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Lung Cancer

Optimal Duration of Chemotherapy in Advanced Non-Small Cell Lung Cancer

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Opinion statement

NSCLC is the leading cause of cancer mortality in the United States. Approximately 30–40% of patients present with advanced stage disease (Stage IIIb with malignant effusion and Stage IV) and the majority of those who present with "earlier" disease will ultimately develop and succumb to metastatic lung cancer. Although platinum-based combination chemotherapy has been shown to impact overall survival and quality of life, it is not curative and less than 25% of patients survive 2 years. Therefore, the benefits of chemotherapy must be weighed against toxicity, inconvenience, and cost. Several randomized trials have shown that there is no added benefit of extending first line, platinum-based chemotherapy beyond four cycles. There was no additional survival benefit and patients experienced increased toxicity with longer durations of therapy. Attempts to improve outcome by planned sequential therapy, i.e. shifting from one cytotoxic regimen to another after a fixed number of cycles have also not been successful. Several new so-called "targeted" therapeutic agents have recently been evaluated in clinical trials to assess whether the efficacy of first line chemotherapy with platinum doublets can be improved with the addition of these agents. These include bevacizumab, epidermal growth factor receptor inhibitors (erlotinib and gefitinib), bexarotene, matrix metalloproteinase inhibitors, and others. Other than bevacizumab, none have demonstrated benefit in this scenario. The design of most of these trials employed the concurrent use of the new agent with six cycles of platinum-based chemotherapy (usually either carboplatin/paclitaxel or cisplatin/gemcitabine) and then continued the new agent until relapse. Three agents have demonstrated benefit in randomized studies in the second line setting, docetaxel, pemetrexed, and erlotinib. No study has evaluated the optimal duration of therapy for these agents, though for erlotinib, it appears that use until progression is optimal. Future studies of novel agents will need to explore not only the potential use of these agents in combination or in comparison with standard therapy, but also the duration of therapy and consider issues of survival, quality of life, and cost.

Introduction

Lung cancer is the leading cause of cancer mortality in the United States. Approximately 85% of lung cancers are non-small cell (NSCLC) and 30–40% of these patients present with advanced stage disease, defined by the presence of malignant effusions (IIIB) or metastatic disease (IV). Although advanced NSCLC is incurable with current therapeutic options, platinum-based chemotherapy has been shown to improve overall survival and quality of life compared to best supportive care [1–4]. Several trials have addressed duration of first line chemotherapy. There was no increased survival benefit but there was increased toxicity when duration was extended beyond 3–4 cycles. There have been no trials addressing duration of second line chemotherapy. Recently, several trials have addressed the question of whether the addition of various targeted agents to first line chemotherapy will improve survival in advanced NSCLC. In many of the trials combining platinum-based chemotherapy with targeted therapy, the duration of chemotherapy was protocol specified for six cycles with continuous administration of the "targeted agent" until progression. Therefore, the issue of optimal duration of these agents has not yet been assessed. This article focuses on the current data about duration of chemotherapy in advanced NSCLC and highlights some of the on-going trials that will likely impact optimization of therapy in the future.

Treatment

- Multiple randomized trials and several meta-analyses have all shown survival benefit of platinum-based chemotherapy over best supportive care. The recommended first line chemotherapy in NSCLC is platinum-based combination chemotherapy. No one regimen has been shown to be superior for first line therapy. Cisplatin or carboplatin with newer agents paclitaxel, vinorelbine, gemcitabine or docetaxel is considered standard of care for patients with preserved performance status (ECOG PS 0-1 and possibly 2). Bevacizumab has recently demonstrated superiority when combined with carboplatin/paclitaxel over carboplatin/paclitaxel alone in selected patients with advanced NSCLC and PS 0-1.
- Non-platinum chemotherapy has also been demonstrated to be beneficial with some randomized trials demonstrating comparable levels of effectiveness in terms survival to platinum based treatment. However, superiority has not been demonstrated and though the toxicity profile is different, it is not clearly superior [5].

Duration of first line chemotherapy in NSCLC

- Evidence and consequent recommendations for the duration of first line chemotherapy in advanced NSCLC has evolved in the past decade. In 1997, a consensus statement by American Society of Clinical Oncology recommended that chemotherapy in advanced stage NSCLC should not be extended beyond eight cycles [6]. These recommendations were based on the only trial completed at that time by Buccheri *et al.* which compared non-platinum based chemotherapy after 2–3 cycles to continuous treatment [7]. No survival benefit was seen in continuous treatment. A revision of these guidelines utilizing the additional information from the studies by Smith and Socinski (see below) in 2003 reduced the recommended number of cycles to six [8].
- In 2001, Smith *et al.* conducted a randomized trial comparing three cycles versus six cycles of mitomycin/vinblastine/cisplatin (MVP) in advanced lung cancer [9]. There was no significant difference between median and 1 year survivals. A total of 72% patients randomized to three courses completed treatment. Only 31% of the patients randomized to

six courses completed treatment. Drop out rate was due to various factors including progression, toxicity, and patient preference.

- Socinski *et al.* reported a phase III randomized trial comparing carboplatin/paclitaxel ×4 cycles versus continuous therapy [10]. At progression, both arms received weekly paclitaxel. Median survival and 1 year survival rates were not statistical different. Quality of life measures were similar. There was significantly increased neuropathy in patients in the continuous therapy arm. Subset analysis on patients who received four cycles of therapy but were eligible to receive more cycles did not show any statistical survival difference with the continuous therapy group. In total 42.5% survived the first year versus 50.2% in the continuous therapy group, $p = 0.9$.
- Von Plessen randomly assigned patients ($n = 297$) to either three or six cycles of carboplatin and vinorelbine and found no benefit from the longer duration of therapy [11]. There were no significant differences in terms of median, 1 year or 2-year survival between the groups and no differences in quality of life or symptom control.
- Patient preference for duration of chemotherapy tends to favor longer durations of chemotherapy, which has posed difficulties in devising randomized trials. For example Smith and colleagues had planned a trial where patients with advanced NSCLC who had responded to three cycles of mitomycin, vinblastine, and cisplatin were randomized to stop chemotherapy or continue for additional three cycles. However, this design was not acceptable to a majority of patients who wanted more chemotherapy. As a result, the trial was modified to randomize patients before initiation of therapy. This desire is likely based upon the perception that there is an advantage of treatment as only 31% of the patients randomized to six courses were able to complete treatment. Similarly, the other randomized trials have demonstrated that there is a significant drop off in the number of patients who can tolerate 6 versus 3–4 courses of therapy either due to progression of disease or toxicity.
- At this time, based upon four fully published randomized trials evaluating the duration of initial chemotherapy for advanced NSCLC, including three with platinum based chemotherapy and two with "modern" regimens, the optimal duration is 3–4 cycles (see Table 1).

Table 1. Randomized trials of duration of chemotherapy in advanced NSCLC

Trial	Regimen	N	Median survival	Toxicity
Buccheri (1989)	MACC × 2–3 cycles MACC × cont.	74	30 wks vs 47	2 TRDs
Smith (2001)	MVP × 3 cycles MVP × 6 cycles	308	6 mo vs 7 mo ($p = .2$)	Increased fatigue ($p = .03$) & nausea ($p = .06$)
Depierre (2001)	MIP × 4(Observation MIP × 4(V	179	One year survival 40.4% vs 52.3 ($p = .44$)	Increased leucopenia, thrombocytopenia, infections, 7 TRDs
Socinski (2002)	CP × 4 CP × cont	230	6.6 mo vs 8.5 mo ($p = .63$)	Increased neuropathy from cycle 4 to 8 (19% vs 43%
Von Plessen (2006)	CV × 3 CV × 6	297	28 wks 32 wks ($p = 0.58$)	Increased anemia and transfusions

MACC, methotrexate, doxorubicin, cyclophosphamide, and lomustine; MVP, mitomycin, vinblastine, cisplatin; CP, carboplatin/paclitaxel; P, paclitaxel; CV, carboplatin/vinorelbine; MIP, mitomycin, ifosfamide, cisplatin; TRD, treatment related deaths.

Planned sequential therapy and/or maintenance chemotherapy

- With the advent of new agents in the 1990's with different mechanisms of action and early indications of benefit for several of these agents (particularly the taxanes) after progression of disease despite platinum based therapy, the question of planned sequential therapy arose. This approach was based upon two assumptions, first, that the benefit of first line platinum based chemotherapy was limited to 3–4 cycles and second that cross over to a different chemotherapy regimen containing an agent (or agents) with a different mechanism of action might be beneficial. Preliminary, institutional phase II trials were promising and a randomized phase II trial was undertaken by the Southwest Oncology Group (SWOG 9806) [12]. Though the results of this trial were better than previous SWOG studies, the approach was not felt to be sufficiently promising to move to a definitive study. A similar trial evaluating cisplatin/gemcitabine followed by docetaxel or docetaxel/gemcitabine followed by docetaxel also failed to demonstrate an advantage for this approach [13].
- A related approach of maintenance chemotherapy has also been evaluated, defined as continuing one or more of the agents already utilized but with altered dose or schedule to allow for chronic administration, has not been demonstrated to be sufficiently active to warrant definitive testing. DePierre *et al.* reported a trial where patients with advanced NSCLC who had either radiographic stability or response to a regimen of mitomycin, ifosfamide, and cisplatin were then randomized to observation versus continued treatment with vinorelbine. Of the 217 patients eligible for the trial, 179 patients or 82% accepted randomization. As stated above, no difference in survival was seen in the maintenance therapy group [14].
- Therefore, based upon current evidence there is no benefit to changing from one cytotoxic regimen to another or for the use of current cytotoxic agents as maintenance therapy.

Continuation of cytotoxic therapy in the patient who is "benefiting from treatment"

- The majority of benefit in terms of measurable response and symptoms occurs in the first two courses of therapy with almost all radiographic responses seen within four courses of treatment. The question of whether continuing therapy in patients who "continue to respond" has not been clearly answered though the weight of evidence is that it does not improve the outcomes of survival or quality of life.
- As noted above, the study by Depierre evaluated the benefit of vinorelbine in patients who had demonstrated response or stability after platinum based therapy and found no advantage. Similarly, Socinski analyzed the benefit in terms of survival for those who were able to receive a full four cycles of therapy versus those who received more than four (thereby excluding patient who had progressive disease or could not tolerate therapy) and found no advantage in terms of survival.
- Based upon current information from randomized trials, there does not appear to be any benefit for continuing cytotoxic therapy even in patients who manifest a response after four courses of therapy.

The impact of initial performance status on duration of chemotherapy

- Performance status is the major prognostic factor in patients with advanced NSCLC. Limited data exists about correlation between performance status and duration of chemotherapy. In Smith *et al.*, there was no difference in survival between patient with poor performance status and duration of chemotherapy. In contrast, the study of Socinski *et al.* found that patients with worse performance status seemed to benefit from prolonged chemotherapy. In this trial, patients with poor performance status (Karnofsky PS of 70–80%) had worse outcomes. When comparing Arm A (four cycles of chemo) with Arm B (continuous cycles of chemo), patients with poor performance status had better outcomes with continuous therapy. Patients with PS 70–80% in arm A had a greater hazard ratio = 2.0, $p = 0.19$ with only 8.0% survival at 1 year compared to 30.7% survival at one year in Arm B (continuous therapy). This analysis was exploratory and the numbers were small. The possible benefit of prolonged treatment with poor performance status patients requires further study.
- At this time, there is inadequate information to make any recommendation regarding duration of therapy depending upon performance status.

Role of targeted agents and duration of first line chemotherapy

- Although current platinum based combination chemotherapy has improved survival compared to supportive care, 1 year survival rates have reached a plateau at 30–35% and improved first line chemotherapy regimens are needed. Bevacizumab, a recombinant anti-vascular endothelial growth factor (VEGF) antibody, was investigated with carboplatin and paclitaxel in a randomized phase II trial [15]. A total of 99 patients were randomized to three groups: carboplatin/paclitaxel (CP), CP + low dose bevacizumab, and CP + high dose bevacizumab. Patients in the bevacizumab groups had overall improved response and time to progression but increased rates of fatal hemoptysis. A phase III trial comparing carboplatin/paclitaxel to carboplatin/paclitaxel/bevacizumab in selected patients with advanced NSCLC (non-squamous histology, no brain metastases, PS 0-1, no bleeding or thrombotic problems, no hemoptysis) has demonstrated improved survival for the bevacizumab arm [16]. In this study (ECOG 4599) bevacizumab was continued until progression of disease. It is interesting that in the pilot trial, patients receiving standard chemotherapy were allowed to cross over to single agent bevacizumab. Though no radiographic responses were seen, the median survival was unexpectedly long (12.2 months), indicating the possibility of benefit. Nineteen patients crossed over at the time of progression and five experienced disease stabilization. Therefore, when employing this agent in a non-study situation, given the design of the randomized trial and the data from the pilot study, continuation until progression is appropriate until additional data regarding optimum use is generated.
- Data from renal cell carcinoma also lend support to the concept of continuous use of anti-VEGF agents. The randomized discontinuation design employed in the studies of sorafenib demonstrated that there was benefit if these agents were continued in patients with stable or radiographically responding disease [17].
- Other targeted agents include epidermal growth factor receptor tyrosine kinase (EGFR TK) inhibitors, which have been studied with platinum

based combination chemotherapy. In the TRIBUTE trial, patients with advanced NSCLC were randomized to erlotinib vs placebo plus up to six cycles of carboplatin and paclitaxel [18]. The median number of cycles of carboplatin and paclitaxel was five for both arms. The median duration on study drug erlotinib was 4.6 months and 5.3 months with placebo. Although erlotinib with concurrent carboplatin and paclitaxel did not improve survival, a subset of patients with mutations in the intracellular EGFR domain and/or never-smokers may gain greater benefit from this combination. More trials are needed to verify these findings. Similarly in INTACT-2, gefitinib in addition to first line chemotherapy (carboplatin and paclitaxel) did not improve survival [19]. Similar results were obtained with combinations of erlotinib and gefitinib with cisplatin and gemcitabine (INTACT-1 and TALENT) [20,21]. Additional clinical investigations are needed to verify sequential regimens and duration schemes for maintenance therapy that might improve efficacy. Of relevance to the issue of duration of therapy, these studies utilized the EGFR TKI indefinitely. A retrospective analysis has demonstrated possible advantage for patients who had stable disease and continued on therapy with the EGFR TKI [22].

- Several phase II and retrospective trials have evaluated EGFR TKI therapy as first line treatment in patients with lung cancer who never smoked and in those with mutations in the EGFR tyrosine kinase site. These studies demonstrate very high rates of response and prolonged survival. Whether this treatment is superior to the initial use of standard therapy is unclear. In these trials, the EGFR TKI was utilized continuously.
- A number of other studies evaluating new agents including bexarotene, matrix metalloproteinase inhibitors (MMPIs), and other agents have failed to demonstrate benefit. In most of these studies, the novel agent was continued until progression was documented.
- At this time there is not sufficient evidence to recommend the use of EGFR TKI therapy in any group as first line therapy. However, patients with no smoking history or other features highly predictive of response (e.g. EGFR mutation, bronchioloalveolar histology) may be considered for this approach, preferably as part of a clinical trial [23–26].

Duration of second line chemotherapy in NSCLC

- Evidence for optimal duration of second line chemotherapy in advanced NSCLC is very limited. In 2004, docetaxel was the first drug approved as second line therapy for advanced NSCLC [27,28]. In these trials, patients were treated with 75 mg/m^2 every 21 days of docetaxel until either unacceptable toxicity or disease progression. In a Canadian trial comparing docetaxel to best supportive care, the median time duration of response was 26.1 weeks. Therefore, approximately 8–9 cycles of therapy were administered to patients with response or stable disease. No trials evaluating duration of docetaxel have been reported.
- Pemetrexed (500 mg/m^2 q 21 days) has also been approved for second-line therapy in advanced NSCLC. Though this approval was ostensibly based upon response rate, in actuality it was due to the comparable survival of this agent with docetaxel and a favorable toxicity profile [29]. In the phase III trial, there was no limit on the number of cycles of therapy and as with docetaxel, no optimal duration of therapy has been

defined. Patients on this trial received a median of four cycles of therapy, but up to 20 were administered.

- The BR 21 trial conducted by National Cancer Institute of Canada showed that single agent erlotinib improves survival, quality of life, and time to progression in patients with advanced NSCLC who had progressed after first or second line chemotherapy [30]. Duration of therapy was continuous until further progression. Erlotinib is an oral agent and its mechanism, targeting of the tyrosine kinase domain of the EGFR is distinctly different than the targets of DNA or tubulin by the conventional cytotoxic agents (platinum, docetaxel, pemetrexed etc). While EGFR targeting can result in cell death, it is likely that there is also an element of tumor suppression (i.e. cells are viable but not dividing) as well. As noted above, data from other TKI agents in renal cell carcinoma indicates that these agents are best administered in a continuous fashion until progression.
- In second line therapy there are no studies clearly addressing the duration of therapy with docetaxel or pemetrexed. Erlotinib was utilized continuously in the BR 21 study and therefore, should be employed until progression of disease is documented.

Future therapies

- Many of the new targeted agents are currently being investigated alone or in combination with other regimens for first line as well as second and third line therapies. These agents have different mechanisms and it is quite possible that, similar to the tyrosine kinase inhibitors, chronic administration will be both beneficial and tolerable.
- Though currently available cytotoxic agents (i.e. agents targeting DNA and tubulin) have not demonstrated benefit with prolonged use, these findings employed doses and schedules based upon the concept that drugs should be administered at the maximum tolerated dose. It is quite conceivable that these agents, employed at lower doses and with novel schedules (e.g. metronomic dosing) may be beneficial when employed for more than the 3–4 cycles currently recommended. While theoretically attractive, such use will require phase III trials.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Cullen MH, Billingham LJ, Woodroffe CM, *et al.*: **Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: Effects on survival and quality of life.** *J Clin Oncol 1999,* **17:**3188 3194.

2. Anonymous: **Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials—Non-small Cell Lung Cancer Collaborative Group.** *BMJ* 1995, **311:**899–909.

3. Wozniak AJ, Crowley JJ, Balcerzak SP, *et al.*: **Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: A Southwest Oncology Group study.** *J Clin Oncol 2001,* **16:**2459–2465.

4. Sandler AB, Nemunaitis J, Denham C, *et al.*: **Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer.** *J Clin Oncol 2000,* **18:**122–130.

5. D'Addario G, Pintilie M, Leighl N, Feld R, Cerny T, Shepherd FA: **Platinum –based versus non-platinum based chemotherapy in advanced non-small cell**

lung cancer: A meta-analysis of the published literature. *J Clin Oncol 2005,* **23:**2926–2936.

6. American Society of Clinical Oncology.: **Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer.** *J Clin Oncol 1997,* **15:**2996–3018.
7. Buccheri GF, Ferrigno D, Curcia A, *et al.*: **Continuation of chemotherapy versus supportive care alone in patients with inoperable non-small cell lung cancer and stable disease after two or three cycles of MACC. Results of a randomized prospective study.** *Cancer 1989,* **63(3):**428–432.
8. •• 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):**330–353.
9. • 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(5):**1336–1343.
10. •• Socinski M, Schell M, 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:**1335–1343.
11. 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):**966–973.
12. Edelman MJ, Clark J, Chansky K, Albain K, Gandara DR: **Randomized phase II trial of sequential chemotherapy in advanced non-small cell lung cancer: Carboplatin/Gemcitabine followed by Paclitaxel or Cisplatin/Vinorelbine followed by Docetaxel (SWOG 9806).** *Clin Cancer Res 2004,* **10(16):**5418–5424.
13. Binder D, Schweisfurth H, Grah C, *et al.*: **Docetaxel/gemcitabine or cisplatin/gemcitabine followed by docetaxel in the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC): results of a multicentre randomized phase II trial.** *Cancer Chemother Pharmacol.* 2006 Oct 10; (Epub ahead of prin).
14. • DePierre A, Quiox E, Mercier M, Breton J, Moro-Sibilot D, Debeiuvre D: **Maintenance chemotherapy in advanced non-small cell lung cancer: A randomized trial of vinorelbine versus observation in patients responding to induction chemotherapy.** *Proc Am Soc Clin Oncol 2001,* **20:**309a
15. Johnson DH, Fehrenbacher L, Novotny WF, *et al.*: **Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer.** *J Clin Oncol 2004,* **22:**2184–2191.
16. • Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH: **Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer.** *N Engl J Med 2006,* **355:**2542–2550.
17. Ratain MJ, Eisen T, Stadler WM, *et al.*: **Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma.** *J Clin Oncol 2006,* **24:**2505–2512.
18. 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:**5892–5899.
19. 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:**785–794.
20. 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:**777–784.
21. Gatzemeier U, Pluzanska A, Szczesna A, *et al.*: **Results of a phase III trial of erlotinib (OSI-774) combined with cisplatin and gemcitabine (GC) chemotherapy in advanced non-small cell lung cancer (NSCLC) [abstract 7010].** *J Clin Oncol 2004,* **22(suppl 14S):**619S
22. Herbst RS, Giaccone G, Schiller J, *et al.*: **Subset analyses of INTACT results for gefitinib (ZD1839) when combined with platinum-based chemotherapy (CT) for advanced non–small-cell lung cancer (NSCLC) [abstract 2523].** *Proc Am Soc Clin Oncol 2003,* **22:**627
23. Paez JG, Janne PA, Lee JC, *et al.*: **EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy.** *Science 2004,* **304:**1497–14500.
24. Lynch TJ, Bell DW, Sordella R, *et al.*: **Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib.** *N Engl J Med 2004,* **350:**2139–2159.
25. Tsao MS, Sakurada A, Cutz JC, *et al.*: **Erlotinib in lung cancer - molecular and clinical predictors of outcome.** *N Engl J Med 2005,* **353:**133–144.
26. Pérez-Soler R, Chachoua A, Hammond LA, *et al.*: **Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer.** *J Clin Oncol 2004,* **22:**3238–3247.
27. Fossella FV, DeVore R, Kerr R, *et al.*: **Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum containing chemotherapy regimens.** *J Clin Oncol 2000,* **18:**2354–2362.
28. Shepherd F, Dancey J, Ramlau R, *et al.*: **Prospective randomized trial of docetaxel vs. best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy.** *J Clin Oncol 2000,* **18:**2095–2013.
29. 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:**1589–1597.

30. Shepard F, Pereira J, Ciulenanu T: **A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer following failure of first line or second line chemotherapy. A National Cancer Institute of Canada Clinical Trials Group trial.** *J Clin Oncol 2004*, **2**:622s