Advanced non-small cell lung cancer: the role of maintenance therapy

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Abstract: Platinum-based chemotherapy has been shown to provide survival benefits in advanced non-small cell lung cancer (NSCLC). Maintenance/consolidation chemotherapy in NSCLC has gained renewed interest with improved tolerability of chemotherapy and the addition of biologic agents. Various studies have evaluated the role of prolonged duration of chemotherapy as well as maintenance/consolidation strategies with both chemotherapy and biologic agents. The available data at this time demonstrates that maintenance or consolidation therapy can improve progression free survival; however this does not result consistently in an improved overall survival. We review the literature with regard to duration of therapy and use of maintenance/consolidation therapy in advanced NSCLC.

Keywords: maintenance therapy, non-small cell lung cancer, overall survival, targeted therapy

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in the United States. Approximately 215,020 people in the United States were expected to be diagnosed with lung cancer in 2008, with an expected 161,840 deaths [Jemal *et al.* 2008]. The majority of these cases would be NSCLC. Chemotherapy, with a platinum doublet, has been considered standard treatment for NSCLC based upon its palliative benefits and improved survival compared with best supportive care [Schiller *et al.* 2002; Non-small cell lung cancer Collaborative Group, 1995; Marino *et al.* 1994; Rapp *et al.* 1988]. The role for targeted agents, including bevacizumab, erlotinib, and cetuximab, has been evaluated and shown to improve overall survival (OS). Maintenance therapy — continuation of part of the initial treating regimen alone or consolidated with an alternate agent after initial treatment has been given — has been of renewed interest as the prolonged tolerability of agents has improved. We review clinical trials evaluating maintenance therapy in advanced NSCLC.

Duration of chemotherapy

In 2004, the American Society of Clinical Oncology (ASCO) recommendation for patients with stage IV NSCLC stated that only up to four cycles of chemotherapy be given to patients who

are not responding to therapy and that first-line chemotherapy should be administered for no more than six cycles even in patients who did respond [Phister *et al.* 2004]. These recommendations were based on two studies that directly addressed the question of duration of chemotherapy in advanced NSCLC [Smith *et al.* 2001; Socinski *et al.* 2002] (Table 1).

A trial by Smith and colleagues challenged the concept that prolonged therapy was superior to a shorter treatment course [Smith *et al.* 2001]. Patients were randomized to receive either three or six courses of mitomycin, vinblastine, and cisplatin. Key endpoints included OS, time to disease progression, and duration of symptom relief. Quality of life (QOL) was also assessed throughout the study. The median survival was 6 and 7 months for the groups receiving three and six cycles, respectively. The time to disease progression and median duration of symptom relief were the same in both arms. QOL was better for patients who received only three cycles of chemotherapy during the time period when patients in the other group were receiving the remainder of their six chemotherapy cycles. A second trial by Socinski and colleagues compared a defined four cycles of chemotherapy with carboplatin and paclitaxel against treatment with the same chemotherapy until disease progression

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Table 1. Trials evaluating maintenance chemotherapy.

Trial	Treatment strategy	Median PFS or TTP	Median survival
Smith <i>et al.</i> [2001]	Mitomycin/vinblastine/cisplatin 3 cycles <i>versus</i> 6 cycles	5 mo <i>versus</i> 5 mo ($p=0.4$)	6 mo <i>versus</i> 7 mo ($p=0.2$)
Socinski <i>et al.</i> [2002]	Carboplatin/paclitaxel 4 cycles <i>versus</i> TTP	Not reported	6.6 mo <i>versus</i> 8.5 mo ($p=0.63$)
von Plessen <i>et al.</i> [2006]	Carboplatin/vinorelbine 3 cycles <i>versus</i> 6 cycles	16 w <i>versus</i> 21 w ($p=0.21$)	28 w <i>versus</i> 32 w ($p=0.75$)
Park <i>et al.</i> [2007]	Cisplatin + either paclitaxel, docetaxel, or gemcitabine 4 cycles <i>versus</i> 6 cycles	4.6 mo <i>versus</i> 6.2 mo ($p=0.001$)	15.9 mo <i>versus</i> 14.9 mo ($p=0.461$)
Brodowicz <i>et al.</i> [2006]	Cisplatin + gemcitabine followed by maintenance gemcitabine <i>versus</i> best supportive care	6.6 mo <i>versus</i> 5.0 mo ($p=0.001$)	13 mo <i>versus</i> 11 mo ($p=0.195$)

mo, months; PFS, progression-free survival; TTP, time to progression; w, weeks.

[Socinski *et al.* 2002]. The median number of cycles given in both groups was four. Overall response rates were 22% in the group receiving four defined courses of chemotherapy, and 24% in the group receiving treatment until disease progression. Only 42% of patients treated until disease progression received five or more cycles. Hematologic and nonhematologic toxicity were similar between both arms except that 14% of patients in the group that received defined chemotherapy developed neuropathy, compared to 27% of patients treated until disease progression.

Since the publication in 2004 of the ASCO guidelines, additional studies have evaluated the optimal duration of first-line therapy. Von Plessen and colleagues demonstrated that six courses of carboplatin and vinorelbine provided no more benefit in terms of OS or QOL compared to three courses of therapy in patients with advanced NSCLC [Von Plessen *et al.* 2006]. This study also showed global QOL to be worse during the extended treatment period for the group that received six courses instead of three courses of therapy – similar to that shown in the Socinski study. The number of blood transfusions was more than doubled in the group receiving six cycles of treatment. Given that treatment for advanced NSCLC is palliative, any treatment that provides no benefit in survival and diminishes QOL cannot be recommended.

Park and colleagues compared two and four additional cycles of cisplatin with either a taxane (paclitaxel or docetaxel) or gemcitabine in Korean patients who did not progress after their first two cycles of the same chemotherapy regimen for NSCLC [Park *et al.* 2007]. This study

was designed as a noninferiority study. The trial did show that time to progression (TTP) was statistically superior with prolonged therapy, 6.2 months *versus* 4.6 months ($p=0.001$). However, this did not translate into an improvement in OS; 14.9 months for six cycles of therapy *versus* 15.9 months for four cycles of therapy ($p=0.461$). Only 63% of patients in the six cycle arm received second-line therapy compared with 74% in the four cycle arm. The authors concluded that this study supported ASCO's recommendation to give four to six cycles of chemotherapy but stated that the improvement in TTP warranted further evaluation of either maintenance or consolidation strategies. QOL was similar in both arms except during the time of extended treatment. During this time, role-functioning was better for the group that only received four cycles of treatment. This study was unique in that it evaluated duration of therapy in patients who responded to initial therapy, whereas the studies by Smith and Socinski described above assigned patients upfront, regardless of response.

Maintenance and consolidation

Maintenance therapy after induction therapy in patients who did not progress on the initial treatment has been evaluated in several studies (Tables 1 and 2). Brodowicz and coworkers evaluated the role of maintenance gemcitabine or best supportive care in patients that had an objective response or stable disease after treatment with cisplatin and gemcitabine [Brodowicz *et al.* 2006]. The primary objective was to show an improvement in median TTP. This objective was met with the group receiving maintenance gemcitabine having a TTP of 6.6 months *versus* 5 months for the best supportive care group

Table 2. Trials evaluating consolidation chemotherapy.

Trial	Treatment strategy	Median PFS	Median survival
Westeel <i>et al.</i> [2005]	Mitomycin/ifosfamide/cisplatin followed by vinorelbine <i>versus</i> best supportive care	5 mo <i>versus</i> 3 mo ($p=0.32$)	12.3 mo <i>versus</i> 12.3 mo ($p=0.48$)
Fidias <i>et al.</i> [2009]	Carboplatin/gemcitabine followed by immediate docetaxel <i>versus</i> delayed docetaxel	5.7 mo <i>versus</i> 2.7 mo ($p=0.0001$)	12.3 mo <i>versus</i> 9.7 mo ($p=0.0853$)
Belani <i>et al.</i> [2009]	Platinum-doublet followed by pemetrexed <i>versus</i> placebo	4.0 mo <i>versus</i> 2.0 mo ($p<0.00001$)	13.4 mo <i>versus</i> 10.6 mo ($p=0.012$)
mo, months; PFS, progression-free survival; TTP, time to progression.			

($p < 0.001$). The median OS throughout the study was 13 months in the maintenance gemcitabine arm and 11 months in the best supportive care arm, which was not statistically significant ($p = 0.195$).

Westeel and colleagues evaluated patients with metastatic NSCLC and randomized those who responded to four courses of mitomycin, ifosfamide, and cisplatin to either observation or consolidation with vinorelbine for up to 6 months [Westeel *et al.* 2005]. Of the 573 registered patients, 227 patients responded to induction chemotherapy. Of the responding patients, 91 patients received consolidation with vinorelbine and 90 patients were observed. Both arms showed a median survival of 12.3 months from date of randomization. Progression-free survival (PFS) was not significantly improved with consolidation vinorelbine therapy. This study differed from Brodowicz's study in that it evaluated an alternate agent with a different mechanism of action than that used in induction therapy. Some have referred to this strategy as 'consolidation therapy'.

Renewed interest in consolidation therapy has been generated in a recent study [Fidias *et al.* 2009]. This phase III study evaluated the role of immediate *versus* delayed second-line therapy with docetaxel after front-line therapy with gemcitabine and carboplatin in patients with advanced NSCLC. The group of patients treated with immediate docetaxel essentially received consolidation therapy since the only patients randomized were those who did not progress on initial therapy. The primary endpoint was OS with secondary endpoints being response rate, PFS, toxicity, and QOL. Of the 566 patients enrolled, 309 patients were randomized to immediate

versus delayed docetaxel. Median OS favored the immediate treatment arm (12.3 months) over the delayed treatment group (9.7 months) but was not statistically different ($p = 0.0853$). PFS did statistically favor ($p < 0.0001$) the immediate arm (5.7 months) over the delayed docetaxel arm (2.7 months). Toxicity and QOL were similar between the two groups. The authors point out that in the immediate docetaxel group, 95% of patients received docetaxel compared with only 37% of patients in the delayed docetaxel arm. This study reinforces the benefit of receiving docetaxel. However, patients who eventually received docetaxel on the delayed arm were reported to do just as well as those receiving it as immediate consolidation. This observation calls into question whether immediate use of docetaxel is necessary, but illustrates that missing the opportunity of receiving second-line docetaxel is detrimental. Therefore, patients not receiving immediate docetaxel require very close observation.

At ASCO 2009, Belani and colleagues evaluated the role of maintenance pemetrexed *versus* placebo in patients who did not progress after four cycles of a platinum doublet [Belani *et al.* 2009]. The primary endpoint was PFS. Of the 663 patients enrolled, there was an improvement of 2 months in PFS favoring the maintenance pemetrexed arm (4.0 months *versus* 2.0 months, $p < 0.00001$). OS results showed a statistically significant improvement in the maintenance pemetrexed arm of 13.4 months *versus* 10.6 months for best supportive care (hazard ratio [HR] = 0.79, 95% confidence interval [CI] 0.65–0.95, $p = 0.012$). A subset analysis in patients with nonsquamous histology demonstrated a statistically significant improvement in PFS (4.4 months *versus* 1.8 months, $p < 0.00001$).

and OS (15.5 months *versus* 10.3 months, $p=0.002$) with maintenance pemetrexed, but no difference in either PFS (9.9 months in maintenance pemetrexed arm *versus* 10.8 months with placebo, $p=0.678$) or OS (2.4 months in maintenance pemetrexed arm *versus* 2.5 months in placebo arm, $p=0.896$) with squamous histology. What are the practical applications of these results in everyday practice? It is noteworthy that even though a majority of patients on the placebo arm received second-line therapy, 81% of patients in the placebo arm never received pemetrexed at any point as part of their therapy. This agent is known to have activity in patients with nonsquamous histology, which is the subset of patients in this trial that benefited from maintenance pemetrexed. This study underscores the value of pemetrexed in the second-line setting for patients with NSCLC with nonsquamous histology but does not resolve the question of proper timing of this agent.

Soon and colleagues reported a meta-analysis evaluating 13 maintenance trials that included a total of 3027 patients [Soon *et al.* 2009]. Some of the trials discussed above were included in the meta-analysis. It showed an improvement in PFS with prolonged chemotherapy, with most benefit seen when third generation chemotherapy agents were used compared to older agents (HR 0.70 *versus* 0.92, $p=0.003$). However, prolonged chemotherapy translated to only a modest improvement in OS (HR=0.92; 95% CI 0.86–0.99, $p=0.03$). The authors do comment that the modest benefit in OS became statistically significant based on the inclusion of one trial in particular where data were extrapolated from an abstract. In addition, given that the goals of therapy for advanced NSCLC are improvement in not only OS but QOL, this analysis also showed more adverse events in patients receiving more therapy. In addition, only seven of the 13 studies evaluated QOL, and of those, five showed no significant differences in QOL. Two studies did show trends towards improved QOL with standard duration chemotherapy as opposed to prolonged chemotherapy.

Maintenance targeted therapy

With a plateau in survival with platinum-based therapy in advanced NSCLC, targeted agents have undergone investigation. Two large phase III international trials combined the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), gefitinib, to standard

chemotherapy [Giaccone *et al.* 2004; Herbst *et al.* 2004]. Both trials used identical designs with the only difference being the platinum doublet used – cisplatin and gemcitabine in INTACT 1 and carboplatin and paclitaxel in INTACT 2. Maintenance monotherapy with either placebo or gefitinib was continued until disease progression or toxicity. Both studies failed to demonstrate improved survival.

More recently, Hida and colleagues compared six courses of a standard platinum-doublet based therapy *versus* three courses of a platinum-doublet based therapy followed by gefitinib maintenance monotherapy [Hida *et al.* 2008]. They reported a statistically significant improvement in PFS favoring the maintenance gefitinib arm ($p < 0.001$) – median PFS 4.6 months in the gefitinib maintenance arm *versus* 4.27 months in the chemotherapy alone arm. OS was not improved between the arms. It should be noted that just over 50% of patients on the chemotherapy arm alone received gefitinib later in their course of therapy after disease progression, possibly accounting for a lack of survival benefit. This trial also did not address the question of optimal timing of gefitinib, immediate *versus* delayed. In addition, all patients were Japanese and those randomized to the gefitinib arm included 79% with adenocarcinoma histology, 36% women, and 30% nonsmokers. These are characteristics of patients that have shown to gain the greatest benefit from EGFR-TKIs.

Another EGFR-TKI, erlotinib, has also shown activity in NSCLC. It was tested in a similar manner to gefitinib in the TRIBUTE trial [Herbst *et al.* 2005]. This trial included 1079 unselected patients with untreated advanced NSCLC. Patients were randomized to receive up to six cycles of chemotherapy with carboplatin and paclitaxel with either erlotinib or placebo. Patients were continued on maintenance erlotinib or placebo after chemotherapy was stopped. The primary endpoint was OS. Median survival was not statistically different between the groups, 10.6 and 10.5 months in the erlotinib and placebo maintenance groups respectively ($p=0.95$). A subset analysis of nonsmokers did show improvement in both OS (22.5 months *versus* 10.1 months) and TTP (6.0 months *versus* 4.3 months) with the addition of the targeted agent. These results were encouraging and provided a specific population that could benefit from the targeted agent however it is not clear that it was

specifically the maintenance therapy that provided the benefit. Gatzemeier and colleagues completed a trial with a similar design but using cisplatin and gemcitabine and showed similar results, including the benefit seen in the subset of nonsmokers [Gatzemeier *et al.* 2007].

Bevacizumab is a monoclonal antibody targeted against vascular endothelial growth factor. It has been shown to have clinical benefit in patients with metastatic breast, colon and renal cancer [Miller *et al.* 2007; Hurwitz *et al.* 2004; Hainsworth *et al.* 2005]. Sandler and colleagues compared treating patients with carboplatin and paclitaxel with or without bevacizumab for six cycles in 878 patients with nonsquamous advanced NSCLC [Sandler *et al.* 2006]. The group receiving bevacizumab continued maintenance bevacizumab until disease progression or intolerable toxicity. OS was improved from 12.3 months in the bevacizumab with chemotherapy arm compared with 10.3 months in the chemotherapy alone arm ($p=0.003$). Median PFS and response rates were also improved in the group receiving bevacizumab *versus* those receiving chemotherapy alone – 6.2 months and 35% *versus* 4.5 months and 15%, respectively. More recently, the AVAIL study showed that PFS and response rate were improved with the combination of cisplatin and gemcitabine with bevacizumab over placebo [Reck *et al.* 2009]. Again, bevacizumab was continued after chemotherapy as maintenance therapy. PFS and response rates were also improved but OS was not. As with erlotinib in previous studies, it can be said that bevacizumab contributed to improved outcomes in the populations studied but it still is not clear if it was the addition to chemotherapy, maintenance therapy, or both that provided the benefit.

Most recently, the role of cetuximab, an anti-EGFR monoclonal antibody, was evaluated in combination with chemotherapy in patients with advanced NSCLC [Pirker *et al.* 2009]. Patients received either cisplatin and vinorelbine with cetuximab followed by maintenance cetuximab or cisplatin and vinorelbine alone without any maintenance therapy. The results showed no difference in PFS between groups (4.8 months in each arm) but an improvement in OS in the cetuximab arm – 11.3 months *versus* 10.1 months ($p=0.0441$). However, the role of maintenance therapy is unknown as the median time of use for maintenance cetuximab was only

4 weeks, suggesting the majority of its benefit was with chemotherapy.

A phase III study presented at ASCO 2009, SATURN, evaluated standard platinum-based therapy followed by either erlotinib or placebo in patients who did not progress on induction therapy [Cappuzzo *et al.* 2009]. One of the primary endpoints was PFS. Of the 877 patients included in the study, PFS was improved in the consolidation erlotinib arm compared to placebo (HR 0.71, 95% CI 0.62–0.82, $p<0.0001$). The subset of patients with a positive EGFR mutation seemed to derive the most benefit with erlotinib in terms of PFS (HR 0.10, 95% CI 0.04–0.25, $p<0.0001$). Only 16% of patients in the placebo arm received erlotinib therapy as part of their further therapy. Another study, ATLAS, treated patients with either four courses of a standard platinum-based regimen with bevacizumab followed by maintenance bevacizumab and erlotinib *versus* the same induction chemotherapy and bevacizumab followed by bevacizumab and placebo in patients who did not progress with induction therapy [Miller *et al.* 2009]. Again the primary endpoint of PFS was met, favoring the maintenance bevacizumab and erlotinib group over maintenance bevacizumab alone – 4.76 months *versus* 3.75 months respectively (HR 0.722, 95% CI 0.592–0.881, $p=0.0012$). The study was stopped early, as per the recommendations of the data monitoring committee, given that the primary endpoint was met. All grade toxicity, predominantly rash and diarrhea, was higher in the SATURN study with maintenance erlotinib and in the ATLAS study with maintenance bevacizumab with erlotinib compared to the control arms. These two studies do not give any clear indication that QOL was improved in the experimental arms, nor do these studies address the question of optimal timing of therapy. OS is reported to be superior with erlotinib in the SATURN trial. Survival data is awaited on the ATLAS trial.

Conclusion

Based on current information, strategies utilizing maintenance chemotherapy or biologic agents have shown improvements in PFS but not a consistent or substantial benefit in OS. The studies done thus far do highlight the need for improved second-line therapies but leave the question of optimal timing of therapy still to be determined. In our opinion, future studies with maintenance therapy should focus on directing specific therapy

for subsets of patients that may derive particular benefit from a cytotoxic or biologic agent. In addition, endpoints should also be geared towards OS and QOL as PFS has not translated well to improvements in survival in many trials. Clinicians must continue to incorporate the trial results known to date into individualizing care for their patients. Improvements in response rate and PFS may have benefits for patients (those with substantial cancer-related symptoms relieved by treatment) even in the absence of improved OS. For others with fewer cancer symptoms, the toxicity (even grade 1 and 2) with prolonged therapy is not warranted.

Conflict of interest statement

Dr Agarwala declares no conflicts of interest. Dr Hanna has received honoraria from Eli Lilly and other remuneration from work on DSMBs for Merck and Celgene.

References

- Belani, C.P., Brodowicz, T., Ciuleanu, T., Kim, J.H., Krzakowski, M., Laack, Y. *et al.* (2009) Maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC: A phase III Study in NSCLC. In ASCO 2009. Orlando, FL; *J Clin Oncol* 27: 18s (suppl; abstr CRA 8000).
- Brodowicz, T., Krzakowski, M., Zwitter, M., Tzekova, V., Ramlau, R., Ghilezan, N. *et al.* (2006) 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* 52: 155–163.
- Cappuzzo, F., Ciuleanu, T., Stelmakh, L., Cienas, S., Szczesna, A., Juhasz, E. *et al.* (2009) SATURN: A double-blind, randomized, phase III study of maintenance erlotinib versus placebo following nonprogression with first-line platinum-based chemotherapy in patients with advanced NSCLC. *J Clin Oncol* 27:15s (suppl; abstr 8001).
- Fidias, P.M., Dakhil, S.R., Lyss, A.P., Loesch, D., Waterhouse, D., Cunneen, J. *et al.* (2009) 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* 27: 591–598.
- Gatzemeier, U., Pluzanska, A., Szczesna, A., Kaukel, E., Roubec, J., De Rosa, F. *et al.* (2007) 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* 25: 1545–1552.
- Giaccone, G., Herbst, R., Manegold, C., Scagliotti, G., Rosell, R., Miller, V. *et al.* (2004) Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: A phase III trial—INTACT I. *J Clin Oncol* 22: 777–784.
- Hainsworth, J.D., Sosman, J.A., Spigel, D.R., Edwards, D.L., Baughman, C. and Greco, A. (2005) Treatment of metastatic renal cell carcinoma with a combination of bevacizumab and erlotinib. *J Clin Oncol* 23: 7889–7896.
- Herbst, R., Giaccone, G., Schiller, J., Natale, R.B., Miller, V., Manegold, C. *et al.* (2004) Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: A phase III trial—INTACT 2. *J Clin Oncol* 27: 785–793.
- Herbst, R.S., Prager, D., Hermann, R., Fehrenbacher, L., Johnson, B.E., Sandler, A. *et al.* (2005) 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* 23: 5892–5899.
- Hida, T., Okamoto, I., Kashii, T., Satouchi, M., Ichinose, Y., Katakami, N. *et al.* (2008) Randomized phase III study of platinum-doublet chemotherapy followed by gefitinib versus continued platinum-doublet chemotherapy in patients with advanced non-small cell lung cancer (NSCLC): Results of West Japan Thoracic Oncology Group trial (WJTOG). In: ASCO 2008. Chicago, IL: *J Clin Oncol* 26: 2008 (May 20 suppl; abstr LBA8012).
- Hurwitz, H., Fehrenbacher, L., Novotny, W., Cartwright, T., Hainsworth, J., Heim, W. *et al.* (2004) Bevacizumab plus irinotecan, fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 350: 2335–2342.
- Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., Murray, T. *et al.* (2008) Cancer statistics, 2008. *CA Cancer J Clin* 58: 71–96.
- Marino, P., Pampallona, S., Preatoni, A., Cantoni, A. and Invernizzi, F. (1994) Chemotherapy *vs* supportive care in advanced non-small-cell lung cancer: results of a meta-analysis of the literature. *Chest* 106: 861–865.
- Miller, K.D., Wang, M., Gralow, J., Dickler, M., Cobleigh, M., Perez, E.A. *et al.* (2007) Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 357: 2666–2676.
- Miller, V.A., O'Connor, P., Soh, C. and Kabbinnar, F. (2009) 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). *J Clin Oncol* 27:18s, (suppl; abstr LBA8002).
- Non-small Cell Lung Cancer Collaborative Group (1995). 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.
- Park, J.O., Kim, S., Ahn, J.S., Suh, C., Lee, J.S., Jang, J.S. *et al.* (2007) 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* 25: 5233–5239.

Phister, D.G., Johnson, D.J., Azzoli, C.G., Sause, W., Smith, T.J., Baker Jr, S. *et al.* (2004) American Society of Clinical Oncology treatment of unresectable non-small cell lung cancer guideline: Update 2003. *J Clin Oncol* 22: 330–353.

Pirker, R., Pereira, J.R., Szczesna, A., von Pawel, J., Krzakowski, M., Ramlau, R. *et al.* (2009) Cetuximab plus chemotherapy in patients with advanced non-small cell lung cancer (FLEX): an open-labeled randomized phase III trial. *Lancet* 373: 1525–1531.

Rapp, E., Pater, J.L., Willan, A., Cormier, Y., Murray, N., Evans, W.K. *et al.* (1988) Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer—report of a Canadian multicenter randomized trial. *J Clin Oncol* 6: 633–641.

Reck, M., von Pawel, J., Zatloukal, P., Ramlau, R., Gorbounova, V., Hirsh, V. *et al.* (2009) A phase III trial of cisplatin and gemcitabine with either placebo or bevacizumab as first line therapy for nonsquamous non-small-cell lung cancer: AVAiL. *J Clin Oncol* 27: 1227–1234.

Sandler, A., Gray, R., Perry, M.C., Brahmer, J., Schiller, J.H., Dowlati, A. *et al.* (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 355: 2542–2550.

Schiller, J.H., Harrington, D., Belani, C.P., Langer, C., Sandler, A., Krook, J. *et al.* (2002)

Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. *N Engl J Med* 346: 92–98.

Smith, I.A., O'Brien, M.E., Talbot, D.C., Nicolson, M.C., Mansi, J.L., Hickish, T.F. *et al.* (2001) 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.

Socinski, M.A., Schell, M.J., Peterman, A., Bakri, K., Yates, S., Gitten, R. *et al.* (2002) 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.

Soon, Y.Y., Stockler, M.R., Askie, L.M. and Boyer, M.J. (2009) Duration of chemotherapy for advanced non-small cell lung cancer: A systematic review and meta-analysis of randomized trials. *J Clin Oncol* 27: 3277–3283.

Von Plessen, C., Bergman, B., Andresen, O., Bremnes, R.M., Sundstrom, S., Gilleryd, M. *et al.* (2006) Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. *Br J Cancer* 95: 966–973.

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

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