Maintenance Therapy for Advanced-Non Small Cell Lung Cancer

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Abstract: Until recently standard first-line treatment for advanced non-small cell lung cancer (NSCLC) consisted of up to 4-6 cycles of platinum-based chemotherapy which contrasted practices in the management of other solid tumors. Curtailing the duration of chemotherapy was a reflection of the rather poor efficacy of regimens for NSCLC and their poor tolerability that did not facilitate long-term use. With the development of new active agents, the concept of prolonging the duration of initial therapy in the absence of disease progression as maintenance or "continuation maintenance" (i.e. same regimen or part of the regimen) or consolidation or "switch maintenance" (i.e. switch to a different agent) has now emerged and is the topic of some controversy. Recent well designed phase III clinical trials showed improvement in overall survival (OS) and/or progression-free survival (PFS) in this setting with agents like docetaxel (PFS, not OS), pemetrexed (OS and PFS), and erlotinib (OS and PFS in one study, PFS only in another). Moreover, bevacizumab and cetuximab were continued until progression after given concurrently with platinum doublets in the two pivotal trials that demonstrated survival benefits with these agents in advanced NSCLC. A major criticism of some maintenance trials has been the lack of cross-over to the study drug in the control arm at the time of progression (i.e. as second-line therapy). In the pemetrexed and erlotinib studies, only about 20% of patients randomized in the placebo arm received the study drug at progression. In the docetaxel study that was the only one that had pre-specified treatment with the same drug at the time of progression, 63% of patients received delayed docetaxel which may have influenced the overall survival difference between the 2 arms. Any survival benefit from maintenance therapy will have to be balanced against expected toxicities, impact on quality of life and associated costs. In conclusion, maintenance therapy has become an option in the treatment of advanced NSCLC. However, treatment decisions should always be individualized and based on patient's performance status and co-morbidities, tumor response, histology, presence of *EGFR* mutations and possibly other emerging biomarkers.

Keywords: NSCLC, maintenance, pemetrexed, erlotinib.

INTRODUCTION

Lung cancer is the leading cause of cancer death in both men and women in the United States and the world [1-4]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and represents about 85% of all lung cancer cases. Most patients present with advanced incurable disease that carries an ominous prognosis if untreated and where systemic chemotherapy has demonstrated a modest survival advantage [5-7]. Standard systemic therapy for patients with stage IV NSCLC and good performance status consists of platinum-based chemotherapy doublets with expected response rates of about 30% and a median survival of 8-12 months [8, 9]. A number of studies have examined the appropriate duration of first-line chemotherapy [10-13]. Until recently it was generally accepted that 4-6 cycles of first-line chemotherapy was sufficient treatment and that continuation of combination chemotherapy beyond that does not produce a survival benefit. However, phase III trials using maintenance with pemetrexed or erlotinib have reported positive results in terms of survival which has led to a re-evaluation of the treatment paradigm in advanced NSCLC. Table **1** summarizes phase III clinical trials in advanced NSCLC that have included a form of maintenance therapy.

Table 1. Phase III Clinical Trials in Advanced NSCLC that Included Maintenance Therapy

Author/Study	Agent	Comments
Fidias [21]	+/- Docetaxel	Improved PFS, not OS
Ciuleanu [17] (JMEN)	+/- Pemetrexed	Improved PFS and OS
Cappuzzo [27] (SATURN)	+/- Erlotinib	Improved PFS and OS
Miller [28] (ATLAS)	Bevacizumab +/- Erlotinib	Improved PFS, not OS
Sandler [9] (E4599)	Bevacizumab	Maintenance was not the study question
Pirker [33] (FLEX)	Cetuximab	Maintenance was not the study question

PFS: progression-free survival; OS: overall survival.

EXTENDING THE DURATION OF CHEMOTHERAPY

The first-line systemic therapy of advanced NSCLC has consisted of 4-6 cycles of platinum based doublet chemotherapy, including combinations with a taxane, gemcitabine, pemetrexed or vinolelbine. Several phase III

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randomized trials failed to demonstrate a survival benefit or an improvement in quality of life for increasing the duration of initial platinum-based doublet chemotherapy [10-13]. The treatment guidelines published by the American Society of Clinical Oncology (ASCO) in 2004 [14] and the 2009 National Comprehensive Cancer Network (NCCN) clinical practice guidelines reflect these findings. It should be noted that some of the older studies had suboptimal design and insufficient sample size.

Curtailing first-line treatment of advanced NSCLC to only 4-6 cycles was primarily a reflection of the limited armamentarium against lung cancer and the toxicities related to chemotherapy that made long-term administration intolerable [15]. This practice contrasts the approach in the treatment of other common solid tumors, like breast cancer and colorectal cancer. With the advent of newer agents, like pemetrexed and erlotinib, the concept of extending the duration of first-line treatment in advanced NSCLC was revisited and was the topic of several recent phase III randomized clinical trials. The terminology is not uniform and, in some cases, confusing. The continuation of systemic treatment in the absence of disease progression following the completion of initial first-line combination chemotherapy with the same agents can be labeled as "maintenance" or "continuation maintenance" and with different agents as "consolidation" or "switch maintenance". We will simply use the term "maintenance" since it has been the most widely adopted term in the literature.

A recent meta-analysis of 13 randomized controlled trials (3027 patients) looked into the benefits of longer duration chemotherapy in patients with advanced NSCLC. This meta-analysis reported a significant improvement in progression-free survival (hazard ratio [HR], 0.75; 95% CI, 0.69 to 0.81; P < .00001), which was even more pronounced in the studies that included third generation chemotherapy agents. The overall survival benefit was more modest but statistically significant (HR, 0.92; 95% CI, 0.86 to 0.99; P = .03) in favor of longer-duration chemotherapy [16]. It is noteworthy that the overall survival results of this meta-analysis were most significantly impacted by a recent randomized maintenance trial in advanced NSCLC involving maintenance single-agent pemetrexed in patients who had not progressed on four cycles of platinum-based chemotherapy [17]. The statistically significant improvement in overall survival was not observed until the pemetrexed maintenance trial was added to the analysis. The meta-analysis also looked into the frequency of adverse events and health-related quality of life (HRQL) and concluded that extending chemotherapy was associated with more frequent adverse events in all 13 trials where it was reported and impaired HRQL in two of seven trials [16]. Therefore, to date, short of maintenance single-agent pemetrexed, there is no evidence that extending initial first-line combination chemotherapy would have a positive impact on overall survival or the health-related quality of life.

CLINICAL STUDIES WITH MAINTENANCE THERAPY

Docetaxel

The role of maintenance therapy with single-agent chemotherapy has been tested in number of randomized clinical trials in advanced NSCLC [18-20]. A trial by Fidias and colleagues tested the role of immediate *vs* delayed second-line treatment with docetaxel after four cycles with carboplatin and gemcitabine [21]. The importance of this design (the specification of immediate *vs* delayed) is increasing the probability that patients in both arms are exposed to the study drug, docetaxel in this case. This arguably allows for a more accurate assessment of the survival role of immediate maintenance *vs* delayed salvage therapy with the same regimen. A total of 566 patients with advanced NSCLC were given 4 cycles of carboplatin and gemcitabine. Of the 398 patients who completed their initial therapy without disease progression, 309 were randomized to immediate maintenance docetaxel (up to 6 cycles) or observation followed by docetaxel initiated at the time of disease progression. Overall, 37% of patients (n = 58) in the observation arm did not receive salvage docetaxel treatment (primarily due to disease progression) compared with 5.2% in the immediate docetaxel arm. This study has shown a significant improvement in progression-free survival favoring the group receiving immediate docetaxel therapy (5.7 *vs* 2.7 months; *P* = 0.0001). There was a modest improvement in overall survival (12.3 *vs* 9.7 months) that did not achieve statistical significance (*P* = .0853). Quality of life results were not statistically different (P = .76) between the two docetaxel groups. One observation that is noteworthy, is that patients on the observation arm who received salvage docetaxel after disease progression, had a median overall survival of 12.5 months, remarkably similar to that of the immediate docetaxel group.

Pemetrexed

A pivotal phase III placebo-controlled randomised trial examined the role of maintenance pemetrexed chemotherapy in patients with advanced NSCLC [17]. Patients must not have progressed during four 21-day cycles of one of the following six initial platinum-based doublet chemotherapy regimens that included gemcitabine-carboplatin, gemcitabine-cisplatin, paclitaxel-carboplatin, paclitaxel-cisplatin, docetaxel-carboplatin, or docetaxel-cisplatin. None of the induction regimens included pemetrexed. A total of 663 patients were randomly assigned (2:1 ratio) to receive pemetrexed plus best supportive care (n=441) or placebo plus best supportive care (n=222) in 21-day cycles until disease progression. The study showed a significant improvement in progression-free survival (4.3 months [95% CI 4.1-4.7] *vs* 2.6 months [1.7-2.8]; hazard ratio [HR] 0.50, 95% CI 0.42-0.61, p<0·0001) in favor of the pemetrexed arm. There was also an improvement in overall survival (13.4 months [11.9-15.9] *vs* 10.6 months [8.7-12.0]; HR 0.79, 0.65-0.95, p=0.012) favoring pemetrexed compared with placebo. It should be noted that 33% of patients in the placebo arm did not receive second-line chemotherapy, and of the patients who received chemotherapy, only 19% received pemetrexed.

Further subgroup analysis has demonstrated a significant impact for histology on the derived benefit from pemetrexed therapy. The improvements in progression-free and overall survival were noted primarily in patients with non-squamous histology (progression-free survival HR 0.44, 95% CI 0.36-0.55; and overall survival HR 0.70, 0.56-0.88), compared with squamous histology (progression-free survival HR 0.69, 0.49-0.98; and overall survival HR 1.07, 0.77-1.50). This

treatment-by-histology interaction suggests that the benefit of maintenance pemetrexed therapy is confined to the non-squamous histology group of NSCLC.

Three randomised phase 3 trials [22, 23] have shown the differential treatment effect (on progression-free and overall survival) for pemetrexed according to the histology of non-small-cell lung cancer. These include the maintenance phase III pemetrexed study [17], a study testing pemetrexed *vs* docetaxel in previously treated patients (n = 571) and another that tested cisplatin plus pemetrexed *vs* cisplatin plus gemcitabine in chemotherapy-naive patients (n = 1,725) with advanced NSCLC [22, 23]. It is unclear why patients with non-squamous histology derive the most benefit from pemetrexed. There is evidence to support a higher expression of thymidylate synthase in patients with squamous cell carcinoma [24, 25]. Therefore, a possible mechanism that has been proposed to explain this differential effect is the differential expression of thymidylate synthase, which has been shown *in vitro* to correlate with sensitivity to pemetrexed [17, 26]. In terms of toxicities, grade 3 or higher toxicities were more frequent with pemetrexed than with placebo (70 [16%] *vs* nine [4%]; p<0·0001), mainly fatigue (22 [5%] *vs* one [1%], p=0·001) and neutropenia (13 [3%] *vs* 0, p=0·006). Overall, in the maintenance pemetrexed arm, only 5% of patients discontinued therapy because of toxicity.

Erlotinib

A double-blind, phase III study (SATURN trial) enrolled 1949 patients with previously untreated advanced NSCLC and tested the role of maintenance erlotinib immediately following platinum-based chemotherapy [27]. Patients were initially treated with 4 cycles of a platinum-based doublet chemotherapy regimen. Those with no evidence of disease progression (n = 889) were randomly assigned to receive maintenance therapy with erlotinib at 150 mg daily or placebo until disease progression. This study has shown significant prolongation in progression free survival with erlotinib therapy (HR: 0.71; 95% CI: 0.62-0.82; $P < .0001$). Erlotinib maintenance therapy also showed a significant improvement in tumor response (CR and PR; 11.9% *vs* 5.4%; $P = .0006$) and disease control (CR, PR, and stable disease; 60.6% *vs* 50.8%; $P = .0035$), whereas grade 3/4 rash (9%) and diarrhea (2%) were both more frequent in the erlotinib arm.

Baseline tumor samples were obtained in the SATURN trial to perform a prospective analysis of the prognostic and predictive value of several biomarkers. Both *EGFR* and KRAS mutation status were assessed by sequencing analysis, *EGFR* gene copy number was determined by FISH, and *EGFR* protein expression was determined by IHC. Biomarker analysis showed that progression-free survival was improved with the use of erlotinib in patients with *EGFR*–positive tumors by immunohistochemistry (IHC) (HR: 0.69; 95% CI: 0.58-0.82; $P < .0001$) or FISH (HR: 0.68; 95% CI: 0.51-0.90; $P = .0068$). Patients with tumors with an *EGFR* mutation derived marked progression-free survival benefit with erlotinib (HR: 0.10; 95% CI: 0.04-0.25; $P < .0001$), however, patients with *EGFR* wild-type also derived benefit (HR:0.78; 95% CI: 0.63-0.96; $P = 0.0185$). In addition, progression-free survival was significantly improved in the patient subgroup with KRAS wild-type tumors (HR: 0.70; 95% CI: 0.57-0.87; $P = .0009$). In histology subgroup analysis, the benefit in progression free survival was not restricted to patients with non-squamous histology as those with squamous cell carcinoma also achieved a significant improvement.

The overall survival data were reported at the 13th World Conference on Lung Cancer (WCLC; August 2009), showing a modest but significant improvement in survival for those receiving erlotinib compared to those receiving placebo (12 months *vs* 11 months; HR 0.81, 95% CI: 0.70 - 0.95; p=0.0088)[27]. At WCLC, researches also reported that the survival benefit was not confined to the group with a favourable *EGFR* status. There was a statistically significant benefit for patients with *EGFR* wild-type tumor. Patients with *EGFR* wild-type tumors receiving erlotinib had a median survival of 11.3 months, compared with 10.2 months for those receiving placebo.

The study presentation didn't provide sufficient details about the type of salvage agents received after disease progression on the trial, but only 21% on the placebo arm have ever received an *EGFR* inhibitor. Therefore, in this trial we see the same issue noted in the maintenance pemetrexed trial where, immediate was received by all patients on the maintenance arm *vs* one fifth of the patients on the placebo arm.

The ATLAS study was another phase III study that was designed to evaluate the combination of bevacizumab and erlotinib *vs* bevacizumab alone, following bevacizumab + platinum-containing doublet chemotherapy, in patients with stage IIIB/IV NSCLC [28]. The primary objective of ATLAS was to compare PFS. Secondary objectives included the assessment of safety, and overall survival. A total of 1,160 patients were enrolled and 768 randomized from May 2005 to May 2008. The DSMC recommended stopping the trial at the second planned interim efficacy analysis, because it met the primary endpoint. The median PFS after randomization was 4.8 months for the combination arm *vs* 3.7 months for placebo arm, HR= 0.722 (95% CI: 0.592-0.881), p = 0.0012. No significant improvement in overall survival has been reported. The safety profile for the combination arm was consistent with known profiles for bevacizumab and erlotinib.

CONTINUATION THERAPY WITH TARGETED AGENT FOLLOWING INITIAL COMBINATION WITH CHEMOTHERAPY

Continuation therapy with a targeted agent following completion of combination chemotherapy has been adopted as a standard with trials testing bevacizumab and cetuximab. It is important to note that these studies were not designed to test the role of maintenance therapy, but simply continuation therapy with the added targeted agent.

Bevacizumab

The E4599 trial randomized patients with non-squamous NSCLC to a maximum of six cycles of carboplatin and paclitaxel alone or in combination with bevacizumab [9]. Patients in the bevacizumab arm with stable disease or responding to therapy were continued on maintenance bevacizumab until disease progression or unacceptable toxicity. Overall survival was significantly improved in favor

of the bevacizumab arm (median 12.3 *vs* 10.3 months, hazard ratio 0.79, 95% CI 0.67-0.92). There were also improvements in the objective response rate (35 *vs* 15 percent), One-year and two-year survival rates (51 *vs* 44 and 23 *vs* 15 percent, respectively) and progression-free survival (6.2 *vs* 4.5 months). Treatment-related deaths were more common with the bevacizumab arm (15 *vs* 2 including 5 due to hemoptysis, 5 due to febrile neutropenia, and 2 due to hematemesis). These events occurred even though patients with squamous histology, brain metastases, or a history of hemoptysis at baseline were excluded. Treatment-related deaths and severe toxicity were more frequent in patients 70 years of age or older.

The benefits of adding bevacizumab to initial systemic combination therapy were also shown in the AVAiL trial [29]. In this study, 1043 patients received cisplatin and gemcitabine plus either bevacizumab (7.5 mg/kg), bevacizumab (15 mg/kg), or placebo. Patients in the bevacizumab arms with stable disease or responding to therapy were continued on maintenance bevacizumab until disease progression or unacceptable toxicity. Patients with non-squamous NSCLC, brain metastases or a history of hemoptysis were excluded. Progression-free survival, which was the primary endpoint, was significantly improved with both doses of bevacizumab: the hazard ratios for PFS were 0.75 (median PFS, 6.7 v 6.1 months for placebo; P = .003) in the low-dose group and 0.82 (median PFS, 6.5 v 6.1 months for placebo; P = .03) in the high-dose group compared with placebo. Objective response rates were 20.1%, 34.1%, and 30.4% for placebo, low-dose bevacizumab, and high-dose bevacizumab, respectively. However, no difference in overall survival was shown.

Cetuximab

Cetuximab is a monoclonal antibody that interferes with the epidermal growth factor pathway by binding to the *EGFR*. After demonstrating promising response and survival data in three randomized phase II trials of cetuximab plus a platinum-based doublet [30-32], 2 phase III trials for previously untreated patients with advanced NSCLC were conducted [33].

The FLEX trial enrolled 1125 patients who were randomly assigned to first-line cisplatin/vinorelbine plus cetuximab or chemotherapy alone [33]. Expression of the *EGFR* by IHC was required for inclusion in the trial. Cetuximab was continued as maintenance monotherapy after completion of chemotherapy until the development of progressive disease or excessive toxicity. Forty four percent of the patients assigned to the cetuximab arm (241/548) had no disease progression or excessive toxicity at the completion of four cycles of chemotherapy. Out of these, 80 percent received maintenance cetuximab. Overall, the addition of Cetuximab was shown to improve overall survival when added to first-line cisplatin/vinorelbine in patients with advanced non-small-cell lung cancer positive for epidermal growth factor receptor (*EGFR*) expression [HR: 0.87 (95% CI: 0.76-1.0; *P* = .044)], median overall survival 11.3 months *vs* 10.1 months for chemotherapy alone. The objective response rate was significantly increased with cetuximab plus chemotherapy (36 *vs* 29 percent with chemotherapy alone; p=0.012). There was no statistically significant difference in progression-free survival (median 4.8 months in both groups, HR 0.94, 95% CI 0.83-1.08). Second-line *EGFR* tyrosine kinase inhibitor use was more frequent in chemotherapy arm compared with cetuximab plus chemotherapy arm27% *vs* 17% (*P* < .05). Serious toxicities were significantly more frequent in the cetuximab plus chemotherapy arm including rash, febrile neutropenia, diarrhea, and infusion-related reactions (10 *vs* <1, 22 *vs* 15, 5 *vs* 2, and 4 *vs* <1 percent, respectively).

In the second phase III trial (BMS-099) 676 patients were randomized to carboplatin plus either docetaxel or paclitaxel for six cycles or the same chemotherapy plus weekly cetuximab, with cetuximab continued until disease progression or excessive toxicity [34].

There was no significant improvement in progression free survival, the primary endpoint of the trial, with the addition of cetuximab (median 4.4 *vs* 4.2 months with chemotherapy alone, HR 0.90). In addition, the increase in overall survival in the cetuximab plus chemotherapy arm was not statistically significant (9.7 *vs* 8.4 months, HR 0.89), although the difference was similar to that noted in the FLEX trial.

A meta-analysis of cetuximab added to first-line chemotherapy [35] included two phase III trials (FLEX and BMS099) as well as two phase II randomized studies [31, 32]. The pooled data from these four trials included 2018 patients, with all histologic subtypes of NSCLC, and showed that the addition of cetuximab is associated with a statistically significant benefit both in terms of OS (HR 0.878, CI 0.795-0.969, *P* = 0.01) and PFS (HR 0.899, CI 0.814-0.993, *P* = 0.036). Overall, the observed benefit appears to be driven by the FLEX trial (given its sample size). The magnitude of benefit is small both in terms of HR (13% reduction in the risk of death) and absolute prolongation of survival (1.2 months of difference in median OS).

IMMEDIATE *VS* DELAYED THERAPY WITH NEWER AGENTS

The concept of maintenance therapy in advanced NSCLC in the absence of disease progression after initial platinum-based chemotherapy is supported by emerging data from randomized trials. However, there are variations in the design of randomized maintenance trials in advanced NSCLC that may impact the way results could be interpreted and applied to clinical practice. Such variations include the timing of the randomization (before starting any therapy or at the time of maintenance), whether a platinum-based regimen was included, the primary endpoint of a trial (PFS or OS), histology (e.g. the role of pemetrexed in non-squamous histology), and finally the role of biomarkers (e.g. *EGFR* mutations as predictive markers for *EGFR* TKIs). A very critical aspect of these studies is the review of second-line therapy patterns in the phase III trials testing maintenance pemetrexed [17] and docetaxel [21], and erlotinib [27] is of major interest. In the maintenance pemetrexed study, 33% of patients in the placebo arm did not receive second-line chemotherapy, and of the patients who received chemotherapy, only 19% received pemetrexed. In the docetaxel study, 37% of patients in the observation arm did not receive intended docetaxel treatment at the time of progression compared with 5% in the immediate

docetaxel arm. In addition, patients on the observation arm who actually received salvage docetaxel after disease progression, had a median overall survival of 12.5 months, that appears similar to that of the immediate docetaxel group.

Therefore, it is still not clearly defined whether immediate therapy carries a true survival advantage over delayed therapy with the same drug given at the time of progression. However, many patients will not be able to receive second line chemotherapy because of early death, toxicities, or symptomatic deterioration and compromised performance status. With maintenance therapy it is assured that systemic therapy is given in almost all patients.

Alternatively, it has been suggested that patients are more likely to derive benefits from subsequent lines of therapy through strategies that may identify disease progression earlier or through the routine administration of effective second-line treatment at a defined time point [36].

Moreover, any survival benefit with maintenance therapy will have to be balanced against expected toxicities as well as the impact on the patient's quality of life. Relevant factors that may help in deciding on a patient's candidacy for maintenance therapy are the patient's disease related symptoms and the disease response status to initial combination chemotherapy. Based on the study by Ciuleanu and colleagues [17], maintenance pemetrexed therapy may be considered for a patient with non-squamous NSCLC and only disease stabilization (no or minor response) after initial non-pemetrexed containing doublet chemotherapy, especially if

Table 2. Planned or Ongoing Randomized Trials of Maintenance Therapy in Advanced NSCLC

Study/Sponsor	ClinicalTrials.gov Identifier	Induction Regimen	Maintenance	Sample Size (No. of Patients)
H3E-MC-JMHD Eli Lilly	NCT00762034	Carboplatin, Pemetrexed, Bevacizumab (4 cycles) Carboplatin, Paclitaxel, Bevacizumab (4 cycles)	Pemetrexed, Bevacizumab Bevacizumab	900
H3E-EW-S124 Eli Lilly	NCT00789373	Cisplatin, Pemetrexed (4 cycles) Cisplatin, Pemetrexed (4 cycles)	Pemetrexed Placebo	900 (2:1 randomization)
H3E-US-S130 Eli Lilly	NCT00948675	Carboplatin, Pemetrexed, (4 cycles) Carboplatin, Paclitaxel, Bevacizumab (4 cycles)	Pemetrexed Bevacizumab	360
AVAPERL1 Hoffmann-La Roche	NCT00961415	Cisplatin, Pemetrexed, Bevacizumab (4 cycles) Cisplatin, Pemetrexed, Bevacizumab (4 cycles)	Bevacizumab Bevacizumab, Pemetrexed	362
ECOG (E5508)	NCT01107626	Carboplatin, Paclitaxel, Bevacizumab (4 cycles) Carboplatin, Paclitaxel, Bevacizumab (4 cycles) Carboplatin, Paclitaxel, Bevacizumab (4 cycles)	Bevacizumab Pemetrexed Bevacizumab, Pemetrexed	1282

the patient has disease related symptoms or the patient has a high tumor burden. This decision has to be balanced against the fact that drug-related grade 3/4 toxicities and discontinuation of therapy due to study drug were statistically significantly higher in the maintenance pemetrexed arm than in the placebo arm (grade 3/4 toxicities 16% *vs* 4%, respectively; $P < .0001$; discontinuation 5% *vs* 1%, respectively) [17]. Individualization of care with attention to the patient's overall condition, tumor histology and response to initial therapy are potential deteminants of decision making and may help avoiding over-treating many patients unnecessarily.

The SATURN trial has shown a modest survival benefit that was not limited to patients with *EGFR* mutation-positive tumors. It has reinforced data from BR.21 [37] that showed that the benefits from erlotinib therapy in NSCLC are seen in all subsets of patients, although the magnitude of benefit is larger for patients with *EGFR* mutation-positive tumors. In terms of histology, in squamous cell carcinoma, erlotinib has superior data to pemetrexed and may be an option as maintenance therapy for these patients. Whether patients should receive immediate *vs* delayed erlotinib remains an open question. Only 21% of patients on the placebo arm ever received an *EGFR* inhibitor. Therefore, it is not clear whether the same survival benefit would be achieved with delayed treatment with erlotinib, while maintaining a better quality of life. In April 2010, the U.S. Food and Drug Administration (FDA) approved erlotinib for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

When first-line therapy contains bevacizumab or cetuximab, these agents are typically continued until disease progression or unacceptable toxicities based on the design of the pivotal trials [9, 33]. However, the added value of maintenance with these agents remains unproven. Combining pemetrexed and bevacizumab as maintenance therapy is worthwhile investigating. A phase II study testing maintenance pemetrexed and bevacizumab in patients with nonsquamous NSCLC following non-progression after 6 cycles of carboplatin, pemetrexed and bevacizumab reported a progression-free survival of 7.8 months (95% CI, 5.2 to 11.5 months) and an overall survival of 14.1 months (95% CI, 10.8 to 19.6 months) [38]. Multiple ongoing and planned phase III trials are evaluating a variety of maintenance therapy strategies (see Table **2**).

CONCLUSIONS AND FUTURE DIRECTIONS

Maintenance therapy with either pemetrexed or erlotinib is currently FDA approved in the U.S. and should be considered as a therapeutic option for selected patients with advanced NSCLC who are progression-free after first-line platinum-based chemotherapy. The decisions on pursuing maintenance therapy will have to be individualized based on multiple factors, including performance status following initial therapy, treatment-related toxicities, histology, and possibly EGFR mutation status. In addition, the disease response status following first-line therapy and whether the patient is symptomatic from her/his disease should be weighed into the decision making on maintenance therapy. Maintenance therapy has altered the treatment paradigms for advanced NSCLC.

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