Lung Cancer in 2013: State of the Art Therapy for Metastatic Disease

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OVERVIEW

Lung cancer is the leading worldwide cause of cancer death and the majority of patients present with metastatic stage IV disease. At diagnosis, clinical, histologic, and molecular features must be considered in therapeutic decision-making for systemic therapy. Molecular testing for at least epidermal growth factor receptor (EGFR) and ALK should be performed in all patients before therapy. Platinum doublet chemotherapy may be considered for “fit” patients who do not have a molecular driver genetic abnormality. Bevacizumab can be considered for addition to the doublet in patients with nonsquamous cancers who have no contraindications. A pemetrexed combination is considered only in nonsquamous histology. Patients with EGFR mutations or ALK fusions should be treated with erlotinib or crizotinib, respectively, even in patients with tumor-related poor performance. The tyrosine-kinase inhibitors (TKIs) may be continued until multisite, symptomatic progression. For patients initially treated with a platinum doublet, maintenance chemotherapy with pemetrexed, erlotinib, gemcitabine, or possibly docetaxel is an option with selection based on clinical features, histology, type of initial therapy, and response to first-line therapy.

The current standard of care for treatment of most patients with advanced non–small cell lung cancer (NSCLC) remains platinum-based doublet chemotherapy for four to six cycles in fit patients. Numerous studies have compared platinum-based doublets containing gemcitabine, paclitaxel, docetaxel, vinorelbine, and pemetrexed, and response and survival rates have been similar in all trials. Several trials examined the role of prolonged platinum doublet chemotherapy, and none reported significant prolongation of either progression-free or overall survival. Furthermore, prolonged therapy was associated with significantly more toxicity, and in some trials, a worsening of quality of life.

Until recently, treatment selection was not based on histologic subtype of NSCLC, but subset analyses of trials comparing pemetrexed-based doublets to other chemotherapy showed poorer outcome in patients with squamous histology, and so this agent is now restricted in the first and second line to patients with nonsquamous cancer.

Single agent therapy may be offered to older patients or those with poor performance status, although recent studies suggest that carboplatin-based regimens may be tolerated well in these subpopulations, with improved response and survival rates.

Inhibition of angiogenesis plays a role in the management of many malignancies, including lung cancer. The monoclonal antibody bevacizumab has demonstrated efficacy (improved response rates and overall survival) in phase II and III trials in combination with first-line chemotherapy in NSCLC. The North American trial evaluated bevacizumab (15 mg/kg) with paclitaxel/carboplatin and showed positive results with improved response and survival rates. However, a global study that evaluated bevacizumab (7.5 or 15 mg/kg) with gemcitabine/cisplatin showed higher response rates and progression-free, but not overall, survival. Furthermore, there was no apparent benefit for 15 mg over 7.5 mg. Many small molecule tyrosine kinase inhibitors (TKIs), including vandetanib, sorafenib, sunitinib, pazopanib, and cediranib, have been studied in phase III trials in combination with standard therapy. To date, no study has had a positive outcome, and in fact some studies have demonstrated significantly poorer outcomes in the TKI arms. Another issue related to angiogenesis therapy relates to the absence of any predictive marker for treatment. Bevacizumab is limited to patients with nonsquamous histology, but that is on the basis of toxicity in patients with squamous cancers, and not a differential response to therapy.

Almost without exception, the trials of first-line chemotherapy were performed without molecular selection. Astonishingly, this was also the case for the early trials of EGFR inhibitors. In the first-line setting, the addition of EGFR TKIs to chemotherapy does not add to response rate or overall survival, and may even have a negative effect on chemotherapy. The trials comparing EGFR TKIs with chemotherapy in molecularly unselected patients (even when clinical selection
filters were applied), all showed significantly worse outcomes for patients with wild-type EGFR tumors who did not receive chemotherapy. These trials emphasize the importance of mutation testing, if EGFR TKI therapy is to be selected over chemotherapy for first-line treatment of advanced NSCLC.

In contrast, four trials suggest that the addition of the EGFR monoclonal antibody cetuximab to chemotherapy may improve response rates and perhaps add to overall survival as well. However, the additional benefit is modest, and cetuximab has not been approved for lung cancer treatment in any jurisdiction. The molecular markers that predict response to EGFR TKIs, including EGFR mutation status, do not appear to play a role in the selection of patients for cetuximab. Also, unlike colorectal cancer, the presence of KRAS mutations does not predict for poorer outcomes from cetuximab in NSCLC.

Both erlotinib and gefitinib have been evaluated as first-line single-agent therapy in selected populations, including elderly patients and those with poor performance status who might not be eligible for chemotherapy. None of these studies suggests that EGFR TKI therapy would be superior to standard chemotherapy in unselected patients. The largest study that compared erlotinib to best supportive care in 670 patients reported no significant prolongation of survival whatsoever, although survival did appear to be prolonged in patients who developed first-cycle rash from erlotinib. In the small subset of patients who had tumor samples available, those with EGFR-mutant tumors derived benefit from erlotinib (median, 10.4 vs. 3.7 months). Results were not reported for those with EGFR wild-type tumors.

To date, there is no molecular predictor of response or survival benefit that reliably aids our selection of patients for chemotherapy. The differential response to pemetrexed for squamous and nonsquamous cancers is thought to be a result of higher expression of one of its target enzymes, thymidylate synthase in the former, but this has not been proven clinically since the trials that led to the observations did not do collect samples for analysis. Thus, thymidylate synthase is not used as a selection tool for treatment, although it is being incorporated into some studies comparing molecular selection with standard chemotherapy for advanced NSCLC. In the adjuvant setting, ERCC1, which is important in the DNA repair pathway, was reported to be both prognostic and predictive of outcome. However, ERCC1 antibodies are not reliable, and so it has not been possible to validate these results. Studies are ongoing in which patients with high ERCC1 levels are assigned to nonplatinum chemotherapy. BRCA1 also plays a role in DNA repair, and studies are ongoing in which treatment assignment is based on BRCA1 levels. The role of KRAS mutations in the selection of patients for both chemotherapy and EGFR therapy remains controversial. It is a weak marker of poor prognosis, but at this time, KRAS cannot be recommended to exclude patients from therapy. Other markers that have been measured include p35, beta-tubulin, RRM1, and p27, to name but a few. None of these markers has demonstrated the level of evidence necessary to use them for patient or treatment selection.

There is no doubt that EGFR activating/sensitizing mutations predict for higher response rates and longer survival in patients receiving EGFR TKI therapy, and that for selection of first-line treatment, EGFR mutation testing is mandatory. However, in the maintenance and more advanced settings, mutation studies have shown consistently that the interaction based on EGFR mutation status is quantitative and not qualitative, with benefit from EGFR TKI therapy seen in patients with mutated and wild-type EGFR; the difference lies only in the magnitude of the benefit. Since crizotinib and other inhibitors of ALK have been and are being developed only in patients with ALK wild-type tumors. However, crizotinib currently is being studied to assess its role as a MET inhibitor, and so this may clarify the role of this agent in the absence of ALK mutation.

**MOLECULARLY TARGETED TREATMENT OF PATIENTS WITH ADVANCED NSCLC**

**Epidermal Growth Factor Receptor (EGFR)**

Studies of premalignancy and of invasive lung cancers demonstrated that EGFR was highly expressed in dysplastic premalignant lesions, with increasing expression associated with increasing degrees of dysplasia and with high expression in up to 80% of invasive lung cancers. These observations made EGFR an attractive therapeutic target, and monoclonal antibodies (e.g., cetuximab) and small molecule TKIs (e.g., gefitinib, erlotinib) were developed. Early trials of these agents in unselected, chemotherapy-resistant, advanced NSCLC showed response rates of less than 10%, but some of these responses were long-lasting. These responses created considerable enthusiasm, leading to randomized trials comparing gefitinib or erlotinib to best supportive care (BSC) in the second- or third-line treatment setting and to combination studies with chemotherapy in the first-line setting. The National Cancer Institute of Canada study comparing erlotinib to BSC in the second or third line setting showed

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**KEY POINTS**

- **Selection of lung cancer therapy should be based on clinical features, histology, and molecular features.**
- **Pemetrexed and bevacizumab are indicated only in nonsquamous histologies.**
- **Molecular analyses of EGFR and ALK alterations are indicated before institution of therapy in all patients with stage IV disease with an adenocarcinoma component, irrespective of clinical features.**
- **EGFR and ALK TKIs may be continued until multisite, symptomatic progression.**
- **Patients successfully treated with first-line platinum doublets may be considered for maintenance therapy options.**
significant improvements in response, PFS, and overall survival associated with erlotinib leading to its approval for this indication.\textsuperscript{14} The randomized trials comparing gefitinib to BSC showed more favorable outcomes with gefitinib, but the differences were not significant.\textsuperscript{15}

In the first-line setting, erlotinib and gefitinib were studied in combination with platinum doublet combinations in unselected patients with advanced NSCLC in four prospective randomized trials.\textsuperscript{16-19} As discussed above, all of these trials showed no benefit and there was some evidence of a worse outcome in the TKI arms during the period of chemotherapy administration. Studies in cell lines suggested that predictive biomarkers might identify which lines would have the most benefit.\textsuperscript{20} The major breakthrough occurred in 2004, when two groups from Boston reported that activating mutations in the \textit{EGFR} gene were associated with response to EGFR TKIs.\textsuperscript{21,22} This observation was subsequently confirmed in many studies and led to randomized clinical trials comparing erlotinib, gefitinib, or afatinib to platinum doublets in patients likely to harbor EGFR mutations or patients with known EGFR mutations. The results of these trials are summarized in Table 1A.\textsuperscript{23-30} In each of these trials, the EGFR TKI produced a higher response and a longer progression-free survival (PFS) compared to chemotherapy in patients with an activating \textit{EGFR} mutation. In contrast, as shown in Table 1B, in trials which included patients without an \textit{EGFR} mutation, chemotherapy produced superior response rates and PFS.\textsuperscript{23,24,26,31} Despite differences in toxicities, patient-reported outcomes favored the TKI in patients with \textit{EGFR} mutations and the chemotherapy in patients with wild-type \textit{EGFR}. On the basis of these results, ASCO, the European Society for Medical Oncology, National Comprehensive Cancer Network, and International Association for the Study of Lung Cancer/Collage of American Pathologists/Association for Molecular Pathology have all issued guidelines recommending that all patients with advanced NSCLC with any adenocarcinoma component undergo molecular analysis for \textit{EGFR} mutations before institution of first-line therapy.\textsuperscript{32-35}

This testing allows those with activating \textit{EGFR} mutations to receive an EGFR TKI, whereas chemotherapy would be selected as first-line therapy in patients without mutation. All of these trials allowed cross-over to the other arm at progression and none showed a significant difference in survival, likely as a result of the cross-over. Survival did favor first-line EGFR TKI in patients with \textit{EGFR} mutation and chemotherapy in those without an \textit{EGFR} mutation, supporting the guideline recommendations.

Patients with \textit{EGFR} mutation who receive an EGFR TKI therapy should remain on the therapy until the time of symptomatic progression.\textsuperscript{36} Some patients may progress in a single site. In these instances, local therapy to the progressing site may be given with continuation of the TKI until there is multisite progression.\textsuperscript{37} The biologic basis for progression and resistance and therapy at progression will not be covered in this manuscript.

### Table 1A. Results of Randomized Trials Comparing an EGFR TKI to Platinum-Doublt Chemotherapy in Previously Untreated Advanced Lung Adenocarcinoma with Activating \textit{EGFR} Mutations

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>OR (%)</th>
<th>MPFS (mo)</th>
<th>MOS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-Signal\textsuperscript{23}</td>
<td>Gefitinib</td>
<td>26</td>
<td>85</td>
<td>8</td>
</tr>
<tr>
<td>Gem/cis</td>
<td>16</td>
<td>38</td>
<td>2.1</td>
<td>25.6</td>
</tr>
<tr>
<td>NEJOG\textsuperscript{24,27}</td>
<td>Gefitinib</td>
<td>114</td>
<td>74</td>
<td>10.8</td>
</tr>
<tr>
<td>Chemo</td>
<td>110</td>
<td>31</td>
<td>5.4</td>
<td>26.6</td>
</tr>
<tr>
<td>OPTIMAL\textsuperscript{28}</td>
<td>Erlotinib</td>
<td>83</td>
<td>83</td>
<td>13.1</td>
</tr>
<tr>
<td>Gem/carbo</td>
<td>72</td>
<td>36</td>
<td>4.6</td>
<td>NR</td>
</tr>
<tr>
<td>EURTAC\textsuperscript{29}</td>
<td>Erlotinib</td>
<td>86</td>
<td>58</td>
<td>9.7</td>
</tr>
<tr>
<td>Piat. doublet</td>
<td>87</td>
<td>15</td>
<td>5.2</td>
<td>NR</td>
</tr>
<tr>
<td>LuxLung\textsuperscript{30}</td>
<td>Gefitinib</td>
<td>230</td>
<td>56</td>
<td>11.1</td>
</tr>
<tr>
<td>Afatinib</td>
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<td>23</td>
<td>6.9</td>
<td>NR</td>
</tr>
<tr>
<td>Pem/cis</td>
<td>615</td>
<td>31</td>
<td>5.3</td>
<td>24.3</td>
</tr>
<tr>
<td>Total/Median</td>
<td>132</td>
<td>Gefitinib</td>
<td>26</td>
<td>85</td>
</tr>
<tr>
<td>Chemo</td>
<td>757</td>
<td>66</td>
<td>10.2</td>
<td>26.2</td>
</tr>
</tbody>
</table>

Abbreviations: carbo, carboplatin; chemo, any platinum doublet; cis, cisplatin; doce, docetaxel; EGFR, epidermal growth factor receptor; gem, gemcitabine; mo, months; MOS, median overall survival; MPFS, median progression-free survival; N, number of patients; NR, not reported; OR, objective response rate; pem, pemetrexed; plat, platinum; plat, doublet, docetaxel/cisplatin, gemcitabine/cisplatin, docetaxel/carboplatin, gemcitabine/carboplatin; TKI, tyrosine-kinase inhibitor.

### Anaplastic Lymphoma Kinase (ALK)

In 2007, Soda and colleagues reported that the \textit{ALK} gene was activated in lung cancer by fusion to the \textit{EMLA} gene on chromosome 2 and that this fusion gene was oncogenic in lung cancer cell lines.\textsuperscript{38} The gene fusion could be detected by a break apart fluorescence in situ hybridization (FISH) test, and by polymerase chain reaction (PCR) analysis. Because subsequent studies showed other gene partners for fusion with \textit{ALK}, the FISH test detected all of these, whereas multiple PCR primers were necessary to detect all possible fusion partners. Thus, the FISH test was developed as a companion diagnostic for ALK TKI therapy with crizotinib. Subsequent studies demonstrated that nearly all tumors with \textit{ALK} rearrangements have high \textit{ALK} protein expression that can be detected by immunohistochemistry (IHC) using anti-ALK antibodies. Thus, \textit{ALK} fusions may be identified by FISH, PCR, IHC, and next-generation sequencing. It is likely that one or more of these other tests will be used in the future, but at present FISH testing is the sole approved diagnostic.
ALK mutations and rearrangements but not ALK ethnicity is associated with a higher frequency of age, female gender, and adenocarcinoma histology. Asian rearrangements include never-smoking status, younger age, female gender, and adenocarcinoma histology. Asian ethnicity is associated with a higher frequency of EGFR mutations but not ALK rearrangements. Nonetheless, EGFR mutations and ALK rearrangements may occur in patients without these clinical features. All of the guidelines recommend testing of all patients, irrespective of clinical features.

More recently, other oncogenic drivers in NSCLC have been reported, and early reports of responses to targeted TKIs have been published. Among these are mutations in HER2, BRAF, PI3KCA rearrangements in ROS and RET, and amplifications in MET and FGFR1. Preliminary results in subjects with ROS fusions treated with the ROS TKI crizotinib suggest response rates and PFS may be similar to those obtained with EGFR TKIs in patients with EGFR mutations or with crizotinib in patients with ALK fusions. These data suggest that routine testing for additional genetic alterations will become standard in the future. Fortunately, the costs of next-generation sequencing and other biomarker tests are decreasing, while reliability and turn-around times are improving. The future is also likely to see combinations of targeted therapies, since single agents produce few complete responses and no cures.

### MAINTENANCE THERAPY

Systemic therapy based on four to six cycles of platinum-based chemotherapy is the standard approach for first-line treatment. Prolonging treatment duration with induction regimens has shown to prolong PFS, without a clinically significant effect on survival, at the cost of relevant toxicity, particularly with platinum agents and taxanes. Following induction treatment, patients without disease progression enter a “watch and wait” period in which periodic disease staging is performed until progression is reported; a second-line treatment is then started. Unfortunately, this strategy frequently fails because at the time of the first follow-up visit, about one-half of these patients present uncontrolled disease, and in a significant proportion, health status is deteriorated to the point that they are not candidates for further treatment.

The availability of drugs with improved adverse effect profiles, such as gemcitabine, erlotinib, or pemetrexed, prompted maintenance therapy studies over the last few years as a means of optimizing tumor control and improving patient outcomes. The rationale for this strategy is obvious, and aligned with clinical practice in other solid tumors (e.g., colorectal cancer, breast cancer, etc.) or other chronic respiratory illness (chronic obstructive pulmonary disease, granulomatosis, etc.).

### Continuation-Maintenance Therapy

Continuation-maintenance therapy refers to the continued administration of a lower-intensity version of the first-line regimen, typically the nonplatinum drug of a doublet, until disease progression or relevant toxicity. A European trial evaluated maintenance gemcitabine compared with BSC after induction treatment with four cycles of gemcitabine and cisplatin. Time to progression, which was the primary endpoint, was significantly longer for patients who received maintenance therapy (3.6 vs. 2 months; p < 0.001). There also was a trend toward longer overall survival (OS) in

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**TABLE 1B. Results of Randomized Trials Comparing an EGFR TKI to a Platinum Doublet in Previously Untreated Advanced Lung Adenocarcinoma with Wild-Type EGFR**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>OR (%)</th>
<th>MPFS (mo)</th>
<th>MOS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-Signal</td>
<td>54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>27</td>
<td>26</td>
<td>2.1</td>
<td>8.4</td>
</tr>
<tr>
<td>Gem/cis</td>
<td>27</td>
<td>52</td>
<td>6.4</td>
<td>21.9</td>
</tr>
<tr>
<td>IPASS</td>
<td>176</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>91</td>
<td>1.1</td>
<td>1.8</td>
<td>12.2</td>
</tr>
<tr>
<td>Taxol/Carbo</td>
<td>85</td>
<td>24</td>
<td>6.5</td>
<td>12.5</td>
</tr>
<tr>
<td>TORCH</td>
<td>380</td>
<td>26</td>
<td>2.2</td>
<td>8.7</td>
</tr>
<tr>
<td>Gem/cis</td>
<td>380</td>
<td>87</td>
<td>5.4</td>
<td>11.6</td>
</tr>
<tr>
<td>Total</td>
<td>990</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR TKI</td>
<td>498</td>
<td>21</td>
<td>2.05</td>
<td>9.7</td>
</tr>
<tr>
<td>Chemo</td>
<td>492</td>
<td>74</td>
<td>6.1</td>
<td>12.0</td>
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Abbreviations: carbo, carboplatin; chemo, any platinum doublet; cis, cisplatin; EGFR, epidermal growth factor receptor; gem, gemcitabine; mo, months; MOS, median overall survival; MPFS, median progression-free survival; N, number of patients; OR, objective response rate; TKI, tyrosine-kinase inhibitor.
the maintenance gemcitabine group. In terms of toxicity, red blood cell transfusions were used more frequently in the gemcitabine arm (20%) compared with placebo (6.3%; p = 0.018), but no significant differences in quality of life (QoL) between the two arms were detected.

Two additional studies with maintenance gemcitabine have been recently reported.44,45 In the first study,44 patients with stable or responsive disease to carboplatin plus gemcitabine were assigned to either gemcitabine with BSC or BSC alone. The study closed after 6 years because of slow accrual, and the large majority of patients had performance status (PS) 2 at study entry. No differences in PFS or OS were found according to the treatment arms. The second study (IFCT-GFPC 0502), however, showed a strong benefit in PFS (3.8 vs. 2.7 months; hazard ratio [HR] 0.55) for those patients who continued gemcitabine treatment.45 This trial randomly assigned patients to observation or two different maintenance regimens, gemcitabine or erlotinib, to patients not progressing to four courses of induction with cisplatin plus gemcitabine. No survival improvement was observed, and secondary analysis suggested that those patients with PS 0 and salvage treatment with pemetrexed, as mandated per protocol, benefited the most from this treatments strategy.

The PARAMOUNT trial was designed to determine if pemetrexed maintenance therapy would improve efficacy over placebo following four courses of cisplatin/pemetrexed.46 The primary objective of this study, PFS, was improved in the pemetrexed maintenance arm compared with placebo (4.1 vs. 2.8 months, HR 0.62). Accordingly, OS was also significantly improved (13.9 vs. 11 months, HR 0.78).47 Drug-related grade 3/4 anemia, fatigue, and neutropenia were significantly higher in patients treated with pemetrexed. No differences in health status were observed as assessed with the EQ-5D questionnaire.

The role of continuation-maintenance therapy with single-agent bevacizumab or cetuximab has never been specifically assessed. The pivotal trials (ECOG 4899 and AVAIL for bevacizumab, and FLEX for cetuximab) were not designed to ascertain the differential effect of these drugs during the induction (with a platinum doublet) and the maintenance phases (the drug alone).48,49 A phase II trial analyzed the contribution of pemetrexed maintenance in combination with bevacizumab in patients exposed during the induction phase to both drugs within a cisplatin triplet. PFS from induction (10.2 vs. 6.6 months, HR 0.50) and from random assignment (7.4 vs. 3.7 months, HR 0.48) were significantly prolonged in the pemetrexed plus bevacizumab arm.50 Mature OS data are expected at the 2013 ASCO Annual Meeting. Regarding the toxicity profile, grade 3–5 hematologic and nonhematologic adverse events occurred in 10.4% and 31.2% of patients in the bevacizumab and pemetrexed arms, respectively.

**Early Second-Line or Switch-Maintenance Therapy**
Switch-maintenance therapy may be defined as the administration of an agent with established activity in advanced NSCLC immediately after completion of the induction chemotherapy phase.42 Fidias and colleagues pioneered the modern use of this approach51 in a clinical trial of 309 patients with nonprogressive disease after four cycles of gemcitabine/carboplatin first-line chemotherapy who were randomly assigned to immediate or delayed second-line docetaxel (at the time of disease progression) for a maximum of six cycles. Median PFS was significantly longer in the immediate as compared to the delayed docetaxel arm (5.7 vs. 2.7 months; p = 0.0001). The observed OS differences between the treatment arms did not quite reach statistical significance (12.3 vs. 9.7 months; p = 0.0853). Approximately 37% of the patients in the delayed treatment arm never received docetaxel because of significant symptomatic deterioration by the time disease progression occurred and investigator’s decision. OS analysis restricted to patients who actually received docetaxel revealed that OS was identical in both arms of the study (12.5 months), suggesting that the trend toward improved OS was a result of a higher proportion of patients in the immediate group who were able to receive docetaxel treatment. Toxicity profiles were similar between the arms and no QoL differences were found.

Two recent placebo-controlled trials of similar design evaluated the role of pemetrexed and erlotinib as maintenance therapy for patients with advanced NSCLC following disease control with four cycles of platinum-based therapy (not including pemetrexed or erlotinib).52,53 Pemetrexed maintenance significantly improved PFS (4.0 vs. 2.0 months; HR 0.60) and OS (13.4 vs. 10.6 months; HR 0.79), and improved outcomes were only evident in patients with nonsquamous histology (PFS HR 0.47; OS HR 0.70). There was a moderate excess of toxicity occurring in patients treated with pemetrexed, particularly neutropenia and fatigue. QoL evaluations showed no differences except a significant delay in worsening of pain and hemoptysis. Similarly, the SATURN trial53 showed a significant prolongation of PFS (12.3 vs. 11.1 weeks; HR 0.71) and OS (HR 0.81) for patients treated with erlotinib maintenance compared with placebo. As expected, rash and diarrhea were the most prevalent side effects. A recent French trial (IFCT-GFPC 0502) has confirmed the effect on PFS of the EGFR TKI in the maintenance setting.45 OS differences did not emerge over the placebo arm in this study of limited size (about 150 patients per arm).

**Implications for Clinical Practice**
In line with the evidence currently available, maintenance therapy represents a treatment option in advanced NSCLC. Maintenance should be discussed with patients whose disease does not progress after four to six cycles of first-line chemotherapy, who are fit (PS 0 to 1) and without persistent chemotherapy-induced toxicity. Patients need to be well informed about potential pros and cons receiving additional therapy without "treatment holidays."

Of the two different strategies, switch or continuation maintenance, the robustness of the efficacy data is not diverse. Looking at individual studies, the hazard ratio for PFS is in the range of 0.6 to 0.7 in most of the trials for both strategies. OS has only significantly improved in the SATURN53 and JMEN52 switch-maintenance trials, and in
the PARAMOUNT trial with the continuation strategy. Indeed, these were the only three trials with a reasonable size (539 to 889 patients) to enable adequately powered comparisons. Since no powered comparative trials of maintenance with different chemotherapy drugs or targeted agents have been conducted, no conclusive data are available yet about the potential advantage of any given therapy. The IFCT-GFPC 0502 trial is the only study that included both the switch- and continuation-maintenance approaches within the same trial, but the two experimental arms were compared separately to the control group, and not to each other. Interestingly, the PFS benefit appeared to be of the same range of magnitude for continuation gemcitabine and switch to erlotinib. An ongoing trial, ECOG 5508, is comparing continuation bevacizumab versus switch to pemetrexed versus combined pemetrexed/bevacizumab treatment for patients without disease progression after four courses of paclitaxel/carboplatin/bevacizumab. Importantly, overall, maintenance studies have not shown a significant detrimental (or beneficial) effect on QoL, and the toxicity depended largely on the agent used, but no unexpected side effects were recorded.

Are all patients benefiting from maintenance treatment? Data are quite limited at the present time to aid patient selection. The only robust recommendation is that patients with PS 2 are not appropriate candidates. Tumor biomarkers have been minimally studied in this context, and their utility, based on the SATURN trial and other evidence, would be restricted to favor EGFR TKI maintenance for patients with EGFR-mutated tumors if they have received induction platinum-based-chemotherapy. Secondary analysis of some trials suggested that switch maintenance would provide greater benefit to patients who did not have an objective response to induction treatment. On the contrary, the French and PARAMOUNT trials showed similar benefit for continuation chemotherapy in patients with stable disease as compared with those whose disease responded to initial platinum-based chemotherapy.

**Maintenance Conclusion**

Maintenance therapy represents a useful strategy to improve patient outcomes in selected candidate patients with advanced NSCLC. Potential advantages and disadvantages, including toxicity, of continuation and switch maintenance should be discussed with the patient. Further prospective clinical trials, with intensive biomarker research-endorsed studies, will be essential to enhance the risk-benefit ratio of this kind of therapy.

### Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “I” indicate leadership positions. Relationships marked “L” are those held by an immediate family member; those marked “U” are uncompensated. Relationships marked with an asterisk (*) are participants in ASCO’s Disclosure Management System Pilot; their disclosure is not limited to subject matter under consideration in this article and includes payments to themselves, an immediate family member (I), and/or their institutions (Inst). For information on the pilot program, or to provide feedback, please visit coipilot.asco.org.

**Employment or Leadership Position:** Paul A. Bunn, ApoLogiC (U), (L). Consultant or Advisory Role: Paul A. Bunn, Allos Therapeutics; Boehringer Ingelheim; Globimmune; Luis Paez-Ares, Lilly; Merck Serono; Pfizer; Roche/Genentech. *Frances A. Shepherd, Roche, Lilly, Bidesix, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Boehringer Ingelheim, Recombio.**

**Stock Ownership:** *Frances A. Shepherd, Pfizer, Lilly.**

**Honoraria:** Paul A. Bunn, Amgen; AstraZeneca; Bayer; Bristol-Myers Squibb; Celgene; Daiichi-Sankyo; Genentech; GlaxoSmithKline; Lilly; Merck; Novartis; Pfizer; Sanofi. *Frances A. Shepherd, Roche, Lilly, GlaxoSmithKline.**

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### References


44. 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).


