squamous NSCLC were randomly assigned to either chemotherapy with cisplatin and gemcitabine alone (n=347), cisplatin and gemcitabine plus bevacizumab 7.5mg/kg (n=345), or cisplatin and gemcitabine plus bevacizumab 15mg/kg (n=351). PFS, the primary endpoint, was significantly better in the bevacizumab arms than the chemotherapy-alone arm (6.7 vs 6.1 months, $p=0.003$ for low-dose bevacizumab and 6.5 vs 6.1 months, $p=0.03$ for high-dose bevacizumab); however, the differences were not translated into OS.[27, 28]

In both trials, bevacizumab was administered from the beginning, concurrently with chemotherapy. There are no conclusive data on the necessity of maintenance bevacizumab; however, a recent randomized trial of bevacizumab for gynecologic

cancer suggested the effectiveness of a maintenance phase.[29] Further investigations are needed also in the field of NSCLC.

***Cetuximab***

Pirker et al. conducted a phase III trial (First-Lin ErbituX in lung cancer: FLEX) in which patients with EGFR-expressing wet IIIB or IV NSCLC were randomized either to chemotherapy with cisplatin and vinorelbine alone (n=568) or cisplatin and vinorelbine plus cetuximab (n=557). In the cetuximab arm, cetuximab was administered concurrently with chemotherapy and was continued after the end of chemotherapy until PD or unacceptable toxicity. Median PFS was 4.8 months in each arm; however, OS was significantly better in the cetuximab arm (median 11.3 vs 10.1 months, HR=0.871 [95% CI: 0.762, 0.996], *p*=0.044). More patients in the chemotherapy-alone arm started second-line chemotherapy without documented disease progression, and analysis of time-to-treatment failure as a posthoc sensitivity analysis for PFS showed a significant benefit for cetuximab.[30] In the other study, in which cetuximab was combined with carboplatin and paclitaxel, in contrast, no survival advantages were demonstrated.[31]

**Switch maintenance (summarized in Table 5)**

***Gefitinib***

Concurrent administration of gefitinib with chemotherapy failed to show survival advantages over chemotherapy alone.[32, 33] The West Japan Thoracic Oncology Group (WJTOG) carried out a phase III trial to evaluate whether gefitinib improves survival as maintenance therapy after platinum-based chemotherapy. In this study, chemotherapy-naïve patients with stage IIIB/IV NSCLC were randomly assigned to either platinum-doublet chemotherapy for up to six cycles (arm A, n=301) or platinum-doublet chemotherapy for three cycles followed by gefitinib until disease progression (arm B, n=302). Median PFS was 4.3 months for arm A and 4.6 months for arm B, and there was a statistically significant difference ($p < 0.001$); however, MST was almost identical between the two arms (12.9 months for arm A, 13.7 months for arm B; $p=0.11$). Exploratory subset analysis revealed possible prolongation with sequential therapy of gefitinib, especially in patients with adenocarcinoma.[34]

The European Organization for Research and Treatment of Cancer (EORTC) conducted a phase III trial in which patients with advanced NSCLC not progressing after 4 cycles of platinum-based chemotherapy were randomized to receive either gefitinib or a matched placebo until progression or unacceptable toxicity. After the inclusion of 173 patients, the trial was prematurely closed to entry due to low accrual.

As a result, 86 and 87 patients were randomized to either gefitinib or placebo, respectively. MST was not statistically different (10.9 months for gefitinib arm and 9.4 months for placebo arm, HR 0.83 [95% CI 0.60, 1.15], p = 0.2); however, PFS was significantly better in the gefitinib arm (medians 4.1 and 2.9 months, HR=0.61 [95% CI: 0.45, 0.83], *p*=0.0015).[35]

***Erlotinib***

As with gefitinib, concurrent administration of erlotinib with chemotherapy was not superior to chemotherapy alone.[36, 37] Sequential Tarceva in Unresectable NSCLC (SATURN) is a randomized, placebo-controlled phase III trial comparing maintenance erlotinib with a placebo. In this trial, 1949 chemo-naïve patients were initially treated with four cycles of platinum-based chemotherapy. Those who did not progress on treatment were then randomized to receive either erlotinib (n=438) or placebo (n=451). Approximately, 45% of patients had adenocarcinoma histology and 40% had squamous cell carcinoma histology in each arm. The primary endpoint was PFS, and patients were stratified by a number of clinical factors as well as their epidermal growth factor receptor (EGFR) protein expression status, assessed by immunohistochemistry, and EGFR gene copy number, assessed by fluorescent in situ hybridization. Both PFS and

OS were significantly better in the erlotinib arm (12.3 weeks vs 11.1 weeks, HR 0.71 [95% CI 0.62, 0.82], $p<0.0001$ for PFS; 12.0 months vs 11.0 months, HR 0.81 [95% CI 0.70, 0.95], $p=0.0088$ for OS). Biomarker analysis showed no significant interaction of EGFR protein expression or EGFR gene copy number. Patients with EGFR-activating mutations in exon 19 or 21 derived significantly greater PFS benefit from maintenance erlotinib (HR 0.10, $p<0.0001$) than those patients with EGFR wild-type tumors (HR 0.78, $p=0.018$); however, OS was not significantly different due to extensive cross-over to erlotinib at the time of progression.[38]

The ATLAS trial was designed to evaluate bevacizumab + erlotinib vs. bevacizumab + placebo following bevacizumab + platinum-containing doublet chemotherapy in patients with chemo-naïve, stage IIIb/IV NSCLC. In the trial, 743 stable and responding patients remained on maintenance bevacizumab and were randomly assigned to receive oral erlotinib 150 mg daily or placebo. The majority of patients included had adenocarcinoma histology (81.3% in erlotinib arm and 82.5% in placebo arm). PFS, a primary endpoint, was significantly better in the erlotinib arm than the placebo arm (4.8 months vs. 3.7 months; HR 0.72 [95% CI 0.59, 0.88], $p=0.0012$). MST was 15.9 months in the erlotinib arm and 13.9 months in the placebo arm, respectively (HR 0.90 [95% CI: 0.74, 1.09], $p=0.2686$). The difference in OS between

the arms was not significant; however, the difference of two months is promising.[39, 40]

## Discussion

Maintenance chemotherapy is a promising strategy in the treatment of NSCLC. Recently, pemetrexed and erlotinib have been approved for maintenance chemotherapy by both the U.S. Food and Drug Administration and European Medicines Agency; however, there has been no conclusive predictor of who will benefit from maintenance chemotherapy and which type of maintenance, continuation or switch, is preferred.

As for which patients may benefit from maintenance chemotherapy, Sun et al. performed an interesting retrospective analysis, according to which, patients with poor PS after first-line chemotherapy, large initial tumor, or smaller decrease in tumor size after first-line chemotherapy were less likely to receive second-line chemotherapy and might derive greater benefit from maintenance chemotherapy.[41] Considering that recent attention to maintenance strategy is based on the advances of second-line chemotherapy with more effective and less toxic agents and that only about half of the patients received second-line chemotherapy, patients with such characteristics should be offered maintenance chemotherapy.

Regarding the type of maintenance strategy, one possibility is that patients

whose response to induction chemotherapy was SD may benefit more from switch maintenance than patients who achieve PR or CR. In fact, patients who had SD after induction chemotherapy had a more pronounced survival benefit with maintenance erlotinib (median 11.9 vs 9.6 months; HR 0.72 [95% CI 0.59, 0.89], $p$=0.0019) than those who had PR or CR (median 12.5 vs 12.0 months; HR 0.94 [95% CI 0.74, 1.20], $p$=0.618) in the SATURN trial.[38] In contrast, it seems that patients who achieved PR or CR may derive more benefit from continuation maintenance than those who have SD after induction chemotherapy. Further analysis of past clinical trials of maintenance chemotherapy may reveal the influence of the response to induction chemotherapy in both continuation and switch maintenance.

**Conflict of interest statement**

There are no potential conflicts of interest related to the article.

## References


1. 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**:92-8.
2. 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**:317-23.
3. 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**:2354-62.
4. 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**:2095-103.
5. 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**:1589-97.
6. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;**353**:123-32.
7. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;**372**:1809-18.
8. Hirsh V. Systemic therapies in metastatic non-small-cell lung cancer with emphasis on targeted therapies: the rational approach. Curr Oncol 2010;**17**:13-23.
9. Gridelli C, Maione P, Rossi A, et al. Potential treatment options after first-line chemotherapy for advanced NSCLC: maintenance treatment or early second-line? Oncologist 2009;**14**:137-47.
10. Stinchcombe TE, Socinski MA. Treatment paradigms for advanced stage non-small cell lung cancer in the era of multiple lines of therapy. J Thorac Oncol 2009;**4**:243-50.
11. Besse B. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2007;**18** Suppl 2:ii30-1.
12. Socinski MA, Crowell R, Hensing TE, et al. Treatment of non-small cell lung cancer, stage IV: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;**132**:277S-89S.

13. Azzoli CG, Baker S, Jr., Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 2009;**27**:6251-66.
14. Smith IE, O'Brien ME, 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 2001;**19**:1336-43.
15. 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 2002;**20**:1335-43.
16. von Plessen C, Bergman B, Andresen O, et al. Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. Br J Cancer 2006;**95**:966-73.
17. Park JO, Kim SW, Ahn JS, et al. 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. J Clin Oncol 2007;**25**:5233-9.
18. Belani CP, Barstis J, Perry MC, et al. Multicenter, randomized trial for stage IIIB or IV non-small-cell lung cancer using weekly paclitaxel and carboplatin followed by maintenance weekly paclitaxel or observation. J Clin Oncol 2003;**21**:2933-9.
19. Brodowicz T, Krzakowski M, Zwitter M, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer 2006;**52**:155-63.
20. Belani CP, Waterhouse D, Ghazal H, et al. Phase III study of maintenance gemcitabine (G) and best supportive care (BSC) versus BSC, following standard combination therapy with gemcitabine-carboplatin (G-Cb) for patients with advanced non-small cell lung cancer (NSCLC). ASCO Meeting Abs 2010;**28**:7506.
21. Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study. ASCO Meeting Abs 2010;**28**:7507.
22. 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 2005;**97**:499-506.
23. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2009;**27**:591-8.
24. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best

supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;**374**:1432-40.

25. Stinchcombe TE, West HL. Maintenance therapy in non-small-cell lung cancer. Lancet 2009;374:1398-400.

26. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;**355**:2542-50.

27. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009;**27**:1227-34.

28. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010;**21**:1804-9.

29. Burger RA, Brady MF, Bookman MA, et al. Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study. ASCO Meeting Abs 2010;**28**:LBA1.

30. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;**373**:1525-31.

31. Lynch TJ, Patel T, Dreisbach L, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol 2010;**28**:911-7.

32. Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 1. J Clin Oncol 2004;**22**:777-84.

33. Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 2. J Clin Oncol 2004;**22**:785-94.

34. Takeda K, Hida T, Sato T, et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a west Japan thoracic oncology group trial (WJTOG0203). J Clin Oncol;**28**:753-60.

35. Gaafar RM, Surmont V, Scagliotti G, et al. A double-blind, randomized, placebo-controlled phase III intergroup study of gefitinib (G) in patients (pts) with advanced NSCLC, non-progressing after first-line platinum-based chemotherapy

(EORTC 08021-ILCP 01/03). ASCO Meeting Abs 2010;**28**:7518.
36. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2005;**23**:5892-9.
37. Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. J Clin Oncol 2007;**25**:1545-52.
38. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010;**11**:521-9.
39. Miller VA, O'Connor P, Soh C, et al. A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). ASCO Meeting Abs 2009;**27**:LBA8002.
40. Kabbinavar FF, Miller VA, Johnson BE, et al. Overall survival (OS) in ATLAS, a phase IIIb trial comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy (chemo) with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). ASCO Meeting Abs 2010;**28**:7526
41. Sun JM, Park JO, Won YW, et al. Who are less likely to receive subsequent chemotherapy beyond first-line therapy for advanced non-small cell lung cancer? Implications for selection of patients for maintenance therapy. J Thorac Oncol;**5**:540-5.

Table 1 Randomized trials for treatment duration of platinum-based chemotherapy in NSCLC

| Author | Regimen | Treatment arms | TTP | MST | 1-year survival (%) |
|---|---|---|---|---|---|
| Smith[14] | MVP | 3 cycles | 5 months | 6 months | 22 |
| | | 6 cycles | 5 months | 7 months | 25 |
| Socinski[15] | Carbo/Pac | 4 cycles | NR | 6.6 months | 28 |
| | | Until PD | NR | 8.5 months | 34 |
| von Plessen[16] | Cis/Vin | 3 cycles | 16 weeks | 28 weeks | 25 |
| | | 6 cycles | 21 weeks | 32 weeks | 25 |
| Park[17] | Cis-based | 4 cycles | 4.6 months | 15.9 months | 59 |
| | | 6 cycles | 6.2 months* | 14.9 months | 62.4 |

NSCLC, non-small-cell lung cancer; MVP, mitomycin + vindesine + cisplatin; Carbo, carboplatin; Pac, paclitaxel;

Cis, cisplatin; Vin, vinorelbine; TTP, time to progression; NR, not reported; MST, median survival time

Table 2 Randomized trials for continuation maintenance of cytotoxic agents in NSCLC

| Author | Induction chemotherapy | Treatment arms | No. of pts | PFS | *p*-value | MST | *p*-value |
|---|---|---|---|---|---|---|---|
| Belani[18] | Carbo/Pac | Pac | 65 | 38 weeks | NR | 75 weeks | NR |
| | | observation | 65 | 29 weeks | | 60 weeks | |
| Brodowicz[19] | Cis/Gem | Gem | 138 | 3.6 months* | <0.001 | 10.2 months | 0.172 |
| | | observation | 68 | 2.0 months | | 8.1 months | |
| Belani[20] | Carbo/Gem | Gem | 128 | 7.4 months | NR | 8.0 months | 0.84 |
| | | observation | 127 | 7.7 months | | 9.3 months | |
| Perol[21] | Cis/Gem | Gem | 154 | 3.8 months* | <0.0001* | NR | NR* |
| | | Erlotinib | 155 | 2.9 months* | 0.002** | NR | NR** |
| | | observation | 155 | 1.9 months | | NR | |

NSCLC, non-small-cell lung cancer; Carbo, carboplatin; Pac, paclitaxel; Gem, gemcitabine; PFS, progression-free survival; MST, median survival time;

NR, not reported; *Gem vs. observation; **Erlotinib vs. observation

Table 3 Randomized trials for switch maintenance of cytotoxic agents in NSCLC

| Author | Induction chemotherapy | Treatment arms | No. of patients | PFS (months) | *p*-value | MST (months) | *p*-value |
|---|---|---|---|---|---|---|---|
| Westeel[22] | MIC | Vin | 91 | 5.0 | 0.32 | 12.3 | 0.48 |
| | | Observation | 90 | 3.0 | | 12.3 | |
| Fidias[23] | Carbo/Gem | Immediate Doc | 153 | 5.7 | 0.0001 | 12.3 | 0.0853 |
| | | Delayed Doc | 156 | 2.7 | | 9.7 | |
| Ciuleanu[24] | Platinum-based | Pem | 441 | 4.3 | ＜0.0001 | 13.4 | 0.012 |
| | | Placebo | 222 | 2.6 | | 10.6 | |

NSCLC, non-small-cell lung cancer; MIC, mitomycine + ifosfamide + cisplatin; Carbo, carboplatin;

Gem, gemcitabine; Vin, vinorelbine; Doc, docetaxel; PFS, progression-free survival; MST, median survival time

Table 4 Randomized trials for continuation maintenance of molecular-targeted agents in NSCLC

| Author | Induction chemotherapy | Treatment arms | No. of patients | PFS (months) | *p*-value | MST (months) | *p*-value |
|---|---|---|---|---|---|---|---|
| Giaccone[32] | Cis/Gem | G250→G250 | 365 | 5.3 months | 0.7633* | 9.8 months | 0.4560* |
| (INTACT 1) | | G500→G500 | 365 | 4.6 months | | 8.7 months | |
| | | Placebo→Placebo | 363 | 5.0 months | | 9.9 months | |
| Herbst[33] | Carbo/Pac | G250→G250 | 345 | 5.8 months | 0.0562* | 9.9 months | 0.6385* |
| (INTACT 2) | | G500→G500 | 347 | 5.5 months | | 9.9 months | |
| | | Placebo→Placebo | 345 | 6.0 months | | 10.9 months | |
| Herbst[36] | Carbo/Pac | E150→E150 | 539 | 5.1 months* | 0.36 | 10.6 months | 0.95 |
| (TRIBUTE) | | Placebo→Placebo | 540 | 4.9 months | | 10.5 months | |
| Gatzemeier[37] | Cis/Gem | E150→E150 | 580 | 23.7 weeks* | 0.74 | 43.0 weeks | 0.49 |
| (TALENT) | | Placebo→Placebo | 579 | 24.6 weeks | | 44.1 weeks | |
| Sandler[26] | Carbo/Pac | Bev15→Bev15 | 417 | 6.2 months* | ＜0.001 | 12.3 months* | 0.003 |
| (E4599) | | Placebo→Placebo | 433 | 4.5 months | | 10.3 months | |
| Reck[27,28] | Cis/Gem | Bev15→Bev15 | 351 | 6.5 months* | 0.03** | 13.4 months | 0.761** |
| (AVAiL) | | Bev7.5→Bev7.5 | 345 | 6.7 months* | 0.003*** | 13.6 months | 0.420*** |
| | | Placebo→Placebo | 347 | 6.1 months | | 13.1 months | |
| Pirker[30] | Cis/Vin | Ctx→Ctx | 557 | 4.8 months | 0.39 | 11.3 months* | 0.044 |
| (FLEX) | | Placebo→Placebo | 568 | 4.8 months | | 10.1 months | |
| Lynch[31] | Carbo/Pac | Ctx→Ctx | 338 | 4.40 months | 0.2358 | 9.69 months | 0.1685 |
| (BMS099) | | Placebo→Placebo | 338 | 4.24 months | | 8.38 months | |

NSCLC, non-small-cell lung cancer; Cis, cisplatin; Gem, gemcitabine; Carbo, carboplatin; Pac, paclitaxel; Vin, vinorelbine; G, gefitinib; E, erlotinib;

Bev, bevacizumab; Ctx, cetuximab; PFS, progression-free survival; MST, median survival time; *global ordered log-rank test; **Bev 7.5mg vs. placebo;

***Bev 15mg vs. placebo

Table 5 Randomized trials for switch maintenance of molecular-targeted agents in NSCLC

| Author | Induction chemotherapy | Treatment arms | No. of patients | PFS (months) | *p*-value | MST (months) | *p*-value |
|---|---|---|---|---|---|---|---|
| Takeda[34] | Platinum-based | G250 | 302 | 4.6 months | <0.001 | 13.7 months | 0.11 |
| (WJTOG 0203) | | Observation | 301 | 4.3 months | | 12.9 months | |
| Gaafar[35] | Platinum-based | G250 | 86 | 4.1 months* | 0.0015 | 10.9 months | 0.2 |
| (EORTC 08021) | | Placebo | 87 | 2.9 months | | 9.4 months | |
| Cappuzzo[38] | Platinum-based | E150 | 438 | 12.3 weeks* | <0.0001 | 12.0 months* | 0.0088 |
| (SATURN) | | Placebo | 451 | 11.1 weeks | | 11.0 months | |
| Miller, Kabbinavar[39,40] | Platinum-based/Bev | Bev +E150 | 370 | 4.76 months* | 0.0012 | 15.9 weeks | 0.2686 |
| (ATLAS) | | Bev | 373 | 3.75 months | | 13.9 weeks | |

NSCLC, non-small-cell lung cancer; G, gefitinib; E, erlotinib; Bev, bevacizumab; PFS, progression-free survival; MST, median survival time