Maintenance Therapy in Advanced Non-small Cell Lung Cancer

Linda E. Coate, MD, and Frances A. Shepherd, MD, FRCPC

Abstract: Non-small cell lung cancer (NSCLC) is the leading cause of cancer death in the industrialized world, and survival rates for advanced disease remain low with standard platinum-based chemotherapy. One treatment strategy that has been investigated extensively in NSCLC is that of “maintenance” therapy. Options for maintenance include maintaining response to initial therapy by continuing the initial combination chemotherapy regimen, continuing only single agent chemotherapy, or by introducing a new agent. Treatments that have been studied in randomized trials to date include chemotherapy, molecularly targeted agents, and immunotherapy approaches. After the development of multiple new agents that show activity in NSCLC and have a tolerable side effect profile, there has been increasing interest recently in this treatment strategy. In this study, we examine the evolution of this strategy by reviewing trials investigating the main treatment paradigms used in maintenance therapy for NSCLC.

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Non-small cell lung cancer (NSCLC) is the leading cause of cancer death in the industrialized world. The majority of patients present with advanced disease for which curative therapy is not available. The current standard of care for treatment of advanced stage NSCLC is platinum-based doublet chemotherapy, which results in modest prolongation of survival and improvement in cancer-related symptoms, but 5% long-term survival at 5 years. Therefore, it is clear that there is scope for improving the current treatment paradigm.

Maintenance therapy is one strategy that has been investigated extensively in recent years as a way of improving outcomes in patients with NSCLC. The challenges that lie in interpreting the literature come from the heterogeneity of studies of maintenance chemotherapy and the lack of consensus with respect to what constitutes maintenance treatment. This heterogeneity has become even more complex with the introduction of molecularly targeted therapy for NSCLC.

For the purpose of this review, we have grouped studies of maintenance chemotherapy under broad headings in an effort to compare and contrast similar trials. The options for maintenance chemotherapy in NSCLC include (1) continuing induction chemotherapy for more cycles than the standard (either by administering a predefined number of “extra” cycles or continuing induction therapy until progression), (2) continuing only the nonplatinum component of induction therapy, and (3) switching to a different cytotoxic chemotherapy agent after induction therapy.

With respect to molecularly targeted therapies, the options include (1) continuing the same targeted therapy that was delivered concurrently with induction chemotherapy after completion of four to six cycles of chemotherapy, (2) introducing a second molecularly targeted agent after completion of the chemotherapy phase, and (3) switching to a new targeted agent, after chemotherapy. In addition, there is interest in inducing the immune system after induction chemotherapy, using immunotherapy.

In most trials, maintenance therapy was offered only to patients who had demonstrated complete response (CR) or partial response (PR) or who had achieved stable disease (SD) status in response to four cycles of induction chemotherapy. We have not included studies of “consolidation” chemotherapy after definitive chemoradiation for locally advanced stage IIIA and “dry” IIIB NSCLC, because these studies usually administered only a short course (2–3 cycles) of chemotherapy after radiation and were not designed as long-term maintenance trials. Thus, the focus of this review is mainly on advanced NSCLC, and data presented are from large randomized phase III studies where possible. We have, however, included details of smaller studies, where there is a paucity of higher quality data.

MATERIALS AND METHODS

PubMed was searched using the following key words: non-small cell lung cancer, chemotherapy, maintenance, prolonged, erlotinib, gefitinib, cetuximab, and antiangiogenic. The proceedings of American Society of Clinical Oncology annual meetings and the proceedings of World Conferences on Lung Cancer from 2003 to 2009 were searched using the same keywords. Preference was given to phase III studies. We limited our search to those articles written in the English language.
Continuation of First-Line Induction Chemotherapy

The American Society of Clinical Oncology guideline for the treatment of advanced NSCLC recommends platinum-based chemotherapy to be administered for no more than six cycles in patients with stage IV NSCLC. This recommendation was based on the results of randomized trials that compared shorter versus longer periods of administration of platinum-based chemotherapy.

The largest randomized trials that compared the administration of different numbers of cycles of the initial cytotoxic chemotherapy regimen are summarized in Table 1. The studies varied with respect to the number of cycles in the “standard” arm (three gave 3 cycles and one gave 4 cycles), and three trials administered six cycles in the experimental arm. Only one trial employed a true “maintenance” approach in the experimental arm with continuation of chemotherapy until progression. There are a number of small studies, or studies reported only in abstract form that use this trial design outline, but we have chosen to review in detail only the phase III, peer-reviewed reports.

Socinski et al. performed a phase III study of 230 patients examining treatment with four cycles of carboplatin and paclitaxel versus carboplatin and paclitaxel until progression. All patients were to receive second-line weekly paclitaxel upon progression. The coprimary end points of this study were overall survival (OS) and quality of life (QoL). Interestingly, the median number of treatment cycles on both arms was four, although in the investigational arm, 42% patients received more than four cycles and 18% received eight or more cycles. Furthermore, in the patients randomized to receive four cycles of chemotherapy, only 57% of patients received the full four cycles of treatment planned. The median survival of patients randomized to receive four cycles of chemotherapy and chemotherapy until progression was 6.6 and 8.5 months, respectively (p = 0.63). Regarding QoL, there were no statistical differences between baseline and week 11 QoL scores. There were no significant differences in toxicity between the two arms, with the exception of neurotoxicity. As might be expected, given the recognized side effect profile of paclitaxel, there was significantly more grade 2 to 4 neurotoxicity experienced by patients randomized to continue chemotherapy past four cycles (27% versus 14%, p = 0.02). The authors concluded that there was no benefit to extending chemotherapy beyond four cycles of treatment.

Smith et al. compared three to six cycles of mitomycin, vinblastine, and cisplatin in 308 patients. Only 72% of patients randomized to receive three cycles of chemotherapy completed treatment and less than one-third of patients (31%) received all six cycles of chemotherapy in the experimental arm. Median time to disease progression (TTP) was 5 months for both arms (p = 0.4), and there was no difference in OS (p = 0.2). There were no differences in QoL between the two groups for the first 9 weeks of treatment, but during weeks 9 to 18, patients continuing on chemotherapy reported significantly more fatigue (p = 0.03).

von Plessen et al. randomized 300 patients to receive either three or six cycles of carboplatin and vinorelbine. As in the study by Smith et al., only 78% of patients received all three cycles of chemotherapy in the three-cycle arm, and only 54% of patients received all six cycles of chemotherapy in the six-cycle arm. Although median progression-free survival (PFS) and OS favored the six-cycle arm, the differences were not significant (p = 0.21 for PFS and p = 0.75 for OS). At 18 and 26 weeks follow-up, there were no differences between the groups in palliation of fatigue, pain, or global QoL.

Park et al. performed a study of slightly different design in which 218 Korean patients were randomized to receive either two or four additional cycles of third-generation, platinum-based chemotherapy, after response to only two induction cycles of chemotherapy. This was a noninferiority study, with OS as its primary end point. This study was designed to demonstrate noninferiority in 1-year survival rate with only two additional cycles, using a noninferiority margin of 15%. Again, there was a disparity seen in terms of completed cycles, with 68.4% of patients receiving all six of their planned cycles of chemotherapy, compared with 92.3%...
of patients receiving all four planned cycles. The difference in the 1-year survival rate between the two groups was 3.4% (95% CI, −8.0 to 14.8) and met the predefined criterion for noninferiority. Median TTP was significantly longer at 6.2 months in the six-cycle group, compared with 4.6 months in the four-cycle group \((p = 0.001)\), although there was no difference in OS, with median survivals of 14.9 and 15.9 months \((p = 0.461)\). The authors of this study postulated that the lack of translation to OS benefit may have been due to a dilution effect from second-line chemotherapy, because 62.7% and 74.4% of the six and four cycle groups, respectively, received second-line treatment \((p = 0.26)\). Toxicity rates were similar in both arms. However, QoL analyses revealed that during the time from the completion of cycle 4 to 3 months later, patients treated with four cycles of chemotherapy showed significant improvement in role functioning, compared with those receiving six cycles \((p < 0.05)\). Patients in the four-cycle arm also experienced less nausea and vomiting, mucositis, and dyspnea, than those receiving six cycles \((p < 0.05)\).

It is important to note that the difference in this study, compared with previous studies, is that only patients who responded after two cycles were randomized to continue. This probably explains the overall higher proportion of patients who went on to receive their full complement of planned chemotherapy, and survived longer, in this study, compared with previous studies. The observation that TTP was increased in responding patients provided the impetus for researchers to investigate whether maintenance therapy in stable and responding patients, particularly with more easily tolerated drugs, could result in a benefit in OS.

**Continuing First-Line Single-Agent Induction Chemotherapy without the Platinum Analogue**

It is widely accepted that toxicity from platinum-based doublet chemotherapy is derived mainly from the platinum component, and that most patients cannot tolerate prolonged administration of platinum-based doublets. Nevertheless, the same does not seem to be the case for third-generation single-agent treatment, as demonstrated in the trials of second-line therapy. In the TAX317\(^{11}\) and TAX320 studies,\(^{12}\) as well as trials comparing docetaxel to topotecan\(^{13}\) or pemetrexed,\(^{14}\) the median number of cycles administered was only 3 to 4. However, treatment was allowed to continue to progression or unacceptable toxicity in all of these studies, resulting in an upper range of 14 to 28 cycles in some patients! In view of this degree of tolerability, a recent strategy has been to investigate the value of continued treatment of responding and stable patients with the nonplatinum component of their induction regimen. Trials of this design are summarized in Table 2.

The Central European Cooperative Oncology Group conducted a phase III randomized, multicenter study in 350 patients with advanced NSCLC to evaluate the effect of gemcitabine maintenance therapy, after gemcitabine and cisplatin initial therapy.\(^{15}\) The primary end point of this study was TTP with secondary end points of overall response rate (ORR), response duration, OS, toxicity, and symptom control. Patients who responded (defined as achieving CR, PR, or SD) after four cycles of induction therapy were randomized in a 2:1 fashion to receive maintenance gemcitabine plus best supportive care (BSC) or BSC alone. It should be noted that the Southwest Oncology Group criteria for response, rather than the more stringent and widely accepted Response Evaluation in Solid Tumors (RECIST), were used. Objective response or SD was seen in 257 patients (73%), but only 215 patients (61%) were randomized to gemcitabine maintenance or BSC. Ultimately, 138 patients received maintenance gemcitabine and 68 received BSC. During the maintenance period, patients received a median of three cycles of gemcitabine (range, 0–38 cycles). The median TTP throughout the study was significantly longer on the gem-

### Table 2. Continuing the Nonplatinum Compound After Induction Treatment for Non-small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>Total Patients</th>
<th>Treatment Arms</th>
<th>Number Randomized</th>
<th>Response Rate (%)</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
<th>(p)</th>
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<tbody>
<tr>
<td>Brodowicz et al.(^{15})</td>
<td>Patients who did not progress after 4 cycles of cisplatin and gemcitabine</td>
<td>354</td>
<td>Maintenance gemcitabine vs. Best supportive care</td>
<td>138 gemcitabine</td>
<td>50.7</td>
<td>6.6 mo</td>
<td>13 mo</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Belani et al.(^{16})</td>
<td>Patients who responded after 16 wk on 1 of 3 differing regimens of carboplatin and paclitaxel</td>
<td>401</td>
<td>Maintenance paclitaxel vs. Observation</td>
<td>65 paclitaxel</td>
<td>45.6</td>
<td>5 mo</td>
<td>11 mo</td>
<td></td>
</tr>
<tr>
<td>POI-01-003-050</td>
<td>Patients who did not progress after 4 cycles of carboplatin and gemcitabine</td>
<td>600</td>
<td>Maintenance gemcitabine vs. Best supportive care</td>
<td>332 have been randomized</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR, not reported.
TABLE 3. Trials Introducing New Chemotherapeutic Agents as Maintenance After Induction Therapy for Non-small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Total Patients</th>
<th>Treatment Arms</th>
<th>Number Randomized</th>
<th>Response Rate (%)</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
<th>p</th>
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<tr>
<td>Westeel et al.</td>
<td>Patients responding to 4 cycles of MIC (stage wet IIIB/IV) or 2 cycles of MIC following radiation therapy (stage III)</td>
<td>573</td>
<td>Vinorelbine vs. Observation</td>
<td>91 vinorelbine</td>
<td>NR</td>
<td>5 mo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.3 mo</td>
<td>0.65</td>
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<tr>
<td>Fidias et al.</td>
<td>Patients who did not progress after 4 cycles of induction carboplatin and gemcitabine</td>
<td>566</td>
<td>Docetaxel immediately following induction vs. Docetaxel administered at time of progression</td>
<td>153 immediate treatment vs. 156 treatment at progression</td>
<td>11.7</td>
<td>5.7 mo</td>
<td>12.3 mo</td>
<td>0.85</td>
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<tr>
<td>Belani et al.</td>
<td>Patients who did not progress after 4 cycles induction therapy with a platinum doublet</td>
<td>660</td>
<td>Pemetrexed vs. Placebo</td>
<td>441 pemetrexed</td>
<td>51.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.3 mo</td>
<td>13.4 mo</td>
<td>0.01</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>222 placebo</td>
<td>33.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.6 mo</td>
<td>10.6 mo</td>
<td></td>
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</table>

<sup>a</sup> From date of randomization.
<sup>b</sup> Disease control rate.
NR, not reported.

...citabine arm, 6.6 months versus 5 months on BSC (p < 0.001). For the maintenance period, patients on maintenance gemcitabine also had a significantly longer TTP of 3.6 months versus 2 months (p < 0.001). Patients with a better performance status had significantly longer TTP, both throughout the study and during the maintenance period. The median OS on the gemcitabine arm was 13 months, compared with 11 months on the BSC arm (p = 0.195). The most notable difference between the gemcitabine arm and the BSC arm during the maintenance phase of this study was the need for transfusion (20% of gemcitabine patients versus 6.3% on BSC, p = 0.018). Of note, maintenance gemcitabine was well tolerated and did not result in deterioration in QoL, compared with BSC.

In a North American study, 401 patients were treated with differing schedules of carboplatin and paclitaxel induction therapy for 16 weeks. Responding patients were then randomly assigned to receive maintenance single-agent paclitaxel, 70 mg/m² weekly, or BSC. The primary end point of this study was TTP. Response was seen in 130 of 390 evaluable patients who were then deemed eligible for randomization in the maintenance phase. Of the patients randomized to the treatment arm, 80% completed one full cycle of paclitaxel, but only 23% completed four cycles. The most common reasons for discontinuing paclitaxel were disease progression and adverse events. Median TTP in the paclitaxel arm was 38 weeks versus 29 weeks in the observation arm (p = 0.124) with median survival times of 75 and 60 weeks (p = 0.243), respectively. The 1-year survival rates were 72% and 60% in the paclitaxel and observation arms, respectively, with 2-year rates of 32% and 26% (p value not reported). During maintenance therapy, 86% of patients in the treatment group experienced at least one adverse event, and 45% reported at least one grade 3 or 4 adverse event. The authors of this study concluded that although the results were provocative, the sample size was too small to draw definitive conclusions regarding the clinical utility of low-dose maintenance paclitaxel.

A much larger study randomizing patients responding to initial therapy with carboplatin and gemcitabine to maintenance gemcitabine has completed accrual and results are awaited. Six hundred patients have been recruited, and 332 were randomized to either maintenance gemcitabine or BSC. The end point of this trial is OS, and hence it is expected that more definitive conclusions may be drawn from this study.

Switching to a New Chemotherapy Agent in Responding and Stable Patients

A long upheld tenet of medical oncology practice relates to the Goldie-Coldman hypothesis that even the smallest detectable cancers contain at least one drug-resistant clone and that increasing numbers of resistant clones emerge as tumors grow and progress. Therefore, the best chance of cure would be to use all effective chemotherapy drugs as early as possible in the treatment course. In practice, this has meant using two different non-cross-resistant chemotherapy regimens in alternating cycles. This strategy has been used in the design of recent maintenance trials in NSCLC in which patients are treated with one schedule of induction chemotherapy and then switched to an alternative, non-cross-resistant agent if they respond to or remain stable on initial therapy.

A French study used this design in a trial of 573 patients with stage IIIIB and IV NSCLC who were treated initially with mitomycin, ifosfamide, and cisplatin (MIC). Those with stage IIIIB disease received two cycles of chemotherapy followed by radiation (55–60 Gy in 30 fractions), and those with “wet” IIIIB and IV disease received four cycles of MIC (Table 3). Of 227 patients who responded, 181 were randomized to receive maintenance treatment with weekly...
vinorelbine for 6 months or BSC. The mean duration of therapy was 13.8 weeks, and only 23% of patients completed the full 6 months of vinorelbine. The most common reasons for stopping chemotherapy prematurely were progressive disease (38%) and treatment toxicity (21%). The median survival in both groups was 12.3 months ($p = 0.48$), and the hazard ratios (HRs) for PFS and OS, after adjustment for stage in the vinorelbine arm relative to the observation arm, were $0.77$ ($p = 0.11$) and $1.08$ ($p = 0.65$), respectively. Median PFS from the date of randomization was 5 months in the vinorelbine group and 3 months in the observation group ($p = 0.32$). Differential toxicity between the treatment arms was not reported. However, the use of MIC chemotherapy with radical radiotherapy might be expected to be more toxic than standard platinum doublet chemotherapy alone. This may explain the high percentage of patients who discontinued therapy early, both because of toxicity and patient choice. A more recent study compared the administration of docetaxel immediately after completion of carboplatin and gemcitabine induction chemotherapy with observation and docetaxel given only at the time of documented progression.\textsuperscript{19} After four cycles of gemcitabine and carboplatin, 309 of 566 patients were deemed to be “nonprogressors” and randomized to either immediate or delayed docetaxel. Of the patients randomized to immediate docetaxel, 94.8\% of patients received at least one treatment cycle, whereas only 62.8\% of patients randomized to delayed treatment ever received docetaxel. The most common reasons for not receiving docetaxel on the delayed arm, were disease progression, patient or investigator decision, and death. The median number of cycles of docetaxel administered on both arms of the study was 4.4. PFS was significantly longer for patients treated immediately (HR not reported, $p = 0.0001$). OS also favored the immediate docetaxel arm (median 12.3 versus 9.7 months [HR not reported]), although the difference did not reach statistical significance ($p = 0.0853$). There were no differences in toxicity or QoL between the two treatment groups. The marked discrepancy in the number of patients receiving the planned treatment in the delayed arm was felt by the authors to be due to declining performance status at the time of progression that precluded further treatment. When the survival of the patients who actually received docetaxel in the delayed arm was compared with that of the treated patients in the immediate arm, no major differences were seen. This suggests that when patients stop first-line chemotherapy, they should be followed closely to detect progression early and at a time when they remain fit for further treatment. The fact that the improvement in PFS did not translate into a significant improvement in OS may simply be a result of the fact that the study was underpowered to detect a significant difference.

Pemetrexed has been shown to be noninferior to docetaxel in the second-line treatment of NSCLC and better tolerated.\textsuperscript{14} The drug has also been shown to be well tolerated in the first-line treatment of nonsquamous NSCLC in combination with a platinum analogue.\textsuperscript{20} The JMEN study compared maintenance chemotherapy with pemetrexed to placebo, in stable and responding patients treated initially with one of three platinum-based induction chemotherapy regimens.\textsuperscript{21} Patients who did not progress were randomized in a 2:1 ratio to receive either pemetrexed or placebo, administered on a 21 day cycle. The primary end point was PFS. There were 660 patients randomized and a prespecified analysis by histology was incorporated into the protocol. Of the patients randomized to pemetrexed, 48\% received $\geq$ 6 cycles of chemotherapy and 23\% received $\geq$ 10 cycles of chemotherapy. There was a significant PFS advantage seen in the group as a whole (HR 0.6, $p = 0.00001$). Subgroup analysis revealed that patients with nonsquamous histology had a HR of 0.47 ($p = 0.00001$, interaction $p$ value 0.036). When OS was examined, there was a significant advantage seen in the entire treatment group (HR 0.79, $p = 0.012$). Furthermore, patients with nonsquamous tumors had a median survival advantage of 5 months (15.5 months versus 10.3 months) and a significant OS benefit (HR 0.7, $p = 0.002$, interaction $p$ value 0.033). There were no significant differences in QoL, and toxicity was modest. In the placebo arm, only 19\% of patients went on to receive pemetrexed at any future point. This means that conclusions regarding earlier versus later administration of pemetrexed cannot be drawn from this trial. However, the survival advantage in patients with nonsquamous tumors is compelling, and in such patients who derive good symptom control from the initial administration of chemotherapy, this may be an acceptable treatment paradigm. Two major drug regulatory bodies, the European Medicines Agency and the Federal Drug Authority, have approved pemetrexed as maintenance chemotherapy in nonsquamous NSCLC.

### Maintenance Therapy with Molecularly Targeted Agents

Several molecularly targeted agents are approved for the treatment of NSCLC, most notably, agents targeting angiogenesis\textsuperscript{22} and the epidermal growth factor (EGF) pathway.\textsuperscript{23} In the first-line setting, bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), and cetuximab, an antibody that targets the EGF receptor (EGFR), have been studied in large randomized trials. Modest improvements in ORR, PFS, and OS have been demonstrated in most studies with the addition of these agents to platinum-based chemotherapy doublets.\textsuperscript{24,25} All studies were designed to continue maintenance antibody therapy in responding and stable patients after completion of chemotherapy. Whether this is necessary, or whether it simply adds to cost and the potential for toxicity, is unknown at this time, because there have been no trials in which responding and stable patients were randomized either to stop or to continue treatment. The EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib have been shown to prolong survival when administered as second-line or third-line therapy in advanced NSCLC.\textsuperscript{26} More recently, they have been evaluated as maintenance therapy in earlier stages of NSCLC. The phase III studies of molecularly targeted maintenance therapy are summarized in Table 4.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Number</th>
<th>Treatment</th>
<th>Number Randomized</th>
<th>Primary End Point</th>
<th>Response Rate (%/H11001</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>SATURN31</td>
<td>Patients with advanced NSCLC who did not progress following 4 cycles of a platinum</td>
<td>1949</td>
<td>Erlotinib vs. Placebo</td>
<td>438 vs. placebo</td>
<td>PFS in all patients</td>
<td>11.9</td>
<td>Median not reported</td>
<td>12 mo</td>
<td>&lt;0.0001</td>
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<td></td>
<td>doublet</td>
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<td></td>
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<td>Bevacizumab plus</td>
<td>373 vs. placebo</td>
<td>PFS</td>
<td>NR</td>
<td>4.76 mo</td>
<td>NR</td>
<td>0.0012</td>
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<td></td>
<td>Patients with advanced NSCLC who did not progress following 4 cycles of platinum</td>
<td>1160</td>
<td>Bevacizumab plus</td>
<td>370 vs. placebo</td>
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<td>doublet given with bevacizumab</td>
<td></td>
<td>erlotinib vs. placebo</td>
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<td>Gefitinib vs. Placebo</td>
<td>118 vs. placebo</td>
<td>OS</td>
<td>NR</td>
<td>8.3 mo</td>
<td>23 mo</td>
<td>0.013</td>
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<td>SWOG 0023</td>
<td>Patients with stage III NSCLC who did not progress following 2 cycles cisplatin/etoposide and concurrent TRT followed by 3 cycles of docetaxel</td>
<td>620</td>
<td>Gefitinib vs. placebo</td>
<td>125 placebo</td>
<td>OS</td>
<td>NR</td>
<td>11.7 mo</td>
<td>35 mo</td>
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<td></td>
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<td></td>
<td>Sorafenib vs. Placebo</td>
<td>51 vs. placebo</td>
<td>Proportion of stable and responding patients at 2 mo</td>
<td>49a</td>
<td>3.3 mo</td>
<td>13.1 mo</td>
<td>0.02 (PFS)</td>
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<tr>
<td>ECOG 250140</td>
<td>Previously treated patients with advanced NSCLC who did not progress following 2 cycles of third-line sorafenib</td>
<td>342</td>
<td>Sorafenib vs. Placebo</td>
<td>32 placebo</td>
<td>Proportion of stable and responding patients at 2 mo</td>
<td>49a</td>
<td>2.0 mo</td>
<td>9.7 mo</td>
<td>0.08 (OS)</td>
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<td>Vandetanib vs. Placebo</td>
<td>53 vs. placebo</td>
<td>PFS</td>
<td>NR</td>
<td>2.7 mo</td>
<td>10.6 mo</td>
<td>0.51 (PFS)</td>
</tr>
<tr>
<td>BR.2041</td>
<td>Patients with SCLC responding to treatment with 4–6 cycles platinum based chemotherapy ± TRT and PCI</td>
<td>107</td>
<td>Vandetanib vs. Placebo</td>
<td>54 placebo</td>
<td>PFS</td>
<td>NR</td>
<td>2.8 mo</td>
<td>11.9 mo</td>
<td>0.9 (OS)</td>
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<td></td>
<td>L-BLP25 vs. BSC</td>
<td>66 vs. BSC</td>
<td>Phase II study</td>
<td>NR</td>
<td>17.4 mo</td>
<td>0.11</td>
<td></td>
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<tr>
<td></td>
<td>Patients with advanced NSCLC who did not progress after any first-line chemotherapy</td>
<td>171</td>
<td></td>
<td>68 BSC</td>
<td>Phase II study</td>
<td>NR</td>
<td>13.0 mo</td>
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<td>Nemunaitis et al.</td>
<td>Patients with advanced NSCLC who were required to have completed or refused conventional therapy</td>
<td>75</td>
<td>Three dose levels of belagenpumatucel-L</td>
<td>20 cohort 1 (1.25 × 10^7) 20 cohort 2 (2.5 × 10^7) 21 cohort 3 (5 × 10^7)</td>
<td>Phase II study</td>
<td>Cohort 11/16 Cohort 23/11 Cohort 32/13</td>
<td>NR</td>
<td>39% 1-yr survival cohort 1, 68% 1-yr survival cohorts 2 and 3 combined</td>
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(Continued)
Maintenance Therapy with EGFR Inhibitors After Induction Chemotherapy

Concurrent administration of erlotinib and gefitinib with chemotherapy was evaluated as part of their drug development programs, but their addition to cytotoxic therapy failed to show benefit even though the oral EGFR TKIs were continued as maintenance after chemotherapy in all trials.27–30 Despite this, however, integrating the administration of these agents with cytotoxic chemotherapy as part of a maintenance treatment paradigm has been of interest. Unlike other agents that have been investigated in the maintenance setting, the EGFR TKIs are administered orally and have fewer side effects relative to cytotoxic chemotherapy.

The sequential Tarceva® in unresectable non-small cell lung cancer trial (SATURN) was a large international study in which 1949 patients were treated initially with four cycles of platinum-based chemotherapy.31 Those who did not progress on treatment (n = 889) were randomized to receive either maintenance erlotinib or placebo. The primary end point was PFS, and the patients were stratified by a number of clinical factors as well as EGFR protein expression status assessed by immunohistochemistry and EGFR gene copy assessed by fluorescent in situ hybridization. Both PFS and OS were significantly longer in the erlotinib arm (HR for PFS 0.71, p < 0.0001; HR for OS 0.81, p = 0.0088). Biomarker analysis showed that there was no significant interaction for EGFR protein expression or EGFR copy number. However, patients with EGFR sensitizing mutations in exons 19 or 21 derived significantly greater PFS benefit from maintenance erlotinib (HR 0.10, p < 0.0001) compared with those patients with EGFR wild-type tumors (HR 0.780, p = 0.018). Furthermore, the treatment by mutation interaction test was highly significant (interaction p < 0.001). In contrast, however, these biomarkers did not predict for a differential OS benefit, likely due to cross-over to erlotinib treatment at the time of progression.

Erlotinib maintenance has also been studied in the first-line setting after induction therapy with paclitaxel/carboplatin and the VEGF monoclonal antibody bevacizumab in a study comparing bevacizumab therapy with or without erlotinib after completion of chemotherapy for advanced NSCLC—the ATLAS trial.32 In this global study, 743 stable and responding patients remained on maintenance bevacizumab and were randomized to receive oral erlotinib 150 mg daily or placebo. PFS was significantly longer in the erlotinib arm (HR 0.72, p < 0.001), although the magnitude of the absolute difference in median PFS was only 1 month. The PFS improvement was seen across multiple subgroups, including those defined by sex, histology, age, and smoking status; molecular subgroup analyses have not been reported. OS results are awaited.

Gefitinib also has been assessed as a maintenance treatment in two randomized trials. The European Organization for the Research and Treatment of Cancer 08021 trial was similar in design to the SATURN study. Initially, all stable and responding patients were eligible for study, but the protocol was amended to require evidence of EGFR protein expression by immunohistochemistry. This resulted in a
slowing of recruitment, which ultimately led to study closure before it reached its target accrual. In the Southwest Oncology Group 0023 trial, patients with inoperable stage III NSCLC received induction etoposide and cisplatin chemotherapy administered concurrently with thoracic radiation, followed by consolidation single-agent docetaxel.33 Responding and stable patients then were randomized to receive oral gefitinib (initially 500 mg daily and subsequently 250 mg daily) maintenance or placebo. This trial was stopped early by the data and safety monitoring committee when survival in the active treatment arm was found to be inferior to that of patients on placebo. The authors suggested three possible reasons for this. (1) There were no molecular correlates reported in this study, and the authors suggested there may have been an undetected imbalance in molecular characteristics between the arms. (2) The authors postulated that poststudy treatments may have been different between the two treatment arms, but this was not recorded on this study and no definitive conclusions can be drawn. (3) Radiation was used in this study, which may change EGFR pathway signaling, resulting in the observed inferior survival seen in the gefitinib arm. Without the requisite information to draw these conclusions, it remains difficult to interpret the meaning of this study; however, given the fact that maintenance EGFR TKI in other settings has shown efficacy, the argument that radiation given before administration may in some way alter signaling through the EGFR pathway seems plausible.

Recently, three randomized trials have compared first-line treatment with EGFR TKIs with combination chemotherapy in clinically selected populations,34–36 and one trial has compared gefitinib with chemotherapy in Asian patients with EGFR sensitizing mutations in exons 19 and 21.37 All these trials have demonstrated a PFS advantage for patients treated with the EGFR TKI. In the trials that selected patients based on clinical characteristics, EGFR molecular profiling studies in a subset of patients revealed that the benefit was greatest in patients whose tumors harbored sensitizing EGFR mutations. On closer examination of the survival curves in these studies, it seems that in the sensitive populations, the curves track closely together during the first few months and only start to separate at the approximate time that chemotherapy would cease in the chemotherapy arms. This observation perhaps suggests that the PFS benefit seen in the EGFR TKI arms may have been due to the prolonged administration of the well-tolerated oral agent, or in other words, maintenance therapy.

**Maintenance Therapy with Angiogenesis Inhibitors After Induction Chemotherapy**

The ability of a tumor to initiate and maintain its own blood supply is a hallmark of cancer.38 Therefore, agents that interrupt this process have long been a focus of oncological therapeutic research. Two trials comparing chemotherapy alone with chemotherapy plus bevacizumab, a monoclonal antibody directed against VEGF, showed improvements in ORR and PFS.24,39 In both studies, bevacizumab continued in responding and stable patients after completion of chemotherapy. In the Eastern Cooperative Oncology Group 4599 trial,24 of the 407 patients starting treatment with chemother-apy and bevacizumab, 215 (53%) continued with bevacizumab monotherapy, and of these patients, 107 (50%) received more than five cycles in this maintenance phase. In the second large bevacizumab trial,39 351 patients were randomized to receive high-dose (15 mg/kg) and low-dose (7.5 mg/kg) bevacizumab. The percentages of patients completing six cycles of chemotherapy and bevacizumab were 49% in the low-dose and 45% in the high-dose bevacizumab groups. Of these, 42% and 41% of patients continued single-agent bevacizumab as maintenance treatment after completion of induction therapy. In fact, 94% of patients eligible to receive single-agent bevacizumab were still receiving maintenance therapy at cycle 7.

It is impossible to determine whether or what proportion of the PFS benefit in the bevacizumab arms of these two trials might have come from the maintenance phase of the treatment as neither trial was designed to answer this question. Indeed, the entire PFS and OS benefits of bevacizumab may have come from the higher response rates in the bevacizumab arms reported in all studies and may not have been due to the prolonged administration of this agent. Considering the potential for toxicity and the cost of this drug, the issue of maintenance therapy with bevacizumab is one that deserves further attention.

As discussed above, the ATLAS study32 evaluated the addition of the oral EGFR TKI erlotinib to bevacizumab after induction chemotherapy. Although there was a statistically significant difference in PFS between the bevacizumab/erlotinib arm and the bevacizumab/placebo arm, with a HR of 0.722 (\(p = 0.0012\)), this was at the expense of added toxicity observed in the bevacizumab/erlotinib arm.

In addition to the monoclonal antibodies, there are a number of oral angiogenesis inhibitors directed against VEGF receptor tyrosine kinases, which have been investigated in combination with chemotherapy. All trials performed to date continued the oral angiogenesis inhibitor after treatment with chemotherapy in responding and stable patients. No study has demonstrated a significant PFS or OS benefit to date, and so, at this time, no conclusions can be drawn concerning the potential for benefit from maintenance therapy with these agents. However, the Cancer and Leukemia Group B 30607 trial is designed to address this question. In this randomized phase II study, patients receive four cycles of platinum-based chemotherapy (bevacizumab is allowed in eligible patients), and responding and stable patients are randomized to receive sunitinib 37.5 mg daily or placebo daily. The primary end point is PFS, and cross-over to sunitinib is allowed at the time of progression. This study does not administer sunitinib during the chemotherapy phase.

In a more advanced setting, the Eastern Cooperative Oncology Group conducted a randomized discontinuation design trial in previously treated patients (E2501). All patients received the oral VEGF response TKI sorafenib 400 mg twice daily for 2 months.40 Responding and stable patients then were randomized to receive sorafenib or placebo maintenance therapy. At the time of progression, patients on placebo were allowed to receive sorafenib again. At the 2-month evaluation point, 22% of placebo patients and 35%
of sorafenib patients continued to have stable or responding disease \((p = 0.01)\) with an overall benefit in PFS favoring sorafenib maintenance treatment \((HR \ 0.50, \ p = 0.01)\). The HR for OS also favored sorafenib, even though 61% of patients on the placebo arm crossed over to sorafenib at the time of progression \((HR \ 0.68, \ p = 0.15)\). This is the first study to suggest that maintenance of response with a VEGF TKI may prolong not only PFS but also OS. These results require confirmation in a larger well-powered study.

Although this overview primarily has dealt with NSCLC, there has been one study of maintenance therapy with the dual EGFR and VEGF TKI vandetanib (Zactima, ZD6474, AstraZeneca, Wilmington, DE) in responding and stable patients with small cell lung cancer.\(^{41}\) In this NCIC Clinical Trials Group BR.20 phase II study, 103 patients were randomized to receive oral vandetanib 300 mg daily or placebo. No benefit was observed for either PFS or OS. However, in multivariate analysis, significant interaction was noted for stage showing a benefit from vandetanib in the limited disease subset.

**Immunotherapy as Maintenance Therapy**

Modulating the immune response in lung cancer is a strategy that is being investigated in the maintenance setting in NSCLC. Initial attempts to modulate the immune system in lung cancer were unsuccessful; however, some of the newer agents have shown promise recently and are undergoing evaluation in phase III studies.\(^{42}\) One agent of interest in this setting is the compound t-BLP25 (Stimuvax; Biomira, Alberta, CA). This is a liposome vaccine targeted to the extracellular core peptide of mucin 1 (MUC1). MUC1 is a transmembrane protein expressed on epithelial cells. The function of MUC1 is not known, but in some studies, it has been shown to be a poor prognostic factor in NSCLC.\(^{45}\) When the results are examined in specific patient subsets. For example, in the trial by Belani et al.,\(^{21}\) the median survival benefit was only 2.8 months, with a HR of 0.79 \((CI \ 95\% \ 0.65-0.95)\), in patients treated with maintenance pemetrexed therapy. However, when the subgroup of patients with nonsquamous histology was examined, the median survival advantage for the treated group increased to 5.2 months, with a HR of 0.70 \((95\% \ CI, \ 0.56-0.88)\). This median survival benefit is larger than that reported in any other studies to date for any chemotherapeutic or molecularly targeted agent in the first-line treatment of NSCLC, and so it cannot be ignored. Furthermore, maintenance pemetrexed was well tolerated, and maintenance therapy was not associated with deterioration in QoL in this study. Thus, this may present an attractive treatment strategy for patients with nonsquamous histology, but before its wide-spread acceptance, further study of the cost implications of this approach must be undertaken.

It is interesting that in the trial by Fidias et al.,\(^{19}\) patients in the safety population who actually received second-line therapy with docetaxel in the “delayed” arm had the same OS as those patients receiving chemotherapy up front. The relative “fall-off” of patients from the delayed group was what caused the delayed group to do less well than those treated up front. This suggests that although there are some patients who safely may receive a treatment holiday after successful induction therapy, other patients will progress quickly after discontinuation of treatment, and a declining performance status as a result of progressive disease may result in those patients never receiving second-line therapy.

**DISCUSSION**

A recent meta-analysis\(^{48}\) confirmed that maintenance chemotherapy in NSCLC improved PFS; less clear was the effect of maintenance chemotherapy on OS. It is worth noting, however, that this meta-analysis did not include any trials of molecularly target agents, and it included some trials discussed above that used relatively outmoded and toxic therapies.

In reality, when the survival benefit derived by unslected patients in maintenance chemotherapy and maintenance molecular therapy trials is examined critically, the benefits must be considered modest, at best, particularly when offset against the cost, toxicity, and inconvenience for patients. However, the data become somewhat more compelling when the results are examined in specific patient subsets. For example, in the trial by Belani et al.,\(^{21}\) the median survival benefit was only 2.8 months, with a HR of 0.79 \((CI \ 95\% \ 0.65-0.95)\), in patients treated with maintenance pemetrexed therapy. However, when the subgroup of patients with nonsquamous histology was examined, the median survival advantage for the treated group increased to 5.2 months, with a HR of 0.70 \((95\% \ CI, \ 0.56-0.88)\). This median survival benefit is larger than that reported in any other studies to date for any chemotherapeutic or molecularly targeted agent in the first-line treatment of NSCLC, and so it cannot be ignored. Furthermore, maintenance pemetrexed was well tolerated, and maintenance therapy was not associated with deterioration in QoL in this study. Thus, this may present an attractive treatment strategy for patients with nonsquamous histology, but before its wide-spread acceptance, further study of the cost implications of this approach must be undertaken.
At present, there are no definitive markers of risk that allow us to identify who these patients might be, but this should be a focus of future research. None of the studies has reported whether patients who achieved confirmed CR or PR status derived greater OS or PFS benefit from maintenance therapy than those who achieved only SD. Furthermore, none of the studies has identified whether degree of response to induction therapy predicts for the likelihood of receiving second-line treatment at the time of progression.

In patients for whom a drug holiday may be appropriate, how long should the holiday be? How best should we monitor patients during a break from treatment? Reaching consensus as to what constitutes the optimal surveillance regimen for those patients who would like a therapeutic break and developing clinical or other biomarkers to predict those patients who fall into a high-risk category for early progression are the two strategies that might go some way toward addressing these therapeutic dilemmas. The converse is also true, because it is difficult to defend exposing patients to treatment toxicity from maintenance chemotherapy if they, in fact, have relatively indolent tumors.

The need to balance benefit and risk is always paramount in oncology, where the therapeutic index is the narrowest of all in clinical medicine. The way in which toxicity is graded is borne from experience of adverse events endured as part of a relatively intense but finite course of treatment. In the maintenance setting, our willingness as clinicians to risk patient exposure to adverse events and the patients’ willingness to accept toxicity may be less, particularly if toxicity may last for months or even years. This is particularly true when the goal of treatment is not cure. What may be acceptable for a number of days as a grade 2 adverse event, experienced a total of six times on a cytotoxic chemotherapy regimen, may not be viewed as acceptable if experienced on an ongoing seemingly endless basis. The degree of toxicity is captured in most trials in a dispassionate objective format. What is often not collected or reported is the effect that toxicity has on patient’s QoL. Therefore, it is critical that all trials of maintenance therapy collect prospective QoL data.

The issue of cost, particularly in these times of global fiscal crisis, and constant political debate in many jurisdictions over health care reform is one that is crucial in any discussion of prolonged, potentially costly treatment. The “one-size-fits all” approach of treating all unselected patients with expensive chemotherapy or molecularly targeted therapies is arguably the approach that is most likely to result in unfavorable pharmacoeconomic profiles for those treatments. To date, most cost-effective analyses have been performed retrospectively, and frequently detailed data have been abstracted from chart review for only a subset of trial patients. The most robust data for any type of analysis come from prospective study, and so, just as with QoL information, health resource utilization data that will allow meaningful cost-effectiveness analyses (CEA) should be collected prospectively in all future maintenance trials. However, a word of caution is necessary when interpreting costs in clinically or molecularly selected subsets of patients, because the cost-effective ratio may not always be that which is expected.

A recent retrospective CEA by Bradbury et al.49 reported differing and favorable economic profiles in patients who demonstrated known clinical and molecular markers of response to treatment with erlotinib. Unexpectedly, however, the cost per year of life gained was not the most favorable in patients with sensitizing mutations in the EGFR gene. This was because these patients derived relatively greater benefit and stayed on treatment longer, thereby incurring considerably higher drug acquisition costs. In view of this, a CEA of the SATURN study would be of considerable interest. Therefore, although the way forward almost undoubtedly lies in personalizing medicine, both to benefit the patients most likely to respond and to spend our health dollar wisely, the true cost savings may arise from not treating those patients who derive no benefit or only marginal benefit.

The mode of treatment delivery is always a consideration, and this is especially true when treatment is prolonged. Patients may prefer oral agents rather than the inconvenience of adhering to an intravenous administration schedule,50 and utilization of oral agents may also mean cost savings from allied costs associated with intravenous regimens.

**CONCLUSION**

The evolution of maintenance therapy has reached an interesting point and we seem to be poised on the verge of a paradigm shift. What constitutes the optimal maintenance treatment strategy is yet to be determined, because there have been no comparative trials of maintenance chemotherapeutic agents against other chemotherapy drugs or against targeted agents. Similarly, the duration of monoclonal antibody therapy has yet to be studied in NSCLC, yet maintenance of these agents has become standard of care after completion of first-line chemotherapy. The trials of pemetrexed and gefitinib suggest that we should be selecting patients based on their clinical and molecular profiles to maximize patient benefit and to reduce the risk of unnecessary toxicity and cost. Retrospective analyses of the reported trials should try to identify those patients at greatest risk from stopping treatment. There is also a need for studies to evaluate patient willingness to receive maintenance therapy, and for those who select to discontinue therapy, there is a need for consensus on surveillance algorithms.

**REFERENCES**


47. Available at: http://clinicaltrials.gov/ct2/show/NCT00676507.

