Maintenance Therapy in Advanced Non-small Cell Lung Cancer

Current Status and Future Implications

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Abstract: Maintenance therapy for patients with advanced non-small cell lung cancer has been an area of intense investigation. Maintenance therapy has been divided into two broad categories: continuation maintenance when the chemotherapy or targeted agent was part of a defined number of cycles of combination therapy and in the absence of disease progression is continued as a single agent or switch maintenance when a third agent is initiated after four cycles of platinum-based double-agent chemotherapy in the absence of disease progression. Two monoclonal antibodies, cetuximab and bevacizumab, are used as continuation maintenance, but the incremental benefit of the maintenance therapy with these agents is undetermined. Phase III trials have not revealed an overall survival benefit for continuation maintenance chemotherapy, and this approach should be considered investigational. Phase III trials have demonstrated an improvement in overall survival with switch maintenance therapy with pemetrexed compared with placebo in patients with nonsquamous histology and erlotinib compared with placebo. Phase III trials have not revealed an improvement in quality of life with maintenance therapy. In the trials of maintenance therapy, 30 to 40% of patients enrolled in the observation or placebo arm did not receive second-line therapy, and among the patients who did receive second-line therapy, there was significant heterogeneity in the therapy. The development of maintenance therapy has raised issues about the role of treatment-free intervals in routine clinical care, trial design issues such as the optimal endpoint, the ethics of a placebo arm, and the implications of maintenance therapy for first-line trials.

Key Words: Erlotinib, Gefitinib, Pemetrexed, Bevacizumab, Docetaxel, Clinical trial.

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Lung cancer is the leading cause of cancer mortality in the United States, and it is estimated that in 2008, there were 1.61 million cases and 1.38 million deaths related to lung cancer worldwide.[1,2] Non-small cell lung cancer (NSCLC) accounts for most of the cases, and most patients with NSCLC are diagnosed with advanced stage disease when the treatment is palliative. Platinum-based double-agent chemotherapy extends overall survival (OS), reduces disease-related symptoms, and improves quality of life (QoL) and is considered the standard of care for patients with a preserved performance status (PS).[3,4] Nevertheless, only approximately 60% of patients will experience disease control at 8 weeks with platinum-based therapy,[5] and the median OS observed in recent trials of platinum-based double-agent chemotherapy was 10 to 13 months.[6–9] Phase III trials have compared a shorter duration to a longer duration of platinum-based chemotherapy; four of the five trials have revealed similar survival between the two treatment arms and less toxicity with shorter duration of therapy.[10–14] In these trials, a substantial proportion of patients enrolled in the longer duration treatment arm experienced either disease progression or unacceptable toxicity and received fewer than the intended cycles of therapy. This may have contributed to the similar OS in the two treatment arms. These results suggested that to extend the duration of chemotherapy, a strategy other than extending the duration of platinum-based therapy would have to be pursued.

Two treatment paradigms to extend the duration of therapy that have been recently investigated include "continuation maintenance" and "switch maintenance." Continuation maintenance describes the paradigm of continuing a targeted or chemotherapy agent that was part of the initial platinum-based therapy after a defined number of cycles of combination therapy. Switch maintenance describes the paradigm when a third agent is initiated before disease progression after completion of four cycles of platinum-based double-agent chemotherapy. The treatment paradigm of switch maintenance extends the duration of therapy and integrates a third agent into the treatment.[15–18] Continuation maintenance has been investigated in trials in which patients receive platinum-based double-agent chemotherapy for a finite duration followed by the continuation of the nonplatinum agent.[19–21] Phase III trials of platinum-based double-agent chemotherapy alone or in combination of the targeted agent bevacizumab or

TABLE 1. Phase III Trials of Continuation Maintenance Chemotherapy

First Author	No. of Patients Enrolled	Chemotherapy Comparison[a]	Median PFS	Median OS
Brodowicz[20]	352	Gemcitabine ($N = 138$)	3.6 mo[b]	10.2 mo[b]
		BSC ($N = 68$)	2.0 mo	8.1 mo
			$p < 0.001$	$p = 0.172$
Belani[21]	519	Gemcitabine ($N = 128$)	7.4 mo[b]	8.0 mo[b]
		BSC ($N = 127$)	7.7 mo	9.3 mo
			HR = 1.09, $p = 0.575$	HR = 0.97, $p = 0.838$
Perol[22]	834[c]	Gemcitabine ($N = 155$)	3.8 mo	NA
		Observation ($N = 155$)	1.9 mo	NA
			HR = 0.55, $p < 0.0001$	HR = 0.86 (95% CI, 0.66–1.12)
Belani[19]	401	Paclitaxel ($N = 65$)	38 weeks	75 weeks
		Observation ($N = 65$)	29 weeks	60 weeks

[a] *N* values represent number of patients randomized.
[b] Data reported from time of randomization.
[c] Three-arm trial, of 834 patients enrolled 464 randomized. Results of erlotinib arm included in Table 3.
BSC, best supportive care; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

cetuximab have revealed an improvement in OS with the addition of bevacizumab or cetuximab.[6,7] The targeted agent was combined with platinum-based double-agent chemotherapy for four to six cycles and then in the absence of disease progression was continued as a single agent.

CONTINUATION MAINTENANCE CHEMOTHERAPY TRIALS

Phase III trials that investigated continuation maintenance with a chemotherapy agent were performed with gemcitabine and paclitaxel (Table 1).[19–22] In the trial by Brodowicz et al.,[20] patients received initial therapy with cisplatin and gemcitabine for four cycles, and patients who did not experience disease progression were randomized to single-agent gemcitabine or observation. The primary objective was time to progression (TTP), and the trial was designed to detect an improvement in TTP for the whole study period of a hazard ratio (HR) of 0.65 (equivalent to a median of 5.5 months in the best supportive care [BSC] and 8.5 months in the gemcitabine arm). OS was a secondary endpoint. Of the 352 patients enrolled, 206 (59%) were randomized to gemcitabine ($n = 138$) or BSC ($n = 68$). Patients in the gemcitabine arm compared with the BSC experience statistically significant longer TTP, but a statistically significant difference in OS was not observed (Table 1). A subset analysis of good and poor PS patients was performed for OS from time from randomization. Patients with good PS (defined as a Karnofsky PS > 80, $n = 99$) in the BSC arm compared with the gemcitabine arm experienced a statistically significant worse survival HR = 2.1 (95% confidence interval [CI], 1.2–3.8; median OS, 8.3 and 22.9 months). Patients with a poor PS (defined as Karnofsky PS ≤ 80, $n = 107$) in the BSC arm compared with the gemcitabine arm experienced similar OS from time of randomization (HR = 0.8, 95% CI, 0.5–1.3; median OS, 7.7 and 7.0 months). In a trial by Belani et al.,[21] patients received four cycles of carboplatin and gemcitabine and were then randomized to gemcitabine or BSC. The primary endpoint was OS, and patients were required to have an Eastern Cooperative Oncology Group (ECOG) of 0 to 2 at the time of enrollment. Of the 512 patients enrolled, 255 (50%) were randomized to gemcitabine ($n = 128$) or BSC ($n = 127$). Maintenance gemcitabine compared with BSC did not improve progression-free survival (PFS) or OS (Table 1). In a Cox regression analysis, variables associated with worsened survival were a PS ≥ 2 compared with a PS $= 1$ and male gender. In the gemcitabine and BSC arms, a high percentage of patients had a PS of ≥ 2 (56% and 58%, respectively), and only a minority of patients received poststudy therapy (16% and 17%, respectively). These trials suggest that patients with a poor PS are unlikely to benefit from a strategy of continuation maintenance with gemcitabine, but the prolonged survival among patients with a good PS in the trial by Brodowicz et al. (22.9 months from time of randomization) suggests that this may be a viable strategy for patients with a good PS.

A three-arm phase III trial investigated the role of maintenance gemcitabine or erlotinib compared with observation after initial therapy with cisplatin and gemcitabine.[22] The primary endpoint of the trial was PFS by independent panel review, and it was not designed to compare the efficacy of maintenance gemcitabine to erlotinib. Patients in all treatment arms were offered pemetrexed at the time of disease progression. Of the 834 patients enrolled, 464 (56%) were randomized to observation ($n = 155$), gemcitabine ($n = 154$), and erlotinib ($n = 155$) (Table 1). The data related to the erlotinib arm will be discussed later in this article in the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) maintenance section. Patients in the gemcitabine arm compared with the observation experienced a significantly longer PFS (Table 1). The OS data are not mature, but no significant difference in OS has been observed at this time. Of the patients randomized to gemcitabine, 60% received pemetrexed, and of the patients randomized to observation, 76% received pemetrexed; the median number of cycles was three in both arms. The response rate to pemetrexed observed in the gemcitabine and observation arms was 8.1% and

15.2%, respectively. Another trial by Belani et al.[19] investigated carboplatin and paclitaxel on three different schedules, and in the absence of disease progression, patients were randomized to weekly paclitaxel or observation. This trial was designed to assess the feasibility of maintenance paclitaxel. A numerically longer PFS and OS were observed with maintenance paclitaxel compared with observation (Table 1). None of the trials that have investigated continuation maintenance therapy with chemotherapy have demonstrated an improvement in OS in the intent-to-treat patient population. The lack of survival benefit may be related to the clinical trials' design, and the use of PFS as the primary endpoint,[20,22] the trial was designed to test the feasibility of maintenance therapy[19] or enrolled a high percentage of patients with a poor PS.[21] At this time, this strategy should be considered investigational.

CONTINUATION MAINTENANCE WITH MONOCLONAL ANTIBODIES

The trials of monoclonal antibodies investigated the combination of a monoclonal antibody with platinum-based double-agent chemotherapy followed by continuation of the monoclonal antibody compared with platinum-based double-agent chemotherapy alone. Thus, the trial design used for these agents does not allow for an assessment of the incremental impact of the single-agent maintenance therapy with the monoclonal antibody. ECOG 4599 compared carboplatin and paclitaxel with and without bevacizumab and demonstrated an improvement in PFS and OS with the addition of bevacizumab. Of the 407 patients assigned to the bevacizumab containing arm, 215 (53%) received single-agent bevacizumab and 107 (26%) received greater than five cycles of therapy.[6] The AVAiL trial compared cisplatin, gemcitabine, and placebo ($n = 347$) to the combination with bevacizumab 7.5 mg/kg ($n = 345$) or 15 mg/kg ($n = 351$) and demonstrated an improvement in PFS but not OS.[8] The number of patients who continued single-agent placebo or bevacizumab was 128 (37%), 145 (42%), and 145 (41%), respectively.[23] The median number of cycles of placebo or bevacizumab patients received in the 7.5 mg/kg and 15 mg/kg groups was five, six, and five, respectively.[23] In the phase III trial of cisplatin and vinorelbine with and without cetuximab, 241 of the 548 patients assigned to the cetuximab arm did not experience disease progression or unacceptable toxicity and were eligible for single-agent cetuximab; 80% of eligible patients received cetuximab.[7] These trials reveal that the continuation of the maintenance monoclonal antibody is feasible and a substantial minority of patients will receive therapy for an extended period of time. To assess the risk and benefits of this strategy accurately, a phase III trial specifically investigating maintenance bevacizumab or cetuximab compared with placebo after initial combination would be required.

SWITCH MAINTENANCE WITH CHEMOTHERAPY

Several trials have investigated the paradigm of switch maintenance, which is defined as the initiation of a third agent after completion of platinum-based double-agent chemotherapy in the absence of disease progression (Table 2).[15–17] For this strategy to be successful, the third agent must be well tolerated and have single-agent activity in NSCLC. The trial by Westeel et al.[15] investigated single-agent vinorelbine or BSC after two cycles of mitomycin-ifosfamide-cisplatin and radiation for patients with stage IIIB and after four cycles for patients with IIIB disease due to pleural or pericardial involvement or stage IV disease. A total of 573 patients were registered, and 227 responded to induction treatment accord-

TABLE 2. Phase III Trials of "Switch" Maintenance Chemotherapy

First Author	No. of Patients Enrolled	Chemotherapy Comparison[a]	Median PFS	Median OS
Westeel[15]	573	Vinorelbine ($N = 91$)	5 mo	12.3 mo
		Observation ($N = 90$)	3 mo	12.3 mo
			HR = 0.77, $p = 0.11$	HR = 1.08, $p = 0.65$
Fidias[16]	566	Immediate Docetaxel ($N = 153$)	5.7 mo	12.3 mo
		Delayed Docetaxel ($N = 156$)	2.7 mo	9.7 mo
			$p = 0.0001$	$p = 0.0853$
Ciuleanu[17]	NA	Pemetrexed ($N = 441$)	4.0 mo[b]	13.4 mo
		Placebo ($N = 222$)	2.0 mo	10.6 mo
			HR = 0.60, $p < 0.0001$	HR = 0.79, $p = 0.012$
Nonsquamous ($N = 481$)		Pemetrexed	4.4 mo[b]	15.5 mo
		Placebo	1.8 mo	10.3 mo
			HR = 0.47, $p < 0.0001$	HR = 0.70, $p = 0.002$
Squamous ($N = 182$)		Pemetrexed	2.4 mo[b]	9.9 mo
		Placebo	2.5 mo	10.8 mo
			HR = 1.03, $p = 0.896$	HR = 1.07, $p = 0.678$

[a] N values represent number of patients randomized.
[b] PFS represents values from independent review.
PFS, progression-free survival; OS, overall survival; HR, hazard ratio; NA, not available.

ing to the World Health Organization criteria[24] (50% decrease in lesions), and 181 (32%) were randomly assigned to weekly vinorelbine ($n = 91$) and observation ($n = 90$). The mean duration of vinorelbine was 13.8 weeks, and 23% of patients completed the intended 6 months of vinorelbine. Patients in the vinorelbine arm compared with BSC did not experience an improvement in PFS and OS. The relatively small number of patients in each of the treatment arms and the modest activity of single-agent vinorelbine in the second-line setting may have contributed to these results.[25]

The trial by Fidias et al.[16] investigated immediate compared with delayed docetaxel, an established second-line agent, in patients who had stable or responding disease after four cycles of carboplatin and gemcitabine. The trial was designed to detect an improvement in OS of 4 months. A total of 566 patients were enrolled, 398 completed the four cycles of carboplatin and gemcitabine, and 309 (55%) patients were randomly assigned to immediate docetaxel ($n = 153$) or delayed docetaxel ($n = 156$). Patients enrolled in the immediate docetaxel compared with the delayed docetaxel arm experience a significant improvement in PFS but no difference in OS (Table 2). Of the patients randomized to the immediate docetaxel arm, 95% ($n = 145$) initiated therapy, whereas on the delayed docetaxel arm, only 63% ($n = 98$) initiated therapy. The toxicity associated with immediate and delayed docetaxel was similar. If an analysis is performed on patients who actually received docetaxel in both arms, the median survival was an identical 12.5 months. In retrospect, the estimated improvement in OS of 4 months for immediate docetaxel may have been overly ambitious.

The trial by Ciuleanu et al.[17] compared maintenance pemetrexed with placebo in patients who had completed four cycles of platinum-based double-agent chemotherapy without evidence of disease progression. The initial therapy did not contain pemetrexed or bevacizumab. In the intent-to-treat patient population, maintenance pemetrexed significantly improved both PFS (by independent review) and OS (Table 2). The benefit was limited to patients with nonsquamous histology. Among patients with nonsquamous histology, patients in the pemetrexed compared with the placebo arm experienced a statistically significant improvement in PFS by independent review and OS (Table 2). In contrast, among patients with squamous histology, a statistically significant improvement in PFS or OS in the pemetrexed compared with the placebo was not observed (Table 2). The primary grade ≥3 drug-related toxicities (fatigue [5% versus 1%, $p = 0.001$] and neutropenia [3% versus 0, $p = 0.006$]) were higher in the pemetrexed than in the placebo group, and treatment-related discontinuations due to drug-related adverse events were higher in the pemetrexed than the placebo arm (5% versus 1%). Patients were unblinded at the time of disease progression, and patients in the placebo arm receive treatment at the discretion of the investigator. Of the patients in the pemetrexed arm, 51% received poststudy therapy (third line), and of the patients in the placebo arm, 67% received poststudy therapy. Of the patients in the placebo arm, 18% of patients received pemetrexed; other standard second-line agents patients received include docetaxel (29%), erlotinib (21%), and gefitinib (10%). Patients also received second-line therapy with vinorelbine (17%), gemcitabine (14%), carboplatin (9%), cisplatin (6%), and paclitaxel (6%). This trial led the approval of maintenance pemetrexed in Europe and the United States for patients with nonsquamous NSCLC who have completed four cycles of platinum-based double-agent chemotherapy.[26,27]

EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS

EGFR TKIs, erlotinib and gefitinib, are established second-line agents, and both have been investigated as maintenance therapy (Table 3). The Sequential Traceva in Unresectable NSCLC (SATURN) trial investigated maintenance erlotinib compared with placebo in patients who did not experience disease progression after four cycles of platinum-based double-agent chemotherapy.[18] The coprimary endpoints were PFS in the intent-to-treat patient population and the PFS in patients with EGFR protein overexpression by immunohistochemistry. A total of 1949 patients initiated therapy with platinum-based therapy and 889 (45%) patients who did not experience progressive disease and met the eligibility criteria were randomized to erlotinib ($n = 438$) or placebo ($n = 451$). Patients in the erlotinib arm compared with the placebo experienced significantly longer PFS and OS (Table 3). The most common grade ≥3 toxicities observed in the erlotinib and placebo arms were rash (9% and 0%, respectively) and diarrhea (2% and 0%, respectively). Of the patients enrolled in the erlotinib and placebo arms, 71% and 72%, respectively, received poststudy therapy. Patients in the placebo arm received a variety of therapies; 21% of patients received EGFR TKI therapy, and other therapies that patients received include taxanes (including docetaxel) 31%, antimetabolites (including pemetrexed) 23%, antineoplastic agents (18%), and platinum agents (12%).

Several subset analyses were performed to investigate the benefit of maintenance erlotinib in different patient populations. An analysis of patients with an activating EGFR mutations ($n = 49$) receiving erlotinib compared with placebo revealed a dramatically longer PFS (HR = 0.10, 95% CI, 0.04–0.25; $p < 0.0001$) but similar OS (HR = 0.83, 95% CI, 0.34–2.02; $p = 0.6810$). Of note, 16 of the 24 patients in the placebo arm subsequently received erlotinib, and the majority of patients have not experienced an event which makes interpretation of the OS data difficult. Patients with wild-type EGFR tumors receiving erlotinib compared with placebo experienced an improvement in PFS (HR = 0.78, 95% CI, 0.63–0.96; $p = 0.0185$) and OS (HR = 0.77, 95% CI, 0.61–0.97; $p = 0.0243$). Patients who had stable disease ($n = 487$) after first-line chemotherapy had a significant benefit of maintenance erlotinib compared with placebo (HR = 0.72, 95% CI, 0.59–0.89; $p = 0.0019$; median OS, 11.9 and 9.6 months, respectively). Patients with a complete or partial response to first-line chemotherapy ($n = 394$) in the erlotinib compared with the placebo arm experienced similar OS (HR = 0.94, 95% CI, 0.74–1.20; $p = 0.618$; median OS, 12.5 and 12.0 months, respectively). Among patients with squamous histology ($n = 360$), patients in the erlotinib arm compared with placebo experienced a statistically signifi-

TABLE 3. Phase III Trials of Maintenance EGFR-TKI Therapy

First Author	No. of Patients Enrolled	Comparison	Median PFS	Median OS
Cappuzzo[18]	1949	Erlotinib ($N = 437$)	12.3 wk	12.0 mo
		Placebo ($N = 447$)	11.3 wk	11 mo
			HR = 0.71, $p < 0.0001$	HR = 0.81, $p = 0.0088$
Perol[22]	834	Erlotinib ($N = 155$)	2.9 mo	NA
		Observation ($N = 155$)	1.9 mo	NA
			HR = 0.82, $p = 0.002$	HR = 0.91 (95% CI, 0.80–1.04)
Kabbinavar[30]	1145	Bevacizumab/erlotinib ($N = 370$)	4.76 mo	14.39 mo
		Bevacizumab/placebo ($N = 373$)	3.71 mo	13.31 mo
			HR = 0.71, $p = 0.0006$	HR = 0.92, $p = 0.5604$
Takeda[32]	604	Platinum doublet → Gefitinib ($n = 300$)[a]	4.6 mo	13.7 mo
		Platinum doublet ($N = 298$)	4.3 mo	12.9 mo
			HR = 0.68, $p < 0.001$	HR = 0.86, $p = 0.11$
Gaafar[31]	173	Gefitinib ($N = 86$)[b]	4.1 mo	10.9 mo
		Placebo ($N = 87$)	2.9 mo	9.4 mo
			HR = 0.61, $p = 0.002$	HR = 0.81, $p = 0.204$

[a] Patients randomized at enrollment to three cycles of platinum-based therapy followed by gefitinib or six cycles of platinum-based therapy.
[b] Study closed due to poor accrual when 173 of intended 598 patients had been enrolled. Patients were enrolled after completion of platinum-based therapy for two to six cycles.
HR, hazard ratio; NA, not available; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; CI, confidence interval.

cantly longer PFS (HR = 076, 95% CI, 0.60–0.95) but did not experience a statistically significant difference in OS (HR = 0.86, 95% CI, 0.68–1.10). Among patients with adenocarcinoma histology ($n = 401$), patients in the maintenance erlotinib arm experienced a statistically significant improvement in PFS (HR = 0.60, 95% CI, 0.48–0.75) and OS (HR = 0.77, 95% CI, 061–0.97).

Based on the results of this trial, maintenance erlotinib was approved by the U.S. Food and Drug Administration in all patients who do not experience disease progression after platinum-based therapy.[28] The European Medicines Agency approved maintenance erlotinib for patients "with stable disease after 4 cycles of standard platinum-based first-line therapy."[29] Patients who experienced a response to first-line therapy are not approved for use of maintenance erlotinib according the European Medicines Agency label.

A three-arm trial investigated maintenance gemcitabine or erlotinib therapy compared with observation after initial therapy with cisplatin and gemcitabine.[22] The trial was designed to compare erlotinib and gemcitabine with observation with the primary endpoint of PFS by independent review. Of the 834 patients who were enrolled, 464 were randomized, and 155 patients were assigned to the erlotinib and observation arms. Patients in the maintenance erlotinib compared with observation experienced a statistically significant improvement in PFS (Table 3). Of the patients enrolled in the erlotinib and observation arms 63% and 76%, respectively, receive pemetrexed; the median number of cycles was three in both arms. The response rate to pemetrexed observed in the erlotinib and observation arms was 10.4% and 15.2%, respectively. The OS data are not mature, but a statistically significant difference in OS has not been observed at this time. Data from analysis by EGFR mutation status are not available yet.

A phase III trial (known as the ATLAS) investigated the combination maintenance therapy for bevacizumab and erlotinib compared with bevacizumab and placebo, and the primary endpoint was PFS.[30] Patients received initial therapy with platinum-based therapy in combination with bevacizumab and in the absence of disease progression were randomized to bevacizumab in combination with placebo or erlotinib. The trial enrollment was discontinued after the second planned interim analysis at the recommendation of the data monitoring committee when the interim analysis revealed that bevacizumab and erlotinib had met the primary endpoint of improvement in PFS. Of the 1145 patients enrolled, 768 patients (67%) did not experience disease progression and were randomized to bevacizumab and placebo ($n = 373$) or bevacizumab and erlotinib ($n = 370$). Patients in the bevacizumab and erlotinib arm compared with bevacizumab and placebo experienced an improvement in PFS but not a statistically significant improvement in OS (Table 3). Patients in the bevacizumab and erlotinib arm compared with bevacizumab and placebo experienced a higher rate of rash (10.4% and 0.5%, respectively) and diarrhea (9.3% and 0.8%, respectively).

An European Organization for Research and Treatment Cancer investigated the role of maintenance gefitinib compared with placebo after a minimum of two or maximum of six cycles of platinum-based therapy in patients who had not experienced disease progression.[31] The study was designed to detect a 3-month increase in OS and was closed due to poor accrual after 173 of the planned 598 patients had been randomized. Patients in the gefitinib arm compared with the placebo experienced a significantly longer PFS but no difference in OS. A West Japan Thoracic Oncology Group trial investigated six cycles of platinum-based double-agent therapy compared with three cycles of platinum-based double-

agent chemotherapy followed by gefitinib until disease progression.[32] The median number of cycles was in both arms was three, and 57% ($n = 172$) of patients in the sequential arm received gefitinib. The patients in the sequential arm compared with the chemotherapy alone arm experienced a significant improvement in PFS, but a statistically significant difference was not observed in OS. Of the patients in the chemotherapy alone and sequential arms, 54.5% and 75.2%, respectively, received EGFR-TKI therapy at some point. In the West Japan Thoracic Oncology Group, the reduced number of patients who received gefitinib immediately after platinum-based double-agent therapy and the high rate of subsequent use of gefitinib, and the reduced number of patients enrolled in the European Organization for Research and Treatment Cancer trial make an assessment of maintenance gefitinib difficult. Data to date do not support the use of maintenance gefitinib.

PATIENT REPORTED OUTCOMES

Historically, a correlation with improvement in symptoms has been associated with radiographic response.[33] In the maintenance setting, the purpose of therapy is to delay progression of disease, and only a minority of patients will experience a radiographic response. Some maintenance trials have assessed a delay in symptom deterioration. In the trial of comparing immediate and delayed docetaxel by Fidias et al., 109 patients in each docetaxel arm completed the Lung Cancer Symptom Scale (LCSS) questionnaire,[34] and the rate of compliance in immediate and delayed docetaxel arms was 85.8% and 71.9%, respectively. The average symptom burden index was not statistically different between the two docetaxel arms ($p = 0.76$), and the majority of patients in both arms had a stable average symptom burden index. In the trial of maintenance erlotinib compared with placebo by Cappuzzo et al., Qol was assessed using the Functional Assessment of Cancer Therapy-Lung,[35] and there was no significant difference for time to deterioration in Qol for patients receiving erlotinib compared with placebo (HR = 0.96, 95% CI, 0.79–1.16). A post hoc analysis of erlotinib compared with placebo revealed a statistically significant improvement in time to pain and analgesic use but not a statistically significant improvement in time to cough and dyspnea. The trial of pemetrexed compared with placebo by Ciuleanu et al. assessed the time to worsening of six symptoms and three summary items using the LCSS.[34] Preliminary results are available, and overall on-study compliance in the pemetrexed and placebo arms was 87.0% and 81.3%, respectively, and for the postdiscontinuation compliance in the pemetrexed and placebo group was 48.1% and 54.5%, respectively. A significant delay in worsening in the symptoms of pain and hemoptysis was observed in the pemetrexed arm compared with the placebo, but no significant difference in the two treatment arms was observed in the other time to worsening comparisons. Importantly, this Qol analysis was in the intent-to-treat patient population, and the therapeutic benefit was limited to patients with nonsquamous histology, and the Qol results may be different in that patient subset. The data from the recent trial of maintenance gemcitabine or gefitinib compared with observation using the LCSS are not available.[22] Both erlotinib and docetaxel demonstrated an improvement compared with placebo in Qol in the second-line setting, but the patients enrolled in the trials had evidence of progressive disease at the time to study enrollment, and patients enrolled in maintenance trials had demonstrated a response or stable disease at the time of enrollment.[36,37] Thus, these represent different clinical scenarios, and the patients may have had differing amounts of disease-related symptoms. The Qol analyses have been interpreted as maintenance therapy is beneficial because it prolongs PFS and/or OS without adversely impacting Qol or interpreted as maintenance therapy fails to improve Qol despite delaying disease progression.

TRIAL DESIGN QUANDARIES

The trials that have investigated maintenance therapy have used different statistical designs and endpoints (PFS or OS). The use of PFS has the advantages of eliminating the confounding factor of poststudy therapies, offering a more rapid assessment of efficacy, and reducing the number of patients required for efficacy analysis compared with an endpoint of OS. Nevertheless, this endpoint is very dependent on the frequency of radiographic assessment and susceptible to interobserver variability in the assessment of disease progression. Furthermore, small absolute improvements in PFS may not translate into clinical benefit or improvement in OS. OS is often considered a more definitive endpoint, but there can be considerable variability in the rate and type of poststudy therapies available and practice patterns. The impact of poststudy therapy is best exemplified by EGFR TKI therapy among patients with an EGFR mutation in whom a high response rate and prolonged PFS are observed but demonstrating an improvement in OS has been difficult.[38–40] In our opinion, because phase III trials have demonstrated an improvement in OS with erlotinib and pemetrexed, the endpoint of OS should be the preferred endpoint for trials seeking to change the standard of care or become a standard maintenance agent. The endpoint of PFS may be the preferred endpoint when investigating a novel agent in the maintenance setting compared with placebo or an established agent. This would allow for more and more rapid assessment of the novel agent and reduce the number of patients exposed to an investigational agent.

Another issue is whether it is still ethical to include a placebo arm in future maintenance trials. Both maintenance pemetrexed and erlotinib have demonstrated an improvement in OS and are approved for use. The trial by Fidias et al. suggests that if patients receive the same second-line therapy, the OS benefit is equivalent. Nevertheless, approximately 30 to 40% of patients in the trials by Fidias et al., Ciuleanu et al., and Cappuzzo et al. in the delayed or placebo arm did not receive second-line therapy. In the recent trial by Perol et al., patients in all arms were offered pemetrexed at the time of disease progression as part of the trial design, and approximately 25% of patients in the observation arm did not receive any further therapy. Thus, it seems even under circumstances when poststudy therapy is included as part of the trial design, a substantial proportion of patients in the observation or placebo arm will not receive second-line therapy. In our opinion, if future maintenance trials include a placebo or observation arm, the therapy at the time of disease progression must be established in the trials' design. This would ensure patients equal access to subsequent

TABLE 4. Select Phase III Trials of Maintenance Therapy or Including Maintenance Therapy

NCT Trial No. (Name)	Initial Therapy		Comparison	Enrollment (No. Randomized)	Primary Endpoint
NCT00789373 (PARAMOUNT)	Cisplatin + pemetrexed × 4 cycle		Pemetrexed + BSC Placebo + BSC	900[41] (n = 558)	PFS
NCT01107626 (ECOG 5508)	Carboplatin, paclitaxel, bevacizumab × 4 cycles		Bevacizumab Pemetrexed Bevacizumab + pemetrexed	1282[42] (n = 897)	OS
NCT00961415 (AVAPERL1)	Cisplatin/pemetrexed + Bevacizumab		Bevacizumab Bevacizumab + pemetrexed	362	PFS
NCT00693992 (CALGB 30607)	Platinum based × 4 cycles		Sunitinib Placebo	244	PFS
NCT00762034[a] (Point Break)	Carboplatin, paclitaxel, and bevacizumab × 4 cycles[b]	→	Bevacizumab	900	OS
	Carboplatin, pemetrexed, and bevacizumab × 4 cycles[b]	→	Bevacizumab + pemetrexed		
NCT00946712[a] (SWOG 0819)	Carboplatin, paclitaxel + bevacizumab × 6 cycles[a]	→	Bevacizumab	1546	OS
	Carboplatin, paclitaxel, bevacizumab + cetuximab × 6 cycles	→	Bevacizumab + cetuximab		
NCT 00948675[a]	Carboplatin and pemetrexed 4 × cycles[a]	→	Pemetrexed	360	PFS[c]
	Carboplatin, paclitaxel, and bevacizumab	→	Bevacizumab		

[a] Patients randomized at the start of therapy.
[b] Patients stratified based on eligibility for bevacizumab; patients ineligible will receive carboplatin and paclitaxel with and without cetuximab.
[c] Endpoint progression-free survival without grade 4 toxicity.
ECOG, Eastern Cooperative Oncology Group; SWOG, Southwest Oncology Group; CALGB, Cancer and Leukemia Group B; OS, overall survival; PFS, progression-free survival; BSC, best supportive care.

therapy, reduce the variability in the type of therapy patients receive, and potentially reduce the percentage of patients who do not receive further therapy. The median PFS in the observation or placebo treatment arms has been 2 to 3 months. If a placebo or observation arm is included, the trial should require a rigorous monitoring for clinical or radiographic evidence of disease progression during this period. The risks associated with a placebo or observation will have to be incorporated into the informed consent process.

The increasing adoption of maintenance therapy may impact the design of first-line trials because an imbalance in the rate and type of maintenance therapy between the treatment arms may influence the OS endpoint. Is it still possible to design a trial that prohibits the use of maintenance therapy to accurately assess the impact of a new therapy? Will patients accept this if they are truly informed and educated about the potential PFS and OS benefits of maintenance therapy? If the poststudy therapy is not included in the trial design, significant heterogeneity of treatments can be observed. On a recent review of the first-line trial of cisplatin and gemcitabine with placebo, low- and high-dose bevacizumab patients received >66 different poststudy treatment regimens.[8]

ONGOING CLINICAL TRIALS

Several phase III trials are investigating maintenance therapy and/or maintenance therapy in combination with first-line therapy, and examples of ongoing trials are presented in Table 4. A phase III trial is investigating continuation maintenance therapy with pemetrexed compared with placebo in patients with nonsquamous NSCLC after initial therapy with four cycles of cisplatin and pemetrexed; the primary endpoint is PFS (NCT00789373).[41] ECOG 5508 is a three-arm phase III trial in patients with nonsquamous NSCLC who are eligible for bevacizumab. Patient who do not experience disease progression after four cycles of carboplatin, paclitaxel, and bevacizumab will be randomized to pemetrexed alone, bevacizumab alone, or the combination of bevacizumab and pemetrexed; the primary endpoint is OS (NCT01107626).[42] A phase III trial is investigating maintenance therapy of bevacizumab with and without pemetrexed after four cycles of cisplatin, pemetrexed, and bevacizumab in patients with nonsquamous NSCLC; the primary endpoint is PFS (NCT00961415).[43] Cancer and Leukemia Group B is investigating sunitinib compared with placebo in patients with advanced NSCLC who did not experience disease progression after four cycles of platinum-based combination therapy; the primary endpoint is PFS (NCT00693992).[43]

Several trials are investigating novel combinations of therapy and have integrated maintenance therapy into the trial design. A phase III trial is comparing the combination of carboplatin, paclitaxel, and bevacizumab for four cycles followed by maintenance bevacizumab to carboplatin, pemetrexed, and bevacizumab for four cycles followed by maintenance pemetrexed and bevacizumab; the primary endpoint is OS (NCT00762034).[43] The Southwest Oncology Group has initiated a phase III trial, S0819, that will investigate the combina-

tion of carboplatin and paclitaxel (with bevacizumab in eligible patients) compared with the carboplatin, paclitaxel, and cetuximab (with bevacizumab in eligible patients) (NCT00946712).[43] Patients in both arms will receive the platinum-based chemotherapy for six cycles and then receive maintenance chemotherapy with bevacizumab alone or in combination with cetuximab. The primary endpoint is OS. Another phase III trial is comparing carboplatin, paclitaxel, and bevacizumab for four cycles followed by bevacizumab maintenance compared with carboplatin and pemetrexed for four cycles followed by pemetrexed maintenance; the primary endpoint is PFS without grade 4 toxicity (NCT00948675).[43]

SUMMARY

Phase III trials have demonstrated an improvement in PFS and OS with pemetrexed among patients with nonsquamous histology and erlotinib maintenance therapy after initial four cycles of platinum-based double-agent chemotherapy. The patients eligible for the maintenance trials were patients who are able to tolerate chemotherapy and whose disease had demonstrated stable disease or response to chemotherapy. This represents 45 to 55% of patients who initiated platinum-based double-agent chemotherapy. Patients randomized to the placebo arm received second-line therapy at a lower rate, and among patients who received second-line therapy, there was significant heterogeneity in the therapies and a substantial proportion of patients who received therapies that have not been validated in second-line setting. These issues raise questions about the magnitude of benefit that would be observed with maintenance therapy compared with the same therapy administered at the time of disease progression. The rate of grade $\geq$3 toxicities observed in maintenance trials has been low, but the trials to date have not revealed an improvement in Qol with maintenance therapy. Our practice is to consider maintenance therapy in patients who have a PS of 0 or 1, have not experienced significant toxicity during first-line therapy, and wish to continue treatment.

The disadvantage of maintenance therapy is that, it commits the patient to continuous treatment through the disease course in a disease in which the primary goal of therapy is palliative, and the OS remains modest. Although the rate of grade $\geq$3 toxicities observed with maintenance therapy has been low, a prolonged exposure to grade 1 and grade 2 toxicities may adversely impact patients' Qol. In our opinion, treatment-free intervals remain an option; however, patients must be observed closely with serial radiographic examinations because the median PFS is approximately 2 to 3 months. The optimal timing and method of observing patients for disease progression are unclear, and patients should be informed of the risks associated with a treatment-free interval.

Given the heterogeneity of NSCLC, it is unlikely that all patients will benefit from maintenance therapy. Our ability to select patients who are most likely to have a limited duration of stable disease or response to platinum-based double-agent chemotherapy and/or benefit from maintenance therapy is limited. The best most molecular marker for benefit of maintenance therapy seems to be the presence of an EGFR mutation; however, many patients are undergoing molecular testing at the time of diagnosis and receive an EGFR TKI as first-line therapy if a mutation is present. Another biomarker that has potential to be useful in the selection of patients for erlotinib maintenance is to use matrix-assisted laser desorption ionization mass spectromy to identify patients who are likely to benefit from EGFR TKI therapy.[44,45] The matrix-assisted laser desorption ionization mass spectromy analysis has shown the ability to estimate prognosis and predict benefit from EGFR TKI based on retrospective data from the BR.21 trial but has not been evaluated in the maintenance setting to date.

The issue of selection of patients who benefit from maintenance therapy is interrelated with economic costs of maintenance therapy because a better method of selecting the patients may improve the benefit observed with the therapy and reduce the number of patients who receive an ineffective therapy. A recent analysis of the cost-effectiveness of pemetrexed as maintenance therapy compared with observation revealed that the incremental cost per life-year gained was $122,371.[46] Nevertheless, this calculation is very dependent on the price of pemetrexed, which can vary significantly depending on the country.[47] The optimal method of estimating the benefit and the acceptable price range for a therapy is unclear at this time. This issue is becoming more important to the oncology community and the public. How to apply these data to the individual patient is unclear.

REFERENCES

1. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277–300.
2. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* June 17, 2010. [Epub ahead of print].
3. Azzoli CG, Baker S Jr, Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2009;27:6251–6266.
4. D'Addario G, Felip E. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009;20(Suppl 4):68–70.
5. Lara PN Jr, Redman MW, Kelly K, et al. Disease control rate at 8 weeks predicts clinical benefit in advanced non-small-cell lung cancer: results from Southwest Oncology Group randomized trials. *J Clin Oncol* 2008; 26:463–467.
6. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355: 2542–2550.
7. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet* 2009;373:1525–1531.
8. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol* 2010;21:1804–1809.
9. 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;26:3543–3551.
10. Socinski MA, Schell MJ, Peterman A, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. *J Clin Oncol* 2002;20:1335–1343.
11. Park JO, Kim SW, Ahn JS, et al. Phase III trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non small-cell lung cancer. *J Clin Oncol* 2007;25:5233–5239.
12. Smith IE, O'Brien ME, Talbot DC, et al. Duration of chemotherapy in advanced non-small-cell lung cancer: a randomized trial of three versus

six courses of mitomycin, vinblastine, and cisplatin. *J Clin Oncol* 2001;19:1336–1343.
13. von Plessen C, Bergman B, Andresen O, et al. Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. *Br J Cancer* 2006;95: 966–973.
14. Barata F, Parente B, Teixeira E, et al. Optimal duration of chemotherapy in non-small cell lung cancer: multicenter, randomized, prospective clinical trial comparing 4 vs. 6 cycles of carboplatin and gemcitabine. *J Thorac Oncol* 2007;2:S666.
15. Westeel V, Quoix E, Moro-Sibilot D, et al. Randomized study of maintenance vinorelbine in responders with advanced non-small-cell lung cancer. *J Natl Cancer Inst* 2005;97:499–506.
16. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol* 2009;27:591–598.
17. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;374:1432–1440.
18. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521–529.
19. Belani CP, Barstis J, Perry MC, et al. Multicenter, randomized trial for stage IIIB or IV non-small-cell lung cancer using weekly paclitaxel and carboplatin followed by maintenance weekly paclitaxel or observation. *J Clin Oncol* 2003;21:2933–2939.
20. Brodowicz T, Krzakowski M, Zwitter M, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. *Lung Cancer* 2006;52:155–163.
21. Belani CP, Waterhouse DM, Ghazal H, et al. Phase III study of maintenance gemcitabine (G) and best supportive care (BSC) versus BSC, following standard combination therapy with gemcitabine-carboplatin (G-Cb) for patients with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2010;28:(suppl; abstr 7506).
22. Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study. *J Clin Oncol* 2010;28:(suppl; abstr 7507).
23. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. *J Clin Oncol* 2009; 27:1227–1234.
24. WHO. Handbook for Reporting Results of Cancer Treatment. Geneva: WHO, 1979. Pp. 48.
25. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354–2362.
26. Available at: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm170660.htm-accessed. Accessed August 16, 2010.
27. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_WC500090680.pdf. Accessed August 16, 2010.
28. Available at: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm209058.htm-accesed. Accessed August 16, 2010.
29. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000618/smops/Positive/human_smop_000085.jsp-accessed. Accessed August 16, 2010.
30. Kabbinavar FF, Miller VA, Johnson BE, et al. Overall survival (OS) in ATLAS, a phase IIIb trial comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy (chemo) with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). *J Clin Oncol* 2010;28:(suppl; abstr 7526).
31. Gaafar RM, Surmont V, Scagliotti G, et al. A double-blind, randomized, placebo-controlled phase III intergroup study of gefitinib (G) in patients (pts) with advanced NSCLC, non-progressing after first-line platinum-based chemotherapy (EORTC 08021-ILCP 01/03). *J Clin Oncol* 2010; 28:(suppl; abstr 7518).
32. Takeda K, Hida T, Sato T, et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a west Japan thoracic oncology group trial (WJTOG0203). *J Clin Oncol* 2010;28:753–760.
33. Cella D, Eton D, Fairclough D, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy (FACT-L) Questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study E5592. *J Clin Oncol* 2002;55:285–295.
34. 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; 73:2087–2098.
35. Cella D, Bonomi A, Lloyd S, et al. Reliability and validity of the of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995;12:199–200.
36. Dancey J, Shepherd FA, Gralla RJ, et al. Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial. *Lung Cancer* 2004;43:183–194.
37. Bezjak A, Tu D, Seymour L, et al. Symptom improvement in lung 'tients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR. 21. *J Clin Oncol* 2006;24:3831–3837.
38. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
39. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121–128.
40. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–2388.
41. Paz-Ares LG, Altug S, Vaury AT, et al. Treatment rationale and study design for a phase III, double-blind, placebo-controlled study of maintenance pemetrexed plus best supportive care versus best supportive care immediately following induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small cell lung cancer. *BMC Cancer* 2010;10:85.
42. Owonikoko TK, Ramalingam SS, Belani CP. Maintenance therapy for advanced non-small cell lung cancer: current status, controversies, and emerging consensus. *Clin Cancer Res* 2010;16:2496–2504.
43. Available at: http://clinicaltrials.gov/-assessed. September 16, 2010.
44. Taguchi F, Solomon B, Gregorc V, et al. Mass spectrometry to classify non-small-cell lung cancer patients for clinical outcome after treatment with epidermal growth factor receptor tyrosine kinase inhibitors: a multicohort cross-institutional study. *J Natl Cancer Inst* 2007;99:838–846.
45. Carbone DP, Seymour L, Ding K, et al. Serum proteomic prediction of outocmes in advanced NSCLC patients treated with either erolitnib/placebo in the NCIC clinical trials group BR. 21 trial. *J Thorac Oncol* 2010;5:s80 (abstract 203O).
46. Klein R, Wielage R, Muehlenbein C, et al. Cost-effectiveness of pemetrexed as first-line maintenance therapy for advanced nonsquamous non-small cell lung cancer. *J Thorac Oncol* 2010;5:1263–1272.
47. Learn PA, Bach PB. Pem and the cost of multicycle maintenance. *J Thorac Oncol* 2010;5:1111–1112.

