

# MAINTENANCE THERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER

## Does emerging evidence support its use?

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### Abstract

Lung cancer is the number one cause of cancer death in Canada. Despite modern advances in systemic therapies, the prognosis for patients with advanced non-small cell lung cancer (NSCLC) remains poor. Clinical trials are exploring various strategies in attempts to improve outcomes in this population, such as the addition of novel targeted agents and the use of alternating and maintenance systemic strategies. Maintenance therapy in advanced NSCLC can be defined as the addition of further systemic therapy in patients who have responded or achieved at least stable disease following standard first-line platinum-based chemotherapy. The present review explores the role of maintenance therapy in advanced NSCLC.

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Malignancies of the lung are the leading cause of cancer mortality worldwide. In the year 2008, it was estimated that 23,900 Canadians were newly diagnosed with lung cancer, with 20,200 deaths.<sup>1</sup> Despite modern advances in systemic therapies, the prognosis for patients with advanced NSCLC remains dismal, with median overall survival (OS) in the order of 8 to 10 months.<sup>2</sup> Current guidelines suggest that a limited duration of chemotherapy is preferable.<sup>3-5</sup> Clinical trials exploring various strategies to improve outcomes in this population have focused on the addition of targeted therapies such as the anti-vascular endothelial growth factor (VEGF) agent bevacizumab and the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) gefitinib and erlotinib, as well as alternating and maintenance systemic strategies.

Maintenance therapy in advanced NSCLC involves adding further systemic therapy in patients who have responded or achieved at least stable disease following first-line platinum-based chemotherapy. Strategies include prolonging chemotherapy duration using the same agents given in induction chemotherapy, using non-cross-resistant chemotherapy agents, and using targeted therapies. The following sections review contemporary clinical trials comparing maintenance therapy to best supportive care (BSC).

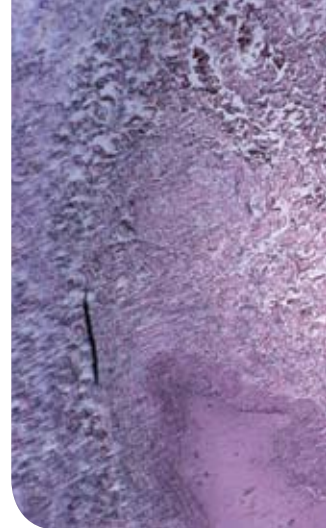
### OPTIMAL DURATION OF FIRST-LINE CHEMOTHERAPY

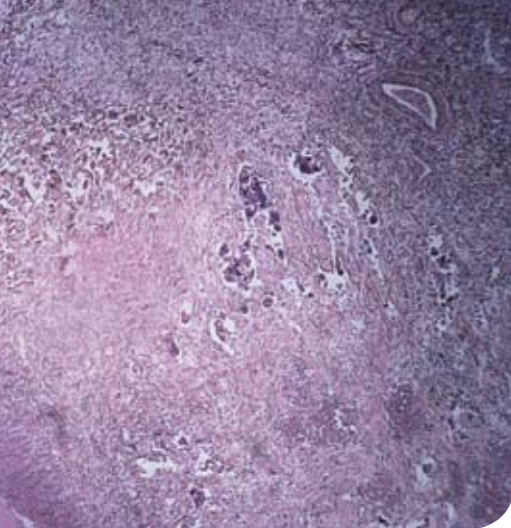
Socinski et al assessed the optimal duration of palliative chemotherapy in patients with advanced NSCLC in a Phase III clinical trial published in 2002.<sup>3</sup> This study randomized 230 patients with Stage IIIB or IV NSCLC to

receive either 4 cycles of carboplatin (area under the curve [AUC] of 6) plus paclitaxel (200 mg/m<sup>2</sup> every 3 weeks) or continuous therapy with the same agents until disease progression (PD). At progression, patients in both arms received second-line paclitaxel (80 mg/m<sup>2</sup> per week). OS and quality of life (QOL) were the primary endpoints. Both arms were well balanced in terms of baseline characteristics. Of the 114 patients randomized to 4 cycles of chemotherapy, 57% completed them all, and of the 116 randomized to continuous therapy, 42% received 5 or more cycles (range 0–19). No statistically significant differences in the primary endpoints of OS or QOL were observed between the two arms, with median OS of 6.6 vs 8.5 months, respectively ( $p = 0.63$ ). However, the patients receiving continuous therapy had an increased incidence of  $\geq$  Grade 2 neuropathy, at 27% vs 14%. After 4 cycles, 19.9% of patients had experienced at least Grade 2 neuropathy, increasing to 43% at Cycle 8. The authors concluded that extending treatment duration beyond 4 cycles provided no clinical benefit.

### MAINTENANCE WITH AGENTS USED IN INDUCTION THERAPY Paclitaxel

Belani et al reported promising results in 2003 with maintenance paclitaxel in a multicentre, randomized Phase II study.<sup>6</sup> Safety and efficacy of three different weekly paclitaxel regimens in combination with carboplatin as first-line therapy in patients with advanced NSCLC were assessed. However, this study was designed to determine the feasibility of maintenance paclitaxel rather than to assess efficacy. A total of 401 chemotherapy-naïve patients with





Stage IIIB or IV NSCLC were enrolled. Patients in Arm 1 received weekly paclitaxel at 100 mg/m<sup>2</sup> for 3 out of every 4 weeks along with carboplatin (AUC of 6) given on Day 1 of the 4-week treatment cycle. Arm 2 differed in that the carboplatin (AUC of 2) was also given weekly for 3 of 4 weeks along with paclitaxel. In Arm 3, patients received two 8-week cycles of paclitaxel at 150 mg/m<sup>2</sup> in Cycle 1 and 100 mg/m<sup>2</sup> in Cycle 2, plus carboplatin (AUC = 2) weekly for 6 of 8 weeks per cycle. Of the 130 patients who achieved at least stable disease, 65 were randomized to weekly paclitaxel (70 mg/m<sup>2</sup> given weekly for 3 of 4 weeks) and 65 to observation. The study's primary endpoints were objective response (OR) and time to disease progression (TTP), with secondary endpoints of OS and safety profile.

Results for patients in Arm 1 were superior, with an OR rate of 32%. In the maintenance phase, both median TTP and OS favoured the paclitaxel group, at 38 and 75 weeks respectively, compared to 29 and 60 weeks for observation only. It is worthwhile to note that during maintenance therapy 86% of patients in the paclitaxel arm reported at least one adverse toxicity (45% Grade 3 or 4), with neutropenia, neuropathy and asthenia the most common. Eventually, 51 of the 65 patients (79%) in the maintenance paclitaxel arm discontinued treatment, with 39% due to PD and 22% due to adverse toxicities. Only 15 of the 65 patients (23%) completed the full 4 cycles of maintenance paclitaxel.

### Gemcitabine

In a multicentre, randomized Phase III study conducted by the Central European Cooperative Oncology

Group (CECOG), Brodowicz et al reported the use of single-agent maintenance gemcitabine vs BSC in patients with advanced NSCLC after cisplatin + gemcitabine first-line chemotherapy.<sup>7</sup> In this study, 352 chemotherapy-naïve patients with Stage IIIB or IV NSCLC received first-line chemotherapy with cisplatin (80 mg/m<sup>2</sup> on Day 1) plus gemcitabine (1250 mg/m<sup>2</sup> on Days 1 and 8), given every 3 weeks for a maximum of 4 cycles. Those who achieved at least stable disease were then randomized in a 2:1 fashion to receive maintenance gemcitabine (1250 mg/m<sup>2</sup> on Days 1 and 8, given every 3 weeks) plus BSC, or BSC alone. TTP was the primary endpoint, and secondary endpoints included OS, OR rate, response duration, toxicity and symptom control — measured by the Lung Cancer Symptom Scale (LCSS), which includes symptoms such as cough, hemoptysis and pain.<sup>8</sup>

Of 352 patients enrolled, 257 responded and 206 of these were randomized: 138 to gemcitabine + BSC, and 68 to BSC only. Overall TTP was 6.6 months in the gemcitabine arm vs 5 months in the BSC arm ( $p < 0.001$ ). During the maintenance phase, TTP was 3.6 vs 2.0 months in the respective arms ( $p < 0.001$ ). However, the difference in OS was not statistically significant, with median OS of 13.0 months with gemcitabine vs 11.0 months with BSC ( $p = 0.195$ ). Although the authors concluded that the toxicity profile was mild, with no episodes of febrile neutropenia reported in the maintenance period, the rate of Grade 3 or 4 neutropenia was 14.9% in the patients receiving maintenance gemcitabine and 20% of these required transfusional support, compared with only 6.3% requiring transfusion in the BSC arm ( $p = 0.018$ ). QOL as measured by the LCSS scale was not statistically significant between the two arms.

### MAINTENANCE TRIALS OF NON-CROSS-RESISTANT CHEMOTHERAPY AGENTS Vinorelbine

Westeel et al from the French Thoracic Oncology Collaborative Group (GCOT) assessed the role of maintenance

vinorelbine vs BSC in chemotherapy-naïve, advanced NSCLC patients who had received induction treatment with mitomycin + ifosfamide + cisplatin (MIC) with or without radiotherapy.<sup>9</sup> This multicentre, randomized Phase III trial enrolled 573 patients out of an initially planned 675. OS, calculated from the date of randomization, was the primary endpoint and secondary endpoints included progression-free survival (PFS, calculated from date of randomization) and toxicity profile. “Non-wet” Stage IIIB NSCLC patients received 2 cycles of MIC given 4 weeks apart followed by thoracic radiotherapy, while “wet” Stage IIIB patients (i.e. those with pleural or pericardial involvement), Stage IIIB patients with supraclavicular node involvement and Stage IV patients received 4 cycles of MIC. Those who had partial or complete response to induction treatment (patients with stable disease were excluded) were then randomly assigned to vinorelbine 25 mg/m<sup>2</sup>/week for 6 months or to no further therapy. Of the 227 patients who responded to induction treatment, 181 were randomly assigned to maintenance vinorelbine ( $n = 91$ ) or observation only ( $n = 90$ ).

No significant differences in OS adjusted for stage were found by intention-to-treat analysis, with a hazard ratio (HR) of 1.08 ( $p = 0.65$ ) for the vinorelbine arm and median OS of 12.3 months for both arms. Similarly, 1- and 2-year survival rates were not statistically different, at 42.2% and 20.1% in the vinorelbine arm vs 50.6% and 20.2% in the observation arm, respectively ( $p = 0.48$ ). The secondary endpoint of PFS also failed to demonstrate a survival difference, with a HR of 1.07 ( $p = 0.11$ ), and median PFS of 5 months in the vinorelbine vs 3 months in the observation arms. Only 21 patients (23%) completed the full course of maintenance vinorelbine for 6 months; treatment was aborted in 19 patients (21%) due to toxicities, with rates of Grade 3 and 4 leukopenia at 35.4% and 59.5% in the MIC-only and MIC plus thoracic radiotherapy cohorts, respectively. No objective QOL data was obtained.

Two main criticisms arise from this study, however. The trial was stopped

early because of slow patient accrual, although a statistical power of 80% was preserved and this factor was unlikely to have significantly affected the study's efficacy. More importantly, vinorelbine is a poor second-line agent, having shown response rates of less than 1%, as reported in the TAX 320 study.<sup>10</sup>

## ASCO 2008 meta-analysis

Soon et al addressed the question of chemotherapy duration in advanced NSCLC in a systematic review and meta-analysis presented at ASCO 2008.<sup>11</sup> The authors addressed the simple question "Is it preferable to continue chemotherapy beyond a standard number of cycles?" The primary objective was to compare effects on OS, with secondary objectives comparing PFS, adverse events (AEs) and QOL. Thirteen studies enrolling a total of 2416 patients were included for analysis.

A highly statistically significant improvement in PFS was observed with longer durations of chemotherapy (primarily with third-generation regimens), with a HR of 0.78 ( $p < 0.00001$ ). However, extending the duration of chemotherapy had little effect on OS (HR 0.94;  $p = 0.10$ ), and this was true for third-generation agents as well as for platinum and non-platinum chemotherapy. Further, limiting chemotherapy duration was favourable in terms of AEs and QOL. Taken together, these results illustrate that extending chemotherapy duration by continuing third-generation agents in a maintenance fashion beyond 3 or 4 cycles only translates into improved PFS but not OS, at the expense of increased toxicities and decreased QOL.

## Docetaxel

Fidias et al assessed the role of maintenance docetaxel in advanced NSCLC patients who responded to initial induction therapy with carboplatin + gemcitabine.<sup>12</sup> This Phase III randomized trial enrolled 566 chemotherapy-naive patients with Stage IIIB or IV NSCLC. Induction chemotherapy consisted of carboplatin (AUC of 5 on Day 1) plus gemcitabine (1000 mg/m<sup>2</sup> on Days 1 and 8), given every 3 weeks for a maximum of 4 cycles. Of

the 398 patients who completed induction therapy, 309 without PD were randomized in a 1:1 fashion to either immediate docetaxel (75 mg/m<sup>2</sup> on Day 1 every 3 weeks, to a maximum of 6 cycles) or BSC with delayed docetaxel at time of PD (akin to its use in a second-line setting). The primary endpoint was OS (measured from time of randomization), with secondary endpoints of OR, PFS (measured from time of randomization), toxicity and QOL using the LCSS questionnaire.

The study failed to meet its primary endpoint, with median OS of 12.3 months for immediate docetaxel vs 9.7 months for delayed docetaxel ( $p = 0.0853$ ). Of 145 patients in the immediate-docetaxel arm, 17 achieved a response, yielding an OR rate of 11.7%, compared to 11.2% in the delayed docetaxel arm. Median PFS, however, was longer with immediate docetaxel at 5.7 months, vs 2.7 months with delayed docetaxel ( $p = 0.0001$ ). Further, for the 153 patients allocated to immediate docetaxel, 27.6% experienced Grade 3 or 4 neutropenia (vs 28.6% in the delayed arm), with adverse toxicities of fatigue and dyspnea reported in 9.7% and 2.8% of patients, respectively. No significant differences in QOL measures were observed between the two groups ( $p = 0.76$ ).

## Pemetrexed

At ASCO 2008, Ciuleanu et al presented results from a Phase III study comparing maintenance pemetrexed + BSC vs placebo + BSC.<sup>13</sup> As pemetrexed has activity as a second-line agent in advanced NSCLC and carries a favourable toxicity profile, the question was raised whether maintenance pemetrexed might improve outcomes in patients who achieve at least stable disease with a standard first-line platinum-based doublet.

The primary endpoint was PFS, and the study was powered to detect a 23% improvement in PFS (HR of 0.767). A total of 663 patients with advanced NSCLC were randomized in a 2:1 fashion to pemetrexed (500 mg/m<sup>2</sup> every 3 weeks) plus BSC vs placebo plus BSC after first-line therapy with 4 cycles of a platinum-based doublet

(cisplatin or carboplatin plus gemcitabine, paclitaxel or docetaxel). The treatment arms were well balanced for baseline demographics. The primary endpoint of PFS was met with a significant improvement in the maintenance pemetrexed arm (4.0 vs 2.0 months, HR = 0.60,  $p < 0.00001$ ). Further, there was a strong trend towards improvement in OS (13.0 vs 10.2 months; HR = 0.80;  $p = 0.06$ ). In a preplanned subgroup analysis, the differences in PFS and OS were more striking in the non-squamous histology subgroup, but patients receiving maintenance pemetrexed had significantly more serious AEs (4.3% vs 0%;  $p = 0.001$ ) and more Grade 3 AEs (14.3% vs 3.6%;  $p < 0.001$ ). The major criticism of this trial was that very few patients in the placebo arm (11%) received pemetrexed after PD. While more patients in the placebo arm received some form of post-study treatment (50% vs 37%), many of these agents are not considered standard second-line agents.

## MAINTENANCE TRIALS OF EGFR-TKIS Gefitinib

Hida et al presented results at ASCO 2008 of a Japanese Phase III study that randomized patients to receive either platinum-doublet chemotherapy only (3 to 6 cycles) or 3 cycles of chemotherapy followed by gefitinib (250 mg/day) until PD.<sup>14</sup> The primary endpoint was OS, with PFS as one of the secondary endpoints. A total of 598 chemotherapy-naive patients with advanced NSCLC were randomized. Both treatment arms were well balanced for age, gender, performance status, smoking status, histology and stage. A marginal but statistically significant improvement in median PFS favoured the gefitinib arm, but there was no difference in the primary endpoint of OS (13.7 months vs 12.9 months; HR = 0.86;  $p = 0.10$ ). A statistically significant improvement in OS was observed in patients with adenocarcinoma, (15.4 vs 14.3 months; HR = 0.79;  $p = 0.03$ ), although the absolute difference was small at approximately one month. Given the higher prevalence of EGFR mutations in Asian patients, it is unclear whether a similar benefit for

**TABLE 1. Contemporary trials of maintenance therapy in advanced NSCLC**

Study Phase	number of patients enrolled/randomized	induction regimen	maintenance regimen (vs BSC)	median overall survival	median progression-free survival
Belani et al <sup>6</sup> Phase II	401/130	carboplatin/paclitaxel	weekly paclitaxel	75 vs 60 weeks ( $p = n/a$ )	38 vs 29 weeks ( $p = n/a$ ) <sup>*</sup>
Westeel et al <sup>9</sup> Phase III	573/181 <sup>†</sup>	MIC +/- radiotherapy	weekly vinorelbine	12.3 vs 12.3 months (HR = 1.08, $p = 0.65$ ) <sup>‡</sup> (primary endpoint)	5.0 vs 3.0 months (HR = 1.07; $p = 0.11$ ) <sup>‡</sup>
Brodowicz et al <sup>7</sup> Phase III	352/206 (2:1 randomization)	cisplatin/gemcitabine	gemcitabine (Days 1 and 8, q 3 weekly)	13.0 vs 11.0 months ( $p = 0.195$ )	6.6 vs 5.0 months ( $p < 0.001$ ) <sup>*</sup>
Fidias et al <sup>12</sup> Phase III	566/309	carboplatin/gemcitabine	docetaxel q 3 weekly <sup>§</sup>	12.3 vs 9.7 months ( $p = 0.0853$ ) <sup>‡</sup> (primary endpoint)	5.7 vs 2.7 months ( $p = 0.0001$ ) <sup>‡</sup>
Ciuleanu et al <sup>13</sup> (abstract) Phase III	663 (2:1 randomization)	platinum doublet	pemetrexed q 3 weekly	13.0 vs 10.2 months (HR = 0.80, $p = 0.06$ )	4.0 vs 2.0 months (HR = 0.60, $p < 0.00001$ ) (primary endpoint)
Hida et al <sup>14</sup> (abstract) Phase III	598	platinum doublet	gefitinib once daily	13.7 vs 12.9 months (HR = 0.86, $p = 0.10$ ) (primary endpoint)	4.6 vs 4.3 months (HR = 0.68, $p < 0.001$ )

MIC = mitomycin, ifosfamide, and cisplatin; BSC = best supportive care; HR = hazard ratio

\* time to progression was used as the primary endpoint, rather than PFS.

† Only patients who achieved a partial or a complete response to induction treatment were randomized: those with stable disease were excluded.

‡ OS and PFS were calculated from the date of randomization onto the maintenance arm, rather than from start date of induction therapy.

§ For patients randomized to the BSC arm, delayed docetaxel was given at time of disease progression.

maintenance gefitinib would be seen in North American patients.

### Erlotinib

An ongoing Phase III study (Sequential Tarceva in Unresectable NSCLC; SATURN), now closed to enrollment, is assessing the role of maintenance erlotinib in EGFR immuno-histochemistry-positive, advanced NSCLC patients following first-line platinum-based doublet chemotherapy. In a recent press release, Roche announced that initial results for the 889 patients indicate that the primary endpoint of PFS was met.<sup>15</sup> Further data are awaited.

### TOWARDS BETTER SURVIVAL AND QOL


First-line platinum-based chemotherapy is the standard of care for suitable patients with advanced NSCLC. When considering initial treatment in this population, it is important to realize that the goals of palliative therapy are to provide symptom control, maintain or improve quality of life and prolong survival, and that the goals of maintenance therapy are identical. Although

extending chemotherapy duration or employing maintenance systemic therapy strategies may prolong PFS, no OS benefits have been consistently demonstrated, as summarized in **Table 1**, and the costs of increased toxicities and decreased quality of life are not negligible. It is therefore imperative that the goals of palliation be carefully weighed against the potential treatment benefits, and currently, maintenance therapy does not appear to achieve these goals.

The most promising data supporting a role for maintenance chemotherapy comes from recent trials examining maintenance docetaxel and pemetrexed.<sup>12,13</sup> Although neither trial demonstrated a statistically significant survival benefit for maintenance chemotherapy in the overall study population, they both showed a strong trend favouring maintenance therapy, and in the pemetrexed trial the survival benefit was statistically significant in the patients with non-squamous histology. These data, however, need to be interpreted in the context of current trends in the first-line treatment of advanced

NSCLC. None of the maintenance trials included the addition of bevacizumab to chemotherapy for eligible patients; this is particularly relevant to the non-squamous population. As well, based on recent evidence of a differential benefit for specific first-line chemotherapeutic agents depending on histology (e.g. squamous vs non-squamous),<sup>16,17</sup> there is an increasing trend to select first-line regimens according to histology, for example pemetrexed for non-squamous histology. At present, it is unclear whether maintenance pemetrexed might improve survival in patients with non-squamous histology who are treated upfront with platinum + pemetrexed as first-line therapy.

Future trials of maintenance therapy in advanced NSCLC should incorporate histology as a pre-stratification factor to assess its potential predictive role. To better define the potential role of maintenance pemetrexed, for example, the trial design should limit the enrollment of advanced NSCLC patients to those with non-squamous histology, with randomization to maintenance pemetrexed vs BSC after

4 cycles of induction platinum + pemetrexed. An industry-sponsored trial based on this design is currently recruiting patients.<sup>18</sup> Similarly, for patients with squamous histology, initial platinum-based chemotherapy would be followed by randomization to maintenance docetaxel or BSC. The endpoints of these trials should include survival (OS and PFS), QOL and cost-effectiveness analyses. Finally, the role of novel biomarkers as predictive factors in the management of advanced NSCLC should also be explored and incorporated into future trial designs. 

## References

1. Cancer Society and National Cancer Institute of Canada: *Canadian Cancer Statistics 2008*. Toronto, Canada, 2008.
2. Schiller JH, Harrington D, Belani CP et al; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *NEJM* 2002;346(2):92-8.
3. 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(5):1335-43.
4. 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(8):966-73.
5. Pfister DG, Johnson DH, Azzoli CG et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22(2):330-53.
6. 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(15):2933-9.
7. 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(2):155-63.
8. Hollen PJ, Gralla RJ, Kris MG et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Psychometric assessment of the Lung Cancer Symptom Scale. *Cancer* 1994;73(8):2087-98.
9. 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(7):499-506.
10. 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(12):2354-62.
11. Soon Y, Stockler MR, Boyer M, Askie L. Duration of chemotherapy for advanced non-small cell lung cancer: An updated systematic review and meta-analysis. *J Clin Oncol* 26: 2008 (May 20 suppl). ASCO 2008, Abstract 8013.
12. Fidas 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(4):591-8.
13. Ciuleanu TE, Brodowicz T, Belani CP et al. Maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC: A phase III study. *J Clin Oncol* 26: 2008 (May 20 suppl). ASCO 2008, Abstract 8011.
14. Hida T, Okamoto I, Kashii T et al. 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). *J Clin Oncol* 26: 2008 (May 20 suppl). ASCO 2008, Abstract LBA8012.
15. Tarceva brings new hope to patients with advanced non-small cell lung cancer. November 7, 2008; Available at [www.roche.com/med-cor-2008-11-07](http://www.roche.com/med-cor-2008-11-07).
16. Scagliotti GV, Parikh P, von Pawel J et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26(21):3543-51.
17. Scagliotti G, Hanna N, Fossella F et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist* 2009;14(3):253-63.
18. A Phase 3, Double-Blind, Placebo-Controlled Study of Maintenance Pemetrexed Plus Best Supportive Care Versus Best Supportive Care Immediately Following Induction Treatment With Pemetrexed + Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer. Available at [www.clinicaltrials.gov/ct2/show/NCT00789373](http://www.clinicaltrials.gov/ct2/show/NCT00789373).