Maintenance Therapy for Advanced Non-small Cell Lung Cancer: Current Status, Controversies, and Emerging Consensus

Taofeek K. Owonikoko1, Suresh S. Ramalingam1, and Chandra P. Belani2

Abstract

Maintenance therapy refers to the use of an active therapeutic agent for extended duration following frontline induction therapy for patients with advanced stage non-small cell lung cancer (NSCLC). Multiple clinical trials reported within the last few months have shown a beneficial role for maintenance therapy especially in select patient groups characterized by histology and/or molecular profile. With the recent approval by the U.S. Food and Drug Administration and European Medicines Agency of pemetrexed for maintenance therapy, a new treatment paradigm has been introduced to the treatment of NSCLC. This article reviews recent data with maintenance therapy in advanced NSCLC and discusses the implications for routine patient care and future drug development.

Non-small cell lung cancer (NSCLC) is a very lethal disease responsible for more than a million deaths worldwide each year. It is often diagnosed at an advanced stage that is only amenable to palliative therapy. Platinum-based combination regimens, the current standard of care for advanced stage NSCLC, result in modest improvements in both overall survival and quality of life (1). Recently, the use of agents that inhibit the epidermal growth factor receptor (EGFR) have emerged as a frontline therapy option for patients whose tumors harbor an activating mutation of the receptor tyrosine kinase. Although it is generally accepted that the EGFR inhibitor therapy should be continued indefinitely until disease progression, the use of chemotherapy has been restricted to a defined number of cycles until recently. Continuation of combination chemotherapy beyond four to six cycles only results in added toxicity without a meaningful improvement in overall survival or progression-free survival (PFS; ref. 2). The current practice of adopting a "wait and watch" approach after achieving maximal response provides the opportunity for patients to experience a "drug holiday"; but is often associated with anxiety about disease progression or resurgence of malignant behavior, with particular concern for clinical deterioration and the inability to receive subsequent therapy.

The addition of molecularly targeted agents such as bevacizumab and cetuximab to combination chemotherapy in the frontline setting is associated with modest improvement in overall survival (1, 3). With this approach, the targeted agent is continued beyond the initial induction phase after achieving maximal response with the combination regimen. Although this is a biologically rational approach, there is no clinical evidence that patient outcomes are improved with such prolonged therapy. Furthermore, the targeted therapy combinations may be best suited for selected subsets of patients with advanced stage NSCLC based on tumor histology, anatomy, and clinical characteristics (4, 5).

The relatively brief duration of disease control even after robust response to first-line chemotherapy has prompted investigators to pursue other novel strategies to delay progression and improve overall survival for advanced stage NSCLC. The availability of well-tolerated novel agents, which are suitable for prolonged administration without engendering serious cumulative toxicity, has provided a new avenue of investigation in recent times. In the past year, three randomized phase III studies have documented improvement in outcome with the use of maintenance therapy for patients with advanced stage NSCLC (6–8). In fact, pemetrexed has received approval for the indication of maintenance therapy by the U.S. Food and Drug Administration (FDA) recently. This important development, therefore, calls for a critical review of the current data and their implications for patient care.

What Is Maintenance Therapy?

The U.S. National Cancer Institute’s medical dictionary defines maintenance therapy as “any treatment that is given to help keep cancer from progressing after it has
Recent Studies of Maintenance Therapy

Prior studies notwithstanding, it can be said that the results of four randomized contemporary studies reported in recent times have re-ignited the debate about the use of maintenance therapy for advanced NSCLC (Table 2). Two of these studies used a cytotoxic agent and the other two employed erlotinib, an EGFR inhibitor. All of these studies showed a significant improvement in PFS (6–8, 18). In addition, statistically significant survival advantage was noted with pemetrexed (6) and erlotinib (SATURN; ref. 7), whereas with docetaxel the impact on survival did not reach the level of significance despite a robust numerical trend (18).

Immediate Versus Delayed Docetaxel

In the study by Fidias and colleagues, following four cycles of first-line chemotherapy with carboplatin and gemcitabine, patients with objective disease response or stable disease were randomized to treatment with docetaxel as maintenance therapy or to watchful waiting and initiation of docetaxel as second-line therapy following disease progression (18). Not surprisingly, there was a clear advantage in PFS with maintenance docetaxel, and despite a near 3-month improvement in survival, the difference did not reach significance. Of the patients randomized to the control arm ("second-line therapy"), only 60% received the planned therapy. Reasons for not initiating planned second-line therapy included toxicity, decline in performance status, and the decision by the treating physician not to administer further therapy. This mirrors the "real world" situation whereby only about two thirds of NSCLC patients receive any form of second-line therapy for advanced-stage disease. Thus, it can be argued that the true benefit with "immediate" docetaxel in this study could be entirely attributed to the higher proportion of patients receiving active therapy in the maintenance setting. This result was supported by a post hoc analysis that documented identical overall survival duration of 12.5 months for patients who received docetaxel on either the experimental or control arm of the study. The frequency and the type of imaging studies used in the control arm have also been cited as unfavorably delaying detection of disease progression, compared with contemporary practice in the United States.

Pemetrexed Versus Placebo

A slightly different trial design was used for the phase III study of pemetrexed as maintenance therapy for advanced NSCLC (6). Patients with advanced disease that achieved stable disease or an objective response following four cycles of platinum-based therapy were randomized (2:1) to pemetrexed or placebo until disease progression. Maintenance therapy with pemetrexed was associated with a superior PFS, the primary endpoint of the study (4 months...
versus 2 months). The overall survival was also improved (13.4 months versus 10.6 months), with a near 5-month improvement in overall survival for the nonsquamous histology subset. The difference in efficacy of pemetrexed based on histology is consistent with data from other recent studies with this agent (19, 20). Maintenance pemetrexed was tolerated well without any evidence of excessive or cumulative toxicity. Approximately 67% of patients on the placebo arm received poststudy therapy compared with 52% on the pemetrexed arm. Pemetrexed was used

<table>
<thead>
<tr>
<th>Table 1. Randomized trials of prolonged or maintenance therapy using older chemotherapy regimens</th>
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<tr>
<td><strong>Trial (Ref.)</strong></td>
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<tr>
<td>Phase III (14)</td>
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Abbreviations: QoL, quality of life; OS, overall survival; MACC, methotrexate, doxorubicin, cyclophosphamide, and lomustine; MVP, mitomycin C, vinblastine, cisplatin; MIC, mitomycin C, ifosfamide, cisplatin; PC, carboplatin, paclitaxel; CV, carboplatin, vinorelbine; GC, gemcitabine, carboplatin; NR, not reported; BSC, best supportive care.
as poststudy therapy in only 19% of patients on the placebo arm because the study did not mandate that patients on the control arm be crossed over to receive pemetrexed at the time of disease progression. The discretion granted to investigators in the choice of second-line therapy has been cited as a major limitation of the study because it failed to provide any insight into the possibility that the benefit of maintenance pemetrexed therapy may be attained by appropriate use of the agents as a salvage therapy at the time of disease progression. Nonetheless, the majority of the patients on the placebo arm received second-line salvage therapy, and given the therapeutic equivalence of the currently available second-line therapies, it is unlikely that this factor unduly influenced the impressive overall results of the study. These results have now led to the approval of pemetrexed for maintenance therapy of NSCLC by the FDA. Furthermore, a third of the patients do not make it to second-line intervention if given a break.

### Erlotinib ± Placebo (SATURN)

Cappuzzo and colleagues evaluated the benefit of erlotinib as a maintenance therapy in patients who were free of progression at the end of four cycles of platinum-based frontline therapy. The median PFS was superior at 12.3 weeks with erlotinib compared with 11.1 weeks with placebo, with a hazard ratio of 0.71 (7). For patients with an EGFR mutation, the improvement in PFS was dramatic with a hazard ratio of 0.10. Though benefit was also noted in patients with wild-type EGFR, it was relatively modest.

The study also documented an improvement in overall survival for patients who received erlotinib as maintenance therapy (12 months versus 11 months). There was, however, no difference in overall survival for patients with mutated EGFR, presumably due to the high degree of poststudy treatment with an EGFR inhibitor. Overall, 55% and 64% of the patients in the erlotinib and placebo arms received poststudy treatment. The toxicities associated with the use of erlotinib were along predictable lines.

### Bevacizumab ± Erlotinib (ATLAS)

The ATLAS study was designed to build on the use of bevacizumab as maintenance therapy for patients who receive it in combination with chemotherapy for first-line treatment. On the basis of the preclinical evidence in support of a favorable interaction between EGFR and vascular endothelial growth factor (VEGF) signaling pathways in...
tumorigenesis (21). The ATLAS study sought to determine whether the combination of bevacizumab and erlotinib is more effective than bevacizumab alone when used for maintenance therapy. A total of 1,160 patients were enrolled for frontline therapy with platinum-based doublet (choice of chemotherapy at investigators’ discretion) along with bevacizumab. Following completion of four cycles, nonprogressing patients (768 or 66%) were randomized to receive bevacizumab alone or in combination with erlotinib. There was a modest improvement in the primary endpoint of improved PFS with the addition of erlotinib (4.8 months versus 3.6 months) and the overall survival analysis is awaited. Although there was an incremental increase in adverse events in patients treated with erlotinib, the number of patients who received further therapy at the time of progression was comparable between both arms (53% versus 50%), indicating that the use of erlotinib did not impair the ability of the patients to receive potentially beneficial therapy. Though the PFS results are along similar lines as the SATURN study, the widespread use of this regimen would depend on the survival results and the overall usage of bevacizumab for first-line therapy. The study did not address the fundamental question of how much additional benefit is derived from the use of bevacizumab as maintenance therapy in patients with advanced nonsquamous NSCLC treated with a bevacizumab-containing induction regimen. Although recognizing the perils of cross-trial comparison, the approximately 4-month median PFS with single-agent erlotinib maintenance in the SATURN trial and 4.8-month median PFS with the combination of erlotinib and bevacizumab in the ATLAS trial, highlights the importance of establishing the relative contribution of each agent when a combination therapy strategy is being evaluated in the maintenance setting. Closely related to this issue is the need to employ clinical and molecular predictive markers to identify the most appropriate group of patients who stand to derive the most benefit from such an intervention. The subset analysis from the SATURN trial showed that the greatest reduction in the risk of progression was observed in patients whose tumors harbor activating EGFR mutations (hazard ratio, 0.1; confidence interval 0.04-0.25; P < 0.0001; ref. 22). Although the biomarker analysis from the ATLAS study is not yet available, it would be interesting to see if the combination of bevacizumab and erlotinib resulted in any additional benefit in this subset of patients. Prospective, carefully designed, subset analyses such as were done in the SATURN and the pemetrexed maintenance trials (6, 22), although not enough to drive definitive management recommendations, represent useful tools to dissect and answer the complex research and clinical questions surrounding maintenance therapy in patients with advanced NSCLC.

### Meta-analysis of Maintenance Therapy Studies

A recent meta-analysis by Soon and colleagues has shed additional light on the efficacy of maintenance therapy (23). The report analyzed studies with three broad trial designs. The first group involved studies that randomized patients to chemotherapy for a shorter versus longer number of courses of therapy. The next group involved studies that randomized patients to a defined length of treatment versus continuation of therapy until progression. The last group of studies involved the addition of a new agent following combination chemotherapy versus observation. Nearly 3,000 patients were enrolled to the studies included in this meta-analysis. Overall, there was a significant improvement in PFS and a modest survival benefit with extended duration of chemotherapy. This analysis did not include the SATURN and ATLAS studies and it would be safe to assume that the overall results of the study would only be strengthened by the addition of these two large studies.

### Implications for Routine Patient Care

The results from the randomized studies described earlier have led to the emergence of maintenance therapy as an efficacious modality to improve outcome for patients with advanced stage NSCLC. The possible use of maintenance therapy should be viewed in the light of the efficacy plateau that has been reached with platinum-based regimens in the first-line therapy setting. The addition of a targeted agent to improve outcomes as first-line therapy has largely been unsuccessful with the exception of the modest benefits noted with bevacizumab and cetuximab (1, 3). In the case of the three drug regimens, one has to contend with the additional toxicities that are specific to the targeted agent. It has become unequivocally clear that patients with EGFR mutation should receive an EGFR tyrosine kinase inhibitor, preferably earlier on during the course of their treatment, i.e., first-line therapy setting or as maintenance therapy. For second-line therapy, the value of patient selection by EGFR mutation status is not entirely clear.

The argument that maintenance therapy represents in reality the earlier use of second-line therapy is certainly valid. Nonetheless, survival advantage ascribed in part to the ability of a greater number of patients to receive such treatments in the immediate aftermath of first-line therapy makes the argument for the use of maintenance therapy stronger. As we strive to make cancer a chronic less fatal disease, the use of prolonged therapy would be inevitable for the majority of the patients to achieve this goal.

### Unanswered Questions about Maintenance Therapy

Despite the many studies conducted to date to establish the benefit or otherwise of maintenance therapy for advanced lung cancer patients, we are still in the early phase of fully characterizing the optimal maintenance strategies to treat patients with NSCLC. A number of important questions remain to be answered and deserve
careful evaluation in the setting of appropriately designed prospective clinical trials. It is most germane to the ongoing contention about the usefulness of maintenance therapy that a clearly defined, reproducible, and measurable endpoint be established. Although most published trials showed a benefit of maintenance therapy in terms of PFS, only the most recently reported prospective trials have shown clear overall survival benefit to date (6, 7). The limitations of using PFS as the basis for the adoption of a new therapy, given the variability in the definition of progression and frequency of response assessment across studies is an important factor to consider in the debate about the optimal utility of maintenance therapy. In addition, the availability of multiple agents that are used in the poststudy setting confounds the impact of maintenance therapy. It is not possible to control for poststudy events in a large clinical trial that will allow fair assessment of a new therapy. Given this real world challenge, the PFS endpoint becomes even more important not just for trials evaluating maintenance treatment strategies, but also for all future definitive therapeutic trials in this patient population. Perhaps, rather than disparaging the utility of PFS as a useful efficacy endpoint, it may be more important to look into ways to standardize PFS assessment in definitive phase III trials, and more importantly, to use available data to guide a broad agreement on what degree of PFS improvement is acceptable as a valid evidence of efficacy in the absence of overall survival benefit.

It is to be noted that survival benefit with maintenance therapy has been primarily seen with the use of an agent the patient has not been exposed to earlier. It is not known whether the benefit of maintenance pemetrexed can be realized in those already treated with this agent as part of their induction therapy. Nonetheless, the phase II trial by Patel and colleagues provided some insight in this regard in which patients treated with carboplatin, pemetrexed, and bevacizumab subsequently received maintenance therapy with pemetrexed and bevacizumab. The survival outcome was promising relative to historical data and has spurred an ongoing phase III trial to address the benefit of such a two-drug maintenance strategy versus standard bevacizumab maintenance (24, 25). This and other prospective studies are necessary to determine whether continuation of one of the drugs used as part of the first-line regimen can be used for maintenance therapy. This is also true for targeted agents that have been continued beyond combination chemotherapy in various studies.

Another major issue involves the lack of data about quality of life with maintenance therapy. Concerns remain about the acute and cumulative toxicity of prolonged therapy and their impact on patients’ quality of life. Unfortunately, not all studies provided carefully collected prospective data about quality of life in the maintenance setting. Where such data were collected, however, the use of newer generation drugs, especially targeted biologic agents, did not seem to impact negatively on the quality of life of patients on active therapy versus those on placebo (7). Although it can be said that there seems to be no major detrimental effect of maintenance therapy from recent studies, this issue needs to be addressed in future clinical trials, particularly for agents that have a narrow therapeutic index. Closely intertwined with the use of appropriate therapeutic agent for maintenance therapy is the selection of the right patient population. By design, all of the recently reported trials enrolled patients who derived some benefit from frontline induction chemotherapy. Preplanned and unplanned subset analysis in these trials, however, showed that select patients characterized by histologic (nonsquamous) or molecular (EGFR mutant) profile derive disproportionately

Fig. 1. Planned phase III evaluation of maintenance therapy comparing pemetrexed, bevacizumab, and the combination of both agents as maintenance regimen following standard frontline therapy for non-small cell lung cancer.
higher benefit from the maintenance therapy in terms of significant reduction in the risk of disease progression and death. Consistent with the evolving practice in the frontline induction therapy setting, using such a well-characterized tumor profile to select patients for maintenance therapy may further improve the therapeutic index leading to a greater survival benefit. Finally, the availability of multiple agents with promising efficacy in the maintenance setting necessitates a formal comparison of these agents in order to establish the best agent for different patient population. For instance, it is unclear whether patients who receive a platinum-based regimen with bevacizumab should continue bevacizumab, switch to another agent, or continue bevacizumab in combination with a second agent for maintenance therapy. The proposed trial by the Eastern Cooperative Oncology Group is a three-arm phase III study to address key issues in maintenance therapy; first is the contribution of maintenance bevacizumab to the overall survival outcome in patients treated with bevacizumab-containing induction regimen. Secondly, the study will clarify whether pemetrexed maintenance is best administered alone or in combination with bevacizumab especially in patients who received bevacizumab for induction therapy (Fig. 1). A comprehensive list of ongoing or planned phase III trials of maintenance therapy in NSCLC is provided in Table 3.

### Implications for Drug Development and Clinical Trials

The use of prolonged treatment strategy has direct implications for drug development with respect to potential cumulative toxicity even with the increasing availability of relatively well-tolerated agents. Because adequate end organ function is requisite for participation in most therapeutic clinical trials, the widespread use of prolonged therapy may render a significant number of patients ineligible for participation in such clinical trials. It will also be important to clearly define the eligibility criteria with

### Table 3. Ongoing or planned Phase III trials evaluating maintenance therapy in patients with NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Sample size</th>
<th>Primary endpoint</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 5508</td>
<td>Paclitaxel + carboplatin + bevacizumab Followed by randomization to: pemetrexed versus bevacizumab versus pemetrexed + bevacizumab</td>
<td>897</td>
<td>OS</td>
<td>Non-Squamous histologies only</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>Pemetrexed/carboplatin/bevacizumab followed by pemetrexed + bevacizumab versus carboplatin/paclitaxel/bevacizumab followed by bevacizumab</td>
<td>900</td>
<td>OS</td>
<td>QoL impact will be assessed; non-squamous histologies</td>
</tr>
<tr>
<td>NCT0789373</td>
<td>Pemetrexed + cisplatin followed by pemetrexed maintenance versus placebo</td>
<td>900</td>
<td>PFS</td>
<td>2:1 randomization of non-progressing patients after four cycles of induction therapy</td>
</tr>
<tr>
<td>NEXT trial</td>
<td>Platinum-based doublet plus cetuximab followed by cetuximab maintenance (500 mg/m² every 2 wk versus 250 mg/m² every week)</td>
<td>1,200</td>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>NCT00948675</td>
<td>Pemetrexed/carboplatin followed by maintenance pemetrexed versus carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab</td>
<td>360</td>
<td>PFS</td>
<td>Without grade 4 toxicity</td>
</tr>
<tr>
<td>CALGB 30607</td>
<td>Platinum-based induction chemotherapy followed by sunitinib versus placebo as maintenance</td>
<td>244</td>
<td>PFS</td>
<td>All histologies</td>
</tr>
<tr>
<td>NCT00693992</td>
<td>Pemetrexed/cisplatin/bevacizumab followed by pemetrexed versus pemetrexed/bevacizumab</td>
<td>362</td>
<td>PFS</td>
<td>Nonsquamous histologies only</td>
</tr>
<tr>
<td>IFCT-GFPC 05.02</td>
<td>Cisplatin/gemcitabine followed by gemcitabine versus erlotin</td>
<td>435</td>
<td>PFS</td>
<td>All histologies</td>
</tr>
</tbody>
</table>

Abbreviations: QoL, quality of life; OS, overall survival.
Conclusions and Recommendations

Maintenance therapy represents a useful strategy to improve patient outcomes in advanced stage NSCLC. With the approval of pemetrexed by the FDA for maintenance therapy, it is necessary to discuss the recent data with patients for whom a drug holiday is considered. In the least, we believe that patients with high-volume disease and symptomatic disease should be strongly considered for maintenance therapy in routine practice. Identification of predictive biomarkers for individual agents used in this setting will greatly enhance the risk-benefit ratio of maintenance therapy. In the era of molecularly targeted therapies for cancer, the use of maintenance therapy can be viewed as another promising approach in the increasing array of possible therapeutic interventions that can be marshaled for improved outcomes for patients with advanced stage NSCLC. Currently available data support the use of pemetrexed in patients with nonsquamous histology that did not receive pemetrexed as part of their induction regimen. In the case of erlotinib, the use of a molecular selection strategy will be necessary to identify a subgroup of patients best suited for maintenance therapy, given the relatively modest survival benefit noted in an unselected patient population. It is our hope that the ongoing studies will provide clarity about the optimal use of the maintenance approach in patients with NSCLC.

Disclosure of Potential Conflicts of Interest


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