REVIEW

http://dx.doi.org/10.4046/trd.2014.76.1.1
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2014;76:1-7

TRD
Tuberculosis and Respiratory Diseases

Update on the Evidence Regarding Maintenance Therapy

Jeong Eun Lee, M.D., Ph.D. and Chae-Uk Chung, M.D., Ph.D.
Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University School of Medicine, Daejeon, Korea

Maintenance therapy has emerged as a novel therapeutic paradigm for advanced non-small-cell lung cancer (NSCLC). Maintenance therapy that aims to sustain a clinically favorable state after first-line chemotherapy has two strategies. Switch maintenance therapy entails switching to a new and non-cross-resistant agent in an alternating or sequential manner, on completion of first-line chemotherapy. Continuous maintenance therapy keeps ongoing administration of a component of the current regimen after four to six cycles of chemotherapy, if there is a stable disease, or better response. Both maintenance therapies can be continued, until disease progression. The potential evidence regarding maintenance therapy includes providing the opportunity to receive additional treatment, through sustaining tumor shrinkage, and delayed emergence of tumor-related symptom. Thus far, debates over the parameters used to predict the effectiveness of maintenance therapy, financial burden, and uncertainty of improving the quality of life exist. Despite many debates, maintenance therapy, which is currently recommended, has been disclosed to be beneficial.

Keywords: Maintenance Chemotherapy; Carcinoma, Non-Small-Cell Lung

Introduction

Maintenance therapy is a new treatment strategy that aims to sustain a reduced tumor size and relieve tumor-related symptoms, in contrast to conventional chemotherapy that aims to maximize tumor cell death.

Based on research data, the National Comprehensive Cancer Network (NCCN) guidelines recommend maintenance therapy in non-small-cell lung cancer (NSCLC) after first-line therapy, and many clinical studies of multiple regimens and modalities are currently underway.

Maintenance therapy can be classified into two types: switch maintenance therapy and continuous maintenance therapy. Switch maintenance therapy involves switching to a different non-cross-resistant regimen in an alternating or sequential fashion if the response is complete remission (CR), partial remission (PR), or stable disease (SD) after four to six cycles of first-line platinum-based combination chemotherapy. Continuous maintenance therapy is to continue one or all component of the current regimen after four to six cycles of chemotherapy if there is a SD or better response. Both maintenance therapies can be continued until disease progression[1].

Much clinical and biological evidence regarding maintenance therapy exists[2]. First, about 20–80% of NSCLC patients cannot receive second-line chemotherapy for multiple reasons, including poor compliance. Maintenance therapy can suppress disease progression and provide the opportunity to receive additional treatment. Second, according to the Goldie-Coldman theory[3], resistant and slowly growing cancer cells remain after first-line chemotherapy which has killed the sensitive and rapidly proliferating cells. Use of different non-cross-resistant chemotherapy regimens is effective in eradicating

Address for correspondence: Jeong Eun Lee, M.D., Ph.D.
Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University School of Medicine, 282 Munhwa-ro, Jung-gu, Daejeon 301-721, Korea
Phone: 82-42-280-8035, **Fax:** 82-42-257-5753
E-mail: naturetoscience2013@gmail.com
Received: Oct. 29, 2013
Revised: Nov. 5, 2013
Accepted: Nov. 13, 2013

the remaining resistant cancer cells. Third, continuing low-dose cytotoxic chemotherapies can damage endothelial cells, ultimately decreasing angiogenesis in the tumor microenvironment. Fourth, maintenance chemotherapy can activate the immune system against tumor cell. Despite number of studies showing an effectiveness of maintenance therapy, many concerns remain regarding the financial burden and uncertainty of improving quality of life (QOL). Additionally, absence of the parameters used to predict the effectiveness of maintenance therapy and debates over whether progression-free survival is the optimal primary endpoint in clinical trials to elucidate benefit of maintenance therapy should be considered in practical application of it.

Updated Guidelines for Maintenance Therapy in NSCLC

NCCN version 2.2013 recommends continuous maintenance therapy using bevacizumab (category 1), cetuximab (category 1), pemetrexed (category 1), bevacizumab plus pemetrexed, and gemcitabine and switch maintenance therapy using pemetrexed, erlotinib, and docetaxel (category 2B). It also recommends that close surveillance of patients without therapy is a reasonable alternative to maintenance.

More specifically, in anaplastic lymphoma kinase-negative non-squamous NSCLC patients, continuation of bevacizumab (category 1), cetuximab (category 1), pemetrexed (category 1), bevacizumab plus pemetrexed, or gemcitabine and switch therapy to pemetrexed or erlotinib improve progression-free survival and overall survival (OS). In patients with squamous cell carcinoma, continuation of cetuximab (category 1) or gemcitabine and switch to erlotinib or doxetaxel (category 2B) are recommended.

Continuation of Platinum-Based Doublet Therapy

Continuation of first-line platinum doublet chemotherapy can be understood in the same context with clinical studies evaluating the optimal chemotherapy duration. More than four to six cycles of platinum-based chemotherapy showed no benefit in increasing the overall response rate (ORR) or survival rate; rather, this chemotherapy regimen augments toxicity. Socinski et al.[4] compared the OS and QOL in two groups of stage IIIb/IV NSCLC patients: arm A (four cycles of carboplatin at an area under the curve of 6 and paclitaxel 200 mg/m^2 every 21 days) or arm B (continuous treatment with carboplatin/paclitaxel until progression). That study showed no overall benefit in OS, ORR, or QOL to continuing treatment with carboplatin/paclitaxel beyond four cycles in advanced NSCLC. Additionally, other studies comparing six cycles and three to four cycles of chemotherapy also demonstrated that progression-free survival (PFS), OS, and the proportion of patients undergoing second-line chemotherapy were not significantly different[5,6].

Continuation of the Non-Platinum Component of First-Line Therapy

Paclitaxel, gemcitabine, pemetrexed, vinorelbine, and doxetaxel can be combined with platinum as first-line chemotherapy for NSCLC patients. Among them, paclitaxel, gemcitabine, and pemetrexed were investigated as maintenance chemotherapy. Belani et al.[7] showed that weekly paclitaxel and carboplatin followed by weekly maintenance paclitaxel (70 mg/m^2, 3 of 4 weeks) was beneficial compared with observation alone after first-line chemotherapy. In this study, the median PFS and OS were 38 and 76 weeks in maintenance therapy group, respectively, and 29 and 60 weeks for the control group, respectively. However, this study did not analyzed statistical significance according to maintenance therapy; therefore, a need for further validation of the efficacy of weekly paclitaxel maintenance therapy exists.

The Central European Cooperative Oncology Group (CECOG) compared gemcitabine maintenance therapy and best supportive care (BSC) after combination chemotherapy using cisplatin (80 mg/m^2) and gemcitabine (1,250 mg/m^2, days 1 and 8)[8]. Patients showing CR/PR or SD after four cycles of first-line chemotherapy were randomized and maintenance arm received gemcitabine (1,250 mg/m^2, days 1 and 8) every 3 weeks until tumor progression. The differences in OS between the two arms were not statistically significant. With statistical significance, the PFS was 6.6 months in the maintenance group compared with 3.6 months in the BSC group. However, subgroup analysis showed that good-performance patients (Karnofsky scale>80) had a shorter OS in BSC arm than in maintenance arm (8.3 months vs. 22.9 months, respectively; hazard ratio (HR), 2.1; n=107). This means that good performance status (PS) can be valuable predictor in maintenance therapy.

Belani et al.[9] compared gemcitabine maintenance therapy and BSC after carboplatin (area under the curve [AUC], 5) and gemcitabine (1,000 mg/m^2, days 1 and 8) combination chemotherapy. No significant difference was found in the overall OS and PFS. And greater than grade 3–4 toxicities were noted in patients treated with gemcitabine maintenance therapy.

Intergroupe Francophone de Cancerologie Thoracique-Groupe Francais de Pneumo-Cancerologie (IFCT-GFPC 0502) is a well-designed controlled study to demonstrate the effects of gemcitabine maintenance therapy. In that study, good-performance patients (European Cooperative Oncology Group [ECOG] grade 1–2) with CR/PR or SD after four cycles of first-line chemotherapy using gemcitabine (1,250 mg/m^2,

days 1 and 8) plus cisplatin (80 mg/m^2, day 1) were randomized to gemcitabine or erlotinib maintenance therapy or BSC until tumor progression. All patients were treated with pemetrexed at progression. PFS was improved in the gemcitabine maintenance therapy group compared with BSC (3.8 months vs. 1.9 months; HR, 0.55; p<0.001); however, no OS benefit for maintenance therapy was observed. The study did not compare the benefits of gemcitabine and erlotinib maintenance therapy.

Continuation maintenance with pemetrexed was validated by the PARAMOUNT study[10]. Patients who did not progress after completion of four cycles of cisplatin plus pemetrexed, had an ECOG PS of 0 or 1, and achieved an induction response (CR, PR, or SD) were randomly assigned to receive maintenance therapy with either pemetrexed (500 mg/m^2 every 21 days) plus BSC or placebo plus BSC until disease progression. Only non-squamous cancer patients with good PS (ECOG 0 or 1) were enrolled in that study. Among the 359 patients randomized to continuation maintenance with pemetrexed, a significant reduction was noted in the risk of disease progression over the placebo group (HR, 0.62; 95% confidence interval [CI], 0.49–0.79; p<0.0001). The median PFS, measured from randomization, was 4.1 months (95% CI, 3.2–4.6) for pemetrexed and 2.8 months (2.6–3.1) for the placebo. A significant benefit in OS was observed in the pemetrexed maintenance therapy group compared with the placebo group (16.9 months vs. 14.0 months, respectively).

Switch Maintenance Therapy Using Cytotoxic Agents

Vinorelbine, paclitaxel, docetaxel, and pemetrexed has been studied as maintenance therapy in NSCLC.

Westeel et al.[11] conducted a randomized trial to compare maintenance vinorelbine therapy with observation. Patients with stage IIIB NSCLC having two cycles of monthly mitomycin-ifosfamide-cisplatin (MIC) followed by radiotherapy and those with "wet" stage IIIB (pleural or pericardial involvement), stage IIIB with supraclavicular node involvement, or stage IV (i.e., metastatic) NSCLC received 4 cycles of monthly MIC were enrolled[11]. Patients who responded to MIC treatment were randomly assigned to receive intravenous vinorelbine at a dose of 25 mg/m^2 for 6 months or no further treatment. No difference in PFS was found between these arms (log-rank p=0.32).

Switch maintenance therapy using paclitaxel also did not show a benefit regarding OS and PFS[12]. In that study, patients were treated with three cycles of GIP (gemcitabine [days 1 and 8]+ifosfamide [day 1]+cisplatin [day 1]) chemotherapy. Patients with CR/PR or SD were randomly assigned to receive GIP maintenance or paclitaxel (225 mg/m^2 per 3 weeks) switch maintenance therapy every 3 weeks. However, no significant difference in OS was observed. Regarding toxicity, the incidence of thrombocytopenia was increased in the GIP group, and that of peripheral neuropathy was increased in the paclitaxel-treated group, but the difference was not statistically significant.

Fidias et al.[13] conducted a phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced NSCLC. The enrolled chemotherapy-naïve patients had either stage IIIB NSCLC with pleural effusion or stage IV NSCLC. Gemcitabine (1,000 mg/m^2) was administered on days 1 and 8 with carboplatin (AUC, 5) on day 1. After 4 cycles of gemcitabine plus carboplatin per 3 weeks, patients who did not show progression were randomly assigned either to an immediate docetaxel group (docetaxel 75 mg/m^2) on day 1 every 21 days (with a maximum of six cycles) or to a delayed docetaxel group using docetaxel after observation and progression of tumor. The median PFS for immediate docetaxel (5.7 months) was significantly greater (p=0.0001) than for delayed docetaxel (2.7 months). The median OS for immediate docetaxel (12.3 months) was greater than for delayed docetaxel (9.7 months), but the difference was not statistically significant (p=0.0853). The QOL results were not significantly different (p=0.76) between two docetaxel groups. Thus, patients seem to have benefited from docetaxel therapy, and the patients in the immediate docetaxel arm trended toward improved OS because a greater number of patients could receive treatment. Treatment was discontinued in 37.2% of patients in the delayed docetaxel group, and the major reason was disease progression. However, in the immediate docetaxel group, only 5% of patients interrupted the treatment, suggesting that NSCLC patients may be healthier and prone to receive additional therapy if maintenance therapy is offered immediately after front-line chemotherapy.

Ciuleanu et al.[14] conducted a randomized, double-blind, phase III study to validate the benefit of pemetrexed maintenance therapy. Patients who had not progressed on four cycles of platinum-based chemotherapy were randomly assigned (2:1 ratio) to receive pemetrexed (500 mg/m^2, day 1) plus BSC or placebo plus BSC in 21-day cycles until disease progression (JMEN study). Pemetrexed maintenance therapy compared with placebo, significantly improved PFS (4.3 months vs. 2.6 months, respectively; p<0.0001) and OS (13.4 months vs. 10.6 months, respectively; p=0.012). With these results, pemetrexed was approved as switch maintenance therapy for NSCLC in the United States and Europe. This study included some squamous NSCLC cases (26% in the pemetrexed group and 30% in the placebo group). Sub-analysis revealed that pemetrexed maintenance is not beneficial toward PFS and OS in squamous NSCLC, a finding that is consistent with the results of a previous study of the effectiveness of pemetrexed used exclusively for non-squamous NSCLC.

Maintenance with Targeted Agents

Targeted therapies, including bevacizumab, cetuximab, erlotinib, and gefitinib, can be used as maintenance therapy for NSCLC. Continuous maintenance therapy with bevacizumab or cetuximab shows a benefit in PFS and OS. The results of clinical trials of erlotinib and gefitinib as continuous maintenance therapy were disappointing, but switch maintenance therapy with erlotinib and gefitinib produced a significant benefit compared with placebo or observation.

1. Bevacizumab

The first clinical study showing the value of bevacizumab as maintenance therapy was conducted by Sandler et al.[15] (ECOG 4599). NSCLC patients were assigned to chemotherapy with paclitaxel and carboplatin alone or paclitaxel and carboplatin plus bevacizumab. Chemotherapy was administrated every 4 weeks for six cycles, and bevacizumab was administered every 3 weeks until disease progression.

The OS was 12.3 months in the group assigned to chemotherapy plus bevacizumab compared with 10.3 months in the chemotherapy-alone group (HR, 0.79; p=0.003). The PFSs in the two groups were 6.2 and 4.5 months, respectively (HR, 0.66; p<0.001). A higher frequency of treatment-related adverse events, such as neutropenic fever, hemorrhage, proteinuria, and hypertension, were observed in the chemotherapy plus bevacizumab group. However, this study was not initially designed to reveal the effect of bevacizumab as maintenance therapy, and some limitations exist regarding conclusions on the effect of bevacizumab maintenance therapy. The AVAiL study demonstrated that bevacizumab plus cisplatin-gemcitabine also significantly improved PFS and ORR, but OS was not increased with bevacizumab[16,17].

Patel et al.[18] conducted a phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous NSCLC. Fifty patients were enrolled initially; among them, 30 patients (60%) completed six cycles of pemetrexed-carboplatin plus bevacizumab therapy and 9 patients (18%) completed 18 cycles of maintenance therapy. The results that the ORR was 55%, and the median PFS and OS were 7.8 months and 14.1 months, respectively, justify a phase III comparison against the standard of care.

2. Cetuximab

Similar to bevacizumab, clinical trials with cetuximab have some limitations in terms of validating the value of cetuximab as maintenance therapy. However, some studies, such as the FLEX and BMS-099 trials, showed the potential benefit of cetuximab as maintenance therapy[19,20].

3. Erlotinib

Erlotinib has been approved in Korea as maintenance therapy in patients with CR/PR and SD after platinum-based chemotherapy. The evidence for a benefit was validated by the Sequential Tarceva in Unresectable NSCLC (SATURN) study[21]. The median PFS was significantly longer with erlotinib than with placebo: 12.3 weeks for patients in the erlotinib group versus 11.1 weeks for those in the placebo group. The PFS benefit with erlotinib therapy is unclear. Prolonged 1 month is questionable benefit. However, frequent fails to receive further treatment in observation arm suggests that maintenance therapy has the potential benefit. The Avastin Tarceva Lung Adenocarcinoma Study (ATLAS) study compared the effects of bevacizumab therapy with or without erlotinib after completion of chemotherapy (platinum plus bevacizumab). This trial was stopped at the second planned interim efficacy analysis because it met the primary endpoint. The median PFS was 4.8 months with bevacizumab plus erlotinib and 3.7 months with bevacizumab alone (HR, 0.722; p=0.0012). The final analysis is in progress.

4. Gefitinib

Gefitinib was validated as a maintenance therapy in NSCLC by multiple, well-designed trials, including the West Japan Thoracic Oncology Group 0203 (WJTOG0203), INFORM (C-TONG 0804), and European Organization for the Research and Treatment of Cancer (EORTC) 08032-ILCP studies. In the WJTOG0203 study, Asian NSCLC patients were randomly assigned to either platinum-doublet chemotherapy up to six cycles or platinum-doublet chemotherapy for three cycles followed by gefitinib 250 mg orally once daily until disease progression[22]. There was a statistically significant improvement in PFS in the gefitinib maintenance group (HR, 0.68; p<0.001); however, the OS results did not reach statistical significance (HR, 0.86; p=0.11). In subset analysis of OS by histologic group, patients in the gefitinib maintenance group with adenocarcinoma did significantly better than patients in the control group with adenocarcinoma (p=0.03). The exploratory subset analyses demonstrate a possible survival prolongation for sequential therapy of gefitinib, particularly in adenocarcinoma patients.

INFROM was a phase III, randomized, placebo-controlled study that evaluated the efficacy and safety of gefitinib versus placebo as maintenance therapy in NSCLC patients with good performance (ECOG 1–2) after four cycles of platinum-based chemotherapy[23]. The median PFS was 4.8 months in the gefitinib maintenance group and 2.6 months in the placebo group (HR, 0.42; p<0.0001). Sub-analysis showed that, in epidermal growth factor receptor (*EGFR*) mutation-positive patients, the PFS of the gefitinib maintenance group was markedly increased (16.6 months vs. 2.8 months in the con-

trol group; HR, 0.17); in *EGFR* mutation-negative patients, no significant difference in PFS was found. This study could not show improvement in OS due to allowance of patient crossover at progression.

The EORTC 08021-ILCP trial was a double-blind, randomized, placebo-controlled phase III study of gefitinib in patients with non-progressing NSCLC after four cycles of platinum-based chemotherapy[24]. This trial was prematurely closed due to low accrual. The results indicated that gefitinib maintenance therapy significantly prolonged the median PFS (4.1 months vs. 2.9 months in the control group; p=0.0015) but did not improve OS. Gefitinib maintenance therapy after platinum-based chemotherapy did not improve OS. Thus, this maintenance treatment is not recommended at present.

Careful Consideration of Maintenance Therapy

In most studies of the effect of maintenance therapy, PFS was the primary endpoint. Additionally, few studies report a significant difference in OS, indicating that maintenance therapy can increase PFS but have little impact on OS. Furthermore, in contrast to the definite standard of OS, that of PFS might differ among researchers. PFS cannot guarantee objectivity without an independent review. Thus, some issues arise concerning the real significance of PFS improvement in patients treated with maintenance therapy. This problem becomes more obvious when evaluating PFS after six cycles of chemotherapy rather than four cycles. In the SATURN study, OS was significantly increased only in the patients who showed SD after four cycles of chemotherapy. These data suggest that the SD in those patients might actually be progressive SD according to the Response Evaluation Criteria In Solid Tumors (RECIST), and so erlotinib maintenance therapy is practically early second-line chemotherapy[25].

Insufficient data exist concerning the proportion of patients treated with second-line chemotherapy and the adequacy of regimens used as second-line treatment. In the PARAMOUNT study, only 4% of patients in the control group received pemetrexed as second-line chemotherapy at disease progression. The increase in PFS and OS with pemetrexed maintenance therapy might be due mainly to whether the patients were treated with pemetrexed, rather than the impact of maintenance therapy.

A clinician's expectation of the outcome of maintenance therapy is not merely an extension of PFS or OS. One of the major goals of maintenance therapy is increasing QOL. However, most clinical trials, except large-scale studies, did not evaluate QOL. Some studies, such as the PARAMOUNT and SATURN studies, reported that maintenance therapy did not affect QOL significantly. The JMEN study evaluated QOL objectively by assessing the time to symptomatic adverse events. The results indicated that pemetrexed maintenance therapy delays significantly serious adverse events such as severe pain or hemoptysis[14]. However, the value of maintenance therapy in terms of improvement of QOL remains to be clarified. When deciding to administer maintenance therapy, the pros and cons of this therapy in terms of multiple aspects should be considered.

Generally, only a proportion of NSCLC patients, ~20–80%, receive second-line chemotherapy. Many studies have reported consistent data that maintenance therapy markedly increases the rate of receiving second-line therapy, and might be a major benefit of maintenance therapy. However, Fidias et al.[13] reported no OS improvement in maintenance therapy using docetaxel. Two possible interpretations of these results can be considered: 1) using docetaxel is an important issue or 2) sufficient PS to receive second-line therapy is more important issue than maintenance therapy.

According to the results of a study in Korea[26], the proportion of patients receiving second-line therapy in Korea is high (86%) compared with that in other countries. The benefit of maintenance therapy in Korea, where most NSCLC patients undergo second-line chemotherapy, should thus be considered carefully.

Conclusions

More than four to six cycles of platinum-based combination chemotherapy increases toxicity and shows no survival benefit although those results in modest improvements in OS and QOL in NSCLC patients. However, recently updated evidence for maintenance therapy is encouraging. Patients are likely to cause tumor related symptom can get benefit from the maintenance treatment, who have a large tumor causing symptoms or no severe adverse event during previous therapy[27]. Thus far, no randomized studies have compared the effect of regimens in maintenance therapy, and the optimal drug for maintenance therapy remains to be identified. Despite much debate, continuous maintenance therapy with pemetrexed and switch maintenance treatment using erlotinib or pemetrexed has been revealed to be beneficial, and these treatments are currently recommended. More comprehensive studies are needed to validate the value of maintenance therapy.

References

1. National Comprehensive Cancer Network. NCCN guidelines version 2.2013. Non-small cell lung cancer [Internet]. Fort Washington: National Comprehensive Cancer Network; 2013 [cited 2013 Feb 1]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
2. Gerber DE, Schiller JH. Maintenance chemotherapy for ad-

vanced non-small-cell lung cancer: new life for an old idea. J Clin Oncol 2013;31:1009-20.
3. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 1979;63:1727-33.
4. Socinski MA, Schell MJ, Peterman A, Bakri K, Yates S, Gitten R, 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.
5. Smith IE, O'Brien ME, Talbot DC, Nicolson MC, Mansi JL, Hickish TF, 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.
6. von Plessen C, Bergman B, Andresen O, Bremnes RM, Sundstrom S, Gilleryd M, 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.
7. Belani CP, Barstis J, Perry MC, La Rocca RV, Nattam SR, Rinaldi D, 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.
8. Brodowicz T, Krzakowski M, Zwitter M, Tzekova V, Ramlau R, Ghilezan N, 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.
9. Belani CP, Waterhouse DM, Ghazal H, Ramalingam SS, Bordoni R, Greenberg R, 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). J Clin Oncol 2010;28(15 Suppl):7506.
10. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012;13:247-55.
11. Westeel V, Quoix E, Moro-Sibilot D, Mercier M, Breton JL, Debieuvre 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.
12. Sculier JP, Lafitte JJ, Lecomte J, Alexopoulos CG, Van Cutsem O, Giner V, et al. A phase III randomised trial comparing sequential chemotherapy using cisplatin-based regimen and paclitaxel to cisplatin-based chemotherapy alone in advanced non-small-cell lung cancer. Ann Oncol 2007;18:1037-42.
13. Fidias PM, Dakhil SR, Lyss AP, Loesch DM, Waterhouse DM, Bromund JL, 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.
14. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, 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.
15. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50.
16. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, 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.
17. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, 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.
18. Patel JD, Hensing TA, Rademaker A, Hart EM, Blum MG, Milton DT, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. J Clin Oncol 2009;27:3284-9.
19. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, 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.
20. Lynch TJ, Patel T, Dreisbach L, McCleod M, Heim WJ, Hermann RC, 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.
21. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, Juhasz E, 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.
22. Takeda K, Hida T, Sato T, Ando M, Seto T, Satouchi M, 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 2010;28:753-60.
23. Zhang L, Shenglin M, Song X, Han B, Cheng Y, Huang C, et al. Efficacy, tolerability, and biomarker analyses from a phase III, randomized, placebo-controlled, parallel group study of gefitinib as maintenance therapy in patients with

locally advanced or metastatic non-small cell lung cancer (NSCLC) (INFORM; C-TONG 0804). J Clin Oncol 2011;29(15 Suppl):LBA7511.
24. Gaafar RM, Surmont V, Scagliotti G, Van Klaveren R, Papamichael D, Welch J, 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). J Clin Oncol 2010;28(15 Suppl):7518.
25. Coudert B, Ciuleanu T, Park K, Wu YL, Giaccone G, Brugger W, et al. Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. Ann Oncol 2012;23:388-94.
26. Gerber DE, Rasco DW, Le P, Yan J, Dowell JE, Xie Y. Predictors and impact of second-line chemotherapy for advanced non-small cell lung cancer in the United States: real-world considerations for maintenance therapy. J Thorac Oncol 2011;6:365-71.
27. Custodio A, de Castro J. Strategies for maintenance therapy in advanced non-small cell lung cancer: current status, unanswered questions and future directions. Crit Rev Oncol Hematol 2012;82:338-60.