Maintenance and Consolidation Therapy in Patients with Unresectable Stage III/IV Non-Small Cell Lung Cancer

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The article discusses L-BLP25 (Merck KGaA, Darmstadt, Germany) as an investigational treatment for non-small cell lung cancer.

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ABSTRACT

Globally, lung cancer is the leading cause of cancer-related mortality. Current chemotherapy combinations for the first-line treatment of advanced disease (stage IIIB with malignant pleural effusion/stage IV) and chemoradiotherapy regimens for the treatment of unresectable locally advanced disease (stage IIIA and IIIB without malignant pleural effusion) appear to have reached an efficacy plateau. The addition of new compounds including targeted agents to standard first-line cytotoxic doublets, administered concurrently and/or as maintenance therapy in patients who have not experienced disease progression after such treatment, has been shown to improve efficacy beyond this plateau in patients with advanced disease. However, to date, such approaches have been less successful in the treatment of patients with unresectable locally advanced stage III disease. The purpose of this review is to summarize the data from recent randomized phase III studies involving agents administered as maintenance or consolidation therapy in the treatment of unresectable stage III/IV non-small cell lung cancer (NSCLC). A possible alternative approach to the use of cytotoxic or molecularly targeted agents in this setting is the administration of therapeutic anticancer vaccines, which are designed to stimulate a host immunological response against the tumor. Current data in relation to the potential of vaccine therapy for NSCLC are therefore also reviewed, with a particular focus on belagenpumatucel-L and L-BLP25 vaccines, which are currently undergoing phase III evaluation as maintenance therapies in patients with unresectable stage III/IV NSCLC who have tumor control following first-line therapy. The Oncologist 2010;15:1034–1042

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INTRODUCTION
Globally, lung cancer remains the most common cancer and the leading cause of cancer-related mortality [1]. In Europe alone, it was estimated that there were 334,800 deaths attributable to the disease in 2006 [2] and the European mean age-adjusted 5-year survival rate for patients diagnosed between 2000 and 2002 was a disappointing 10.9% [3]. Approximately 80% of tumors are of the non-small cell lung cancer (NSCLC) subtype [4] (predominantly squamous cell carcinomas, adenocarcinomas, and large cell carcinomas). Clinicopathological stage at diagnosis assessed according to the International System for Staging Lung Cancer based on tumor node metastasis status remains a key predictor of survival time [5].

Patients with early-stage NSCLC may be cured by surgical resection, with adjuvant chemotherapy significantly improving relapse-free and overall survival in this setting compared with surgery alone [6]. However, largely as a consequence of the lack of symptoms during the early stages and the absence of a proven screening technology, most patients with NSCLC currently present with unresectable disease either locally advanced (stage III) or metastatic to distant sites (stage IV) [7, 8].

Standard first-line treatment for patients of good performance status with advanced NSCLC (stage IIIB with malignant pleural effusion or stage IV on the previous staging system, now both included as stage IV in the revised system [8]) remains palliative chemotherapy. This generally comprises one of several equally effective cytotoxic doublets, which include a platinum analogue combined with either vinorelbine, gemcitabine, a taxane, or for patients with nonsquamous disease, pemetrexed [9–11]. The addition of a targeted agent (either cetuximab or bevacizumab) to such regimens has been shown to significantly improve overall survival for certain combinations compared with the same chemotherapy alone [12, 13] but not for others [14, 15]. Standard treatment for patients with stage III disease, which is not associated with malignant pleural effusion but which is unresectable, comprises chemotherapy combined with thoracic radiation (chemoradiotherapy) [16–18]. Whether the efficacy of such approaches can be improved by the use of maintenance therapy has recently been investigated in a series of studies. The purpose of this review is to summarize phase III study data relating to maintenance and consolidation therapy for unresectable stage III/IV NSCLC.

MAINTENANCE AND CONSOLIDATION THERAPIES FOR UNRESECTABLE NSCLC
Maintenance therapy has been defined as treatment that is administered after the end of a defined number of chemotherapy cycles, in patients whose tumor has been controlled, and which continues typically until the occurrence of unacceptable toxicity or disease progression. In contrast, when postchemotherapy systemic treatment is continued instead for a fixed period of time/number of cycles, it is termed consolidation therapy. A further distinction may be drawn in relation to whether the agents used in maintenance or consolidation therapy have been administered in the first-line combination (or have an essentially similar mode of action to one of those agents) or whether they have a different mode of action. In the latter case, such therapy may be termed early second-line treatment [19]. However, while these different classifications may help to define the nature of particular studies, perhaps the most important point to make is that agents used in long-term maintenance therapy will probably need to be those associated with minimal toxicity, if quality of life for the patient is not to be impacted upon negatively. For consolidation therapy, administered over a defined and typically shorter period of time, it may be that the risk/benefit ratio will permit the use of agents that are associated with higher levels of toxicity.

ADVANCED NSCLC
As a substantial fraction of patients with advanced NSCLC will not receive second-line treatments, commonly because of rapid disease progression and a corresponding drop in performance status, attention has turned increasingly to the role of consolidation and maintenance therapy in improving overall survival times in this setting [20]. Targeted therapies are also increasingly becoming the focus of clinical research in the treatment of advanced NSCLC [21]. Randomized studies have demonstrated that the addition of targeted agents to standard first-line regimens and their continued administration as maintenance therapies or the use of particular agents as maintenance therapy following standard first-line treatment are both effective strategies in relation to improving overall survival.

CYTOTOXIC AGENTS AS CONSOLIDATION OR MAINTENANCE THERAPIES
The optimum timing of second-line therapy was explored in a phase III randomized study in which patients with stage IIIB with pleural effusion or stage IV NSCLC received a planned four cycles of gemcitabine plus carboplatin as first-line treatment [22]. The 309 on-study patients who did not have disease progression at this point were randomized to receive immediate docetaxel consolidation therapy (six cycles maximum) or best supportive care (BSC) until disease progression, at which time and if fit enough, they received the same docetaxel regimen (delayed docetaxel). Although toxicity profiles were broadly comparable and quality of
life not significantly different between patients in the immediate versus delayed docetaxel groups, progression-free survival (PFS) was significantly longer for patients in the immediate docetaxel group (median 5.7 versus 2.7 months, p = .0001). There was also a trend for superior survival for patients in this arm (median 12.3 versus 9.7 months in the delayed docetaxel arm, p = .085).

Maintenance therapy with a cytotoxic agent was also shown to be an effective approach in the randomized, double-blind phase III JMEM study comparing the antifolate compound pemetrexed plus BSC with placebo plus BSC in 663 patients with advanced (stage IIIB/IV) NSCLC who had not progressed on four cycles of platinum-based chemotherapy which did not include pemetrexed [23]. The administration of pemetrexed resulted in improved overall survival (median 13.4 versus 10.6 months, hazard ratio [HR] 0.79, p = .012), response rate, and PFS in patients who had responded to the initial chemotherapy. A clear interaction between treatment efficacy in relation to overall survival time and histology was apparent (p = .033) with benefit seen predominantly in patients with nonsquamous histology (median 15.5 versus 10.3 months, respectively, HR, 0.70, p = .002).

Although both of these studies confirmed that the administration of consolidation or maintenance therapy with an agent not used in the first-line treatment regimen improved clinical outcome, neither trial was informative as to whether the benefit was primarily as a consequence of increased anticancer activity of the three-drug sequential regimens or whether it was essentially due to more patients being exposed to three treatment agents as a consequence of early second-line therapy. Indeed, in the study evaluating immediate versus delayed docetaxel, median survival for patients who actually received docetaxel in the delayed arm (63%) was the same at 12.5 months as that of the safety population of patients in the immediate docetaxel arm, suggesting that the second explanation may have been more likely in this particular case. However, regardless of the underlying mechanism, the key point is that these particular treatment strategies appeared to improve clinical outcome in this setting, with pemetrexed maintenance therapy significantly improving overall survival compared with placebo.

**Targeted Agents as Maintenance Therapies**

A series of randomized studies have clinically validated the epidermal growth factor receptor (EGFR) as an effective molecular target in relation to the treatment of advanced NSCLC. In the first-line setting, the phase III FLEX (First-Line Erbitux in Lung Cancer) study included 1125 randomized patients with EGFR-expressing stage IIIB disease with malignant pleural effusion or stage IV disease who were unselected according to tumor histology. The study demonstrated that the addition of the EGFR-specific monoclonal antibody cetuximab to cisplatin and vinorelbine followed by cetuximab maintenance therapy significantly improved survival when compared with cisplatin and vinorelbine alone (median 11.3 versus 10.1 months, HR 0.87, p = .044) [13, 24]. A second study, BMS099 (Bristol-Myers Squibb 099), exploring taxane plus carboplatin with or without cetuximab as first-line treatment for advanced NSCLC, showed a similar overall survival benefit for the addition of cetuximab, (administered concurrently with chemotherapy and as a maintenance treatment until disease progression) to a standard cytotoxic doublet. However, given the number of patients in the study, this difference was not statistically significant (median 9.7 versus 8.4 months, HR 0.89, p = .169) [14].

The vascular endothelial growth factor has also been shown to be an effective therapeutic target in this setting in the Eastern Cooperative Oncology Group (ECOG) 4599 study, which demonstrated that the addition of bevacizumab to paclitaxel plus carboplatin followed by bevacizumab maintenance therapy significantly improved overall survival compared with paclitaxel plus carboplatin alone in the first-line treatment of advanced NSCLC (median 12.3 versus 10.3 months, HR 0.79, p = .003) [12]. Another study, AVAiL (Avastin in Lung Study), exploring cisplatin plus gemcitabine with either bevacizumab, at 7.5 or 15 mg/kg, or placebo (each administered concurrently with chemotherapy and as a maintenance treatment until disease progression), demonstrated a significant improvement in PFS in the primary analysis for patients with advanced NSCLC receiving chemotherapy plus bevacizumab at both dose levels compared with chemotherapy plus placebo [25]. However, an overall survival benefit was not demonstrated for either the 7.5 or 15 mg/kg bevacizumab regimens (median 13.6 and 13.4 versus 13.1 months, HR 0.93 and HR 1.03, p = .420 and p = .761, respectively) [15].

The design of these four randomized studies does not allow for conclusions to be drawn as to whether the clinical benefit associated with the addition of the targeted agent to standard first-line chemotherapy was conferred during the chemotherapy, maintenance, or indeed both phases of treatment. To specifically demonstrate that a particular agent is effective as maintenance therapy, alternative study designs are required.

The double-blind randomized phase III Sequential Tarceva in Unresectable NSCLC (SATURN) study of maintenance erlotinib (an EGFR tyrosine kinase inhibitor [TKI]) versus placebo in patients with advanced, recurrent, or metastatic disease who had not progressed following...
four cycles of platinum-based first-line chemotherapy demonstrated that erlotinib maintenance therapy significantly reduced the risk of disease progression (median PFS 12.3 versus 11.1 weeks, HR 0.71, \( p < .0001 \)), improved disease control, and improved overall survival (HR 0.81, \( p = .009 \)) in this setting compared with placebo [26, 27]. Another phase III study also showed promising results for a second EGFR TKI, gefitinib, administered as maintenance therapy [28]. In the West Japan Thoracic Oncology Group (WJ-TOG)0203 study, 604 chemotherapy-naive patients with advanced (stage IIIB/IV) NSCLC were randomized to receive three cycles of platinum doublet chemotherapy followed by gefitinib daily, or six cycles of platinum doublet chemotherapy alone. PFS was significantly longer in the gefitinib maintenance arm (median 4.6 versus 4.3 months, HR 0.68, \( p < .001 \)) and overall survival significantly improved in patients in this arm with adenocarcinoma (median 15.4 versus 14.3 months, HR 0.79, \( p = .03 \)). Gefitinib maintenance therapy failed to significantly improve overall survival for the full population compared with platinum doublet chemotherapy alone [28].

The potential of maintenance therapy to improve outcomes in the treatment of advanced disease has been further demonstrated in the randomized double-blind phase IIIb ATLAS study. Seven hundred sixty-eight patients with locally advanced, recurrent, or metastatic (stage IIIb/IV) nonsquamous NSCLC who had received four cycles of first-line chemotherapy plus bevacizumab and who had not experienced disease progression or unacceptable toxicity were randomized to receive bevacizumab plus erlotinib or bevacizumab plus placebo as maintenance therapy. The trial was halted at the second planned interim efficacy analysis after a significant improvement in PFS (median 4.8 versus 3.7 months, HR 0.72, \( p = .001 \)) was demonstrated in the bevacizumab plus erlotinib arm [29].

**Unresectable Stage III NSCLC**

Patients with unresectable locally advanced stage III disease (IIIA and IIIB without malignant pleural effusion) also comprise an important target population in clinical research. Although there is a better chance of a positive outcome in such patients given that overt disease is limited to the thoracic cavity, it has become clear in recent years that a plateau has been reached in terms of what is achievable with chemotherapy and radiotherapy in this setting. Survival figures currently observed in selected patients with stage III NSCLC treated with concurrent chemoradiotherapy are in the order of a median survival time of 17 months and a 3-year survival rate of 25% [30]. Although these clearly represent an improvement in outlook from only a few years ago, novel strategies which improve survival while not increasing toxicity to unacceptable levels are urgently needed. To this end, attention has turned to whether the incorporation of consolidation or maintenance therapy into treatment regimens for stage III disease might improve clinical outcome. Although current data are somewhat limited, several randomized studies have been carried out in this setting.

Subsequent to the Southwest Oncology Group (SWOG) S9504 phase II study, which demonstrated the feasibility and tolerability of docetaxel as consolidation therapy following concurrent chemoradiotherapy in patients with stage IIIB disease [31], the potential of this approach was further investigated in a phase III study conducted by the Hoosier Oncology Group and US Oncology [32]. Eligible patients with unresectable stage IIIA or IIIB NSCLC initially received 50 mg/m² cisplatin days 1 and 8 plus 50 mg/m² etoposide days 1–5, every 28 days for two cycles, administered concurrently with chest radiation (33 fractions to 59.40 Gy). One hundred forty-seven patients who did not experience progression were subsequently randomly assigned to 75 mg/m² docetaxel every 21 days in three cycles or observation. During the 9 weeks following randomization, more patients were hospitalized in the docetaxel compared with the observation arm (29% versus 8%). Incidence rates of pneumonitis and infection were also significantly higher in the docetaxel arm and there were four treatment-related deaths. On the basis of evidence of futility following an interim analysis of overall survival time, the data and safety monitoring board recommended the early closure of this study. Median overall survival time was 21.2 months in the docetaxel arm compared with 23.2 months in the observation arm (\( p = .883 \)). Consolidation therapy with docetaxel therefore appeared to have increased toxicity without improving overall survival in this setting.

Another randomized phase III study, SWOG S0023, investigated gefitinib as maintenance therapy following chemoradiotherapy and docetaxel consolidation therapy [33]. Untreated patients with stage III disease received 50 mg/m² cisplatin days 1 and 8 plus 50 mg/m² etoposide days 1–5, every 28 days, for two cycles with concurrent thoracic radiation (total dose 61 Gy). Four to 8 weeks after the completion of radiotherapy, 429 eligible patients without progressive disease were reregistered to receive up to three cycles of 75 mg/m² docetaxel, day 1 every 21 days. Three to 6 weeks after the last dose of docetaxel, 243 eligible patients who had not experienced disease progression were randomly assigned to receive gefitinib maintenance therapy or placebo for 5 years or until the occurrence of disease progression or unacceptable toxicity. The study was subsequently closed early after an unplanned interim analysis.
rejected the hypothesis of a 33% improvement in median survival in the gefitinib arm at the $p = .0015$ level. At a median follow-up time of 27 months, the median overall survival time from the date of random assignment was 23 months in the gefitinib arm compared with 35 months in the placebo arm (HR 0.63, $p = .013$). The reason for the inferior overall survival in the gefitinib arm was not clear and did not appear to be the result of imbalance between the treatment groups in relation to baseline characteristics or toxicity. Indeed, the toxic death rate was only 2% for patients receiving gefitinib compared with 0% for those receiving placebo.

These two phase III studies have therefore proved to be disappointing in that neither docetaxel consolidation therapy or gefitinib maintenance following docetaxel consolidation therapy appear to have improved overall survival in patients with stage III NSCLC who had received chemoradiotherapy. Although other ongoing randomized studies are exploring the role of various targeted agents as maintenance therapy in the treatment of advanced stage IIIB/IV disease, including investigations of sunitinib and ZD6474 (vandetanib) administered following disease control after platinum-based first-line treatment, further studies are investigating the potential of therapeutic vaccines as maintenance treatments. The use of therapeutic vaccines in this setting represents a novel approach and a number of phase III trials are currently under way to assess the potential of this strategy.

**IMMUNOTHERAPY FOR UNRESECTABLE STAGE III/IV NSCLC**

Although tumor-specific immune responses have been detected in patients, for a tumor to have developed to an advanced stage, pre-existing immunity must have been insufficient for tumor eradication. Possible reasons for this poor immunological response include acquired or innate host tolerance to tumor-associated antigens, tumor development in an immunoprivileged site, or the expression of tumor-associated proteins that have suppressed the activity of cytotoxic T lymphocytes [34]. Therapeutic anticancer vaccines are intended to provoke or augment an adaptive immune response to the patient’s tumor cells. There are therefore two challenges associated with developing a successful anticancer vaccine therapy: the identification of a specific antigenic stimulus that will be recognized as immunogenic by the patient’s immune system [35] and the creation of an efficient delivery system to stimulate a sufficiently large immune response to the antigen and thereby yield a clinically relevant result. Two vaccines that exemplify different approaches are currently being investigated in phase III studies as maintenance treatments following chemotherapy or chemoradiotherapy for stage III or IV NSCLC: belagenpumatucel-L in patients with stage III/IV disease and the liposomal vaccine L-BLP25 in patients with unresectable stage III disease. These vaccines are designed to present different antigenic stimuli to the host immune system.

Belagenpumatucel-L is a nonviral vaccine derived from extracts of four allogeneic NSCLC cell lines, which have been transfected with a plasmid encoding a transforming growth factor (TGF)-β2 antisense transgene. The antisense construct was designed to suppress the expression of TGF-β2 within the tumor cells comprising the vaccine and thereby hopefully increase the immunogenicity of this complex preparation. A three-arm phase II study evaluated the safety and efficacy of intradermal immunization with three different dose levels of this vaccine in 75 patients with stage II, III, or IV NSCLC [36]. Belagenpumatucel-L, which was used as an upfront rather than maintenance therapy in this study, was well tolerated and a dose-related survival benefit was demonstrated for patients receiving the higher versus lower doses of the vaccine ($p = .007$). A response rate of 15% was reported for 61 patients with stage IIIB/IV disease. In a subsequent analysis, patients with both a cellular and humoral immune response to this vaccine had improved overall survival compared with those classified as immune response negative (median 32.5 versus 11.6 months, $p = .011$) [37]. An ongoing randomized phase III vaccine study (STOP: Survival, Tumor-free Survival, Overall Survival, and Progression-Free Survival) is comparing the overall survival of patients with stage IIIA (T3, N2 only), IIIB, or IV NSCLC receiving belagenpumatucel-L or placebo. Patients with stable disease or an objective response after first-line platinum-based chemotherapy with or without concomitant radiotherapy will be randomized to receive intradermal belagenpumatucel-L or placebo.

A different basic approach has been employed in the development of the L-BLP25 vaccine. Rather than using an extract of whole tumor cells as a complex antigenic stimulus, the L-BLP25 vaccine is based on a specific protein, mucin 1 (MUC1), which is widely expressed in normal tissues, but which is post-translationally modified in tumor cells to expose a novel antigenic site [38]. MUC1, encoded by the MUC1 gene on human chromosome 1q22, is a heavily glycosylated transmembrane protein that is found on the apical surface of a wide range of normal epithelial cells from different tissues. In tumor cells, the extracellular domain of MUC1 may be abnormally glycosylated, exposing to the host immune system a highly immunogenic core peptide of the protein consisting of a 20-amino acid tandem repeating sequence [39]. L-BLP25 is a liposome-based vaccine consisting of a synthetic 25-amino acid lipopeptide derived
from the tandem repeat region of MUC1, together with the nonspecific adjuvant monophosphoryl lipid A and three different lipids [40]. The use of a liposome-based delivery system was intended to facilitate uptake of the antigenic peptide by antigen-presenting cells, and preclinical studies found that L-BLP25 was indeed capable of inducing a cellular immune response in mice [41].

MUC1 is strongly expressed in normal lung tissue and is commonly expressed in tumors and non-neoplastic lesions (hyperplasia, metaplasia) of the bronchial tissue [42, 43]. The pattern and level of MUC1 expression in tumors has also been associated with poor prognosis in patients with NSCLC [44–47]. Furthermore, the 1-year survival rate was higher in patients with NSCLC who had high compared with low levels of natural MUC1 antibodies [48]. Such observations provided a biological rationale, suggesting that inducing an anticancer immune response to MUC1 using a vaccination strategy might be an effective approach in the treatment of NSCLC. L-BLP25 is the first investigational lung cancer vaccine to enter phase III clinical testing in the treatment of unresectable stage III NSCLC; its structure and proposed mode of action are illustrated in Figure 1.

**CLINICAL TRIALS WITH L-BLP25**

A phase I study which recruited 17 patients with stage IIIB/IV NSCLC demonstrated that L-BLP25 could be safely administered in this setting [49]. Two subsequent phase II studies established an effective dose and schedule [50] and facilitated the design of a randomized phase IIIB trial to evaluate the efficacy and safety of L-BLP25 in patients with stage IIIB/IV NSCLC whose disease responded to or was stable after first-line therapy [51]. A total of 171 patients were enrolled and randomized to receive L-BLP25 with BSC or BSC alone. Patients in the L-BLP25 arm received low-dose cyclophosphamide 3 days prior to treatment with L-BLP25 at 1000 μg/wk for 8 weeks. The primary endpoint of the study was overall survival. After a median follow-up time of 52 months, patients receiving L-BLP25 had a median overall survival time of 17.2 months compared with 13.0 months in the control arm, although this difference did not reach statistical significance (HR 0.75, adjusted p = .085). A stronger trend toward longer overall survival time in the L-BLP-25 compared with the control arm was observed in the subgroup of 65 stage IIIB patients with locoregional disease (median 30.6 versus 13.3 months, HR 0.55; Fig. 2), whereas no benefit from the vaccine was apparent for patients with stage IIIB with malignant pleural effusion/stage IV disease (median 15.1 versus 12.9 months, respectively, HR 0.91) [51; 52, and updated data presented at meeting]. This perhaps indicates that patients with a lower tumor burden may have a greater chance of deriving a significant clinical benefit from this particular immunotherapy. It is conceivable that vaccines based on different antigenic stimuli may work better in particular settings, according to the typical gene expression pattern of the tumor cells and characteristic host immune capability at a given stage of disease. In this respect, the broader antigenic profile of complex cell-based vaccines such as belagenpu-
matucel-L may be more suited to the treatment of advanced stage metastatic disease.

No significant toxicity was reported in the L-BLP25 arm of this study, with grade 1 flu-like symptoms and adverse events related to cyclophosphamide being the most frequent side effects. Quality of life (QoL) analysis revealed a clear advantage for the L-BLP25 over the BSC arm, with more patients in the vaccine arm demonstrating a clinically meaningful improvement or no change in QoL and more patients in the BSC arm demonstrating a clinically meaningful worsening in the trial outcome index [51]. A safety analysis of 16 patients from this study who received L-BLP25 for between 2.0 and 7.7 years concluded that long-term use of the vaccine was without identifiable safety issues and that there was no evidence of autoimmune reactions with prolonged use [53].

The results of this phase II study therefore showed that maintenance therapy with L-BLP25 in patients with unresectable locoregional stage IIIB NSCLC is at least feasible and may have the potential to prolong survival in this patient group. To investigate this hypothesis further, the efficacy and safety of L-BLP25 is now being evaluated in a large phase III study [40]. The multicenter, randomized, double-blind, placebo-controlled Stimulating Targeted Antigenic Responses To NSCLC (START) trial will enroll more than 1,300 patients with stage III NSCLC who have previously completed chemoradiotherapy treatment and who have stable disease or an objective clinical response. Accrual into START is ongoing; if L-BLP25 is found to be effective in this trial, then vaccination could replace watchful waiting as the standard of care following chemoradiotherapy treatment for patients with stage III NSCLC.

CONCLUSIONS
Despite continuing improvements in chemoradiotherapy regimens and the recent clinical validation of particular agents as maintenance treatments in advanced disease, there remains an unmet need for new therapies with clinically proven value in the treatment of unresectable stage III NSCLC. Initial randomized trials of maintenance therapies in this setting have been disappointing. Whether the novel approach of administering therapeutic vaccines to patients with tumor control after first-line chemotherapy or chemoradiotherapy improves survival in patients with stage III and IV disease is also currently being explored in phase III studies. As these studies mature, it will be possible to assess whether the use of anticancer vaccines may be an effective strategy in the treatment of NSCLC.

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