Lung Cancer: New Biological Insights and Recent Therapeutic Advances

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Abstract

Approximately 1.6 million new cases of lung cancer are diagnosed each year throughout the world. In many countries, the mortality related to lung cancer continues to rise. The outcomes for patients with all stages of lung cancer have improved in recent years. The use of systemic therapy in conjunction with local therapy has led to improved cure rates in both resectable and unresectable patient groups. For patients with advanced stage disease, modest but real improvements in overall survival and quality of life have been achieved with systemic chemotherapy. A major focus of research has been the development of molecularly targeted agents and the identification of biomarkers for patient selection. Patients with non-small cell lung cancer with mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase domain achieve response rates of greater than 70% and superior progression-free survival when treated with an EGFR tyrosine kinase inhibitor compared with standard chemotherapy. This has now emerged as the preferred therapeutic approach for the subset of patients with a mutation in exons 19 or 21 of the EGFR. Another promising targeted approach involves the use of an anaplastic lymphoma kinase (ALK) inhibitor in patients with a translocation involving the echinoderm microtubule-associated protein-like 4 (EML4) and -ALK genes. Finally, a paradigm shift in favor of maintenance therapy for patients with advanced stage disease has gained strength from recent data. All of these advances have been made possible by developing a greater understanding of the biology, the discovery of novel anticancer agents, and improved supportive care measures. This article reviews the major strides made in the treatment of lung cancer in the recent past. CA Cancer J Clin 2011;61:91–112.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with nearly 1.4 million deaths each year. Of the 1.6 million new cases of lung cancer diagnosed each year, approximately 220,000 are diagnosed in the United States. There has been an overall decrease in the incidence of lung cancer in men, although in women this trend has only been noted very recently in the United States. In contrast, in many parts of the world the number of cases and deaths related to lung cancer is on the rise. It is also increasingly becoming a disease of the elderly, with a median age at diagnosis of approximately 70 years. Lung cancer is diagnosed at an advanced stage in a majority of patients, which is the primary reason behind the high mortality rate associated with this disease. Early detection continues to be an elusive goal, and substantial numbers of patients diagnosed with localized disease are often unsuitable for curative surgical procedures due to concomitant medical illness.

Non-small cell lung cancer (NSCLC), which includes adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and bronchioalveolar carcinoma, accounts for nearly 85% of all cases of lung cancer. Cigarette smoking is the most common etiological factor, accounting for nearly 85% of patients with lung cancer.

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Nonetheless, the number of cases of lung cancer diagnosed in never-smokers has also increased in recent times. Despite the positive trend of a reduction in smoking habits in the general population, it is estimated that lung cancer will continue to be a major health problem for the next 40 to 50 years. Small cell lung cancer (SCLC) incidence relative to NSCLC has decreased in recent years, although it continues to be a lethal disease for the majority of patients.

In the past few decades, lung cancer has gone from an untreatable disease with dismal outcomes to one that has a number of novel therapeutic options, and more recently, to a disease for which individualized treatment options have become available. There has been a tremendous increase in the understanding of the biological mechanisms that underlie lung cancer development, which has led to the identification of novel therapeutic targets. In addition to conventional clinical factors, treatment decisions can now be made based on biological factors related to the tumor, at least for a subset of patients with NSCLC. There is a greater emphasis on identifying dominant molecular pathways that drive an individual patient’s tumor. This has paved the way for the evaluation of novel strategies to modulate such molecular targets for the treatment of NSCLC. In addition to molecularly targeted approaches, newer chemotherapeutic agents with a favorable therapeutic index have also been developed. This has enhanced the ability to make refinements to well-established systemic therapy strategies and to develop newer methods to achieve disease control. This article reviews the recent developments in the treatment of lung cancer that have contributed to improved patient outcomes.

**Staging of Lung Cancer**

Under the leadership and coordination of the International Association for the Study of Lung Cancer (IASLC), an updated staging manual for lung cancer (American Joint Committee on Cancer, seventh edition) was published and adopted for general use in early 2010. The new staging system incorporates major changes that allow for an improved ability to determine overall prognosis. The “T” status of tumors is now categorized into less than 2 cm, 2 cm to 3 cm, 3 cm to 5 cm, 5 cm to 7 cm, and greater than 7 cm. The lymph node descriptors remain unchanged in the new staging system. Metastatic disease has been further divided into M1a disease or M1b disease based on the presence or absence of extrathoracic disease. Malignant pleural effusion has been upstaged to M1a based on its poorer prognosis compared with the rest of the T4 descriptors from the older system. The other major change involves the categorization of additional nodules in the same lobe and other ipsilateral lobes as T3 and T4, respectively. Although the overall treatment guidelines are not likely to be affected, this new stage categorization will lead to improved prognostic determination and better stratification of patients on randomized clinical trials.

**Biology of Lung Cancer**

Advanced molecular biology techniques have greatly accelerated the understanding of cancer biology. The application of such technology to lung cancer research has led to the recognition of lung cancer as a molecularly diverse set of tumor types whose only commonality is their origination in the lung. Lung cancer classification is far more complex than the simplistic grouping into small cell and non-small cell variants that was once thought to represent a homogeneous tumor population with a comparable outcome when treated in a similar fashion. It is now well accepted that the histologic subdivision of lung cancer based on light microscopy uses only one of many phenotypic manifestations of the genetic changes that underlie lung cancer development. Histologic appearance may accurately predict biologic behavior as noted with the clinically indolent course of a pure bronchioloalveolar-type carcinoma relative to an invasive lung adenocarcinoma or the malignant course of a sarcomatoid variant of NSCLC, now known to represent epithelial-mesenchymal transition, a hallmark of cancer dedifferentiation. More important to the understanding and management of lung cancer, however, is the crystallization of the theory that, similar to other cancer types, lung cancer development is a result of a stepwise progression of malignant transformation of normal respiratory epithelium. This transformation is driven by the cumulative effect of genetic alterations induced predominantly by inhaled carcinogens from tobacco smoke, an implicated etiologic factor in more than 85% of all cases of lung cancer diagnosed in the
Western world.\textsuperscript{16,17} The Noguchi classification of lung adenocarcinoma is a pioneering effort to relate tumor histology with clinical and radiologic characteristics.\textsuperscript{12,15} This has resulted in the identification of atypical adenomatous hyperplasia and adenocarcinoma in situ as preinvasive neoplastic lung lesions that serve as precursors to invasive lung adenocarcinoma through a progressive transformation into the type A, B, and C adenocarcinomas with lepidic growth (referring to growth along alveolar structures) characterized by an increasing component of invasive carcinoma but showing excellent survival outcome, and the type D, E, and F solid–type adenocarcinomas with a well-recognized poor prognosis.\textsuperscript{12,15} Well-designed molecular biology investigations over the last decade have also led to the recognition that genetic and molecular alterations in the host as well as in the lung cancer cells drive the biology of the tumor. These changes represent important footprints of biologic drivers and can be used for tumor classification,\textsuperscript{9-11,18-20} response prediction,\textsuperscript{19} and assigning prognosis,\textsuperscript{18,21-23} or even as targets of therapy. Molecular prognostic models of lung cancer have been developed that are based on genomic signatures of the disease,\textsuperscript{18-22} or based on the interplay between several prognostic markers that have been determined to be individually important in prognosis.\textsuperscript{24} A very diverse range of genetic abnormalities has been described in lung cancer. Genome-Wide Association Studies revealed a strong association between lung cancer risk and a single-nucleotide polymorphism variant in the region of chromosome 15q25.1, which contains the nicotinic acetylcholine receptor genes \textit{(CHRNA5, CHRNA3, and CHRNBA4)}, thereby providing a genetic basis for variation in susceptibility to the addictive potential of tobacco products, the foremost etiology of lung cancer.\textsuperscript{25-28} Further support for an important role for host biology in lung cancer came from the observation that polymorphisms in genes encoding detoxifying enzymes, glutathione S-transferases (glutathione S-transferase Mu 1 [GSTM1], glutathione S-transferase M3 [GSTM3], glutathione S-transferase P [GSTP1], and glutathione S-transferase theta-1 [GSTT1]), may predispose toward lung cancer development because of an increased susceptibility to the effect of tobacco carcinogens.\textsuperscript{29-31}

The most frequently described acquired genetic aberrations within the tumor involve the tumor protein \textit{p53} (TP53), \textit{KRAS}, fragile histidine triad (\textit{FHIT}), epidermal growth factor receptor (\textit{EGFR}), cyclin-dependent kinase 2a (\textit{CDKN2}), \textit{LKB1}, retinoblastoma (\textit{RB}), and \textit{Myc} genes.\textsuperscript{32-34} Larger genomic mishaps such as chromosomal deletions involving the short arms of chromosomes 1, 3, and 9 (del 1p36, del 3p, and del 9p, respectively) are also frequently observed in different lung cancer histologic subtypes and stages.\textsuperscript{35-38} More recently, inversion translocation of the echinoderm microtubule–associated protein-like 4 (\textit{EMLA4}) and anaplastic lymphoma kinase (\textit{ALK}) genes on chromosome 2 (2p21 and 2p23) was shown to characterize a small subset of NSCLC with a characteristic clinical and histologic profile.\textsuperscript{39} The discovery of other molecularly defined lung cancer subsets is likely to be hastened by this finding.

Epigenetic modulation leading to changes in the level of DNA methylation or histone acetylation may result in aberrant gene function. The role of epigenetic changes in lung cancer biology is underscored by the finding that aberrant tumor protein p16 (TP16) gene promoter methylation in sputum precedes the detection of lung cancer for up to 3 years in smokers and may therefore represent an early molecular event in the biology of this disease.\textsuperscript{42} Furthermore, promoter hypermethylation of cadherin 13 (CDH13), TP16, RASSFIA, and APC in patients with early stage NSCLC correlated with early disease recurrence.\textsuperscript{43} Given the regulatory role of chromatin structure in gene expression and the implication of chromatin structural alteration in cancer development and progression, markers of epigenetic changes provide early warning signs of cancer and may also predict the benefit of epigenetic therapy in lung cancer.\textsuperscript{44-47} The increasing number of molecular, genetic, and histologic alterations characteristic of lung cancer has now been woven into a multistep carcinogenesis model for this cancer type (Fig. 1).\textsuperscript{15} These biologic advances will have a major impact on the development of innovative treatment options for lung cancer in the years to come.

The development of high-throughput NexGen sequencing capability and advanced data information management systems have further advanced the integration of genomic information into cancer management from a mere promise to a realistic possibility in the very near future.\textsuperscript{48} The Cancer Genome Atlas (TCGA) is a gargantuan collaborative project built on these technological advancements. It is sponsored by the National Cancer Institute (NCI) and the...
National Human Genome Research Institute of the National Institutes of Health to establish genomic changes in the 20 most common cancer types with the goal of facilitating the understanding and ability to exploit genomic changes in cancer for diagnostic, prognostic, and therapeutic endpoints. The TCGA began with ovarian cancer and glioblastoma with plans to expand to other tumor types including lung cancer. Another high-impact research endeavor is the Lung Cancer Mutation Consortium study, which was designed to perform focused screening for driver oncogenic mutations in 1000 patients with stage IIIB/IV NSCLC (ClinicalTrials.gov identifier NCT01014286). Although this is a much more modest effort than the TCGA, it has specific goals achievable in the short to medium term leading to a better understanding of the complex biology of lung cancer and the identification of predictive, prognostic markers as well as potential new treatment targets.

**Early Stage NSCLC**

Approximately one-third of the patients with NSCLC present with early stage disease. Surgical resection is considered the standard therapy for patients with stage I, II, and certain subsets of stage IIIA NSCLC. Among patients with early stage NSCLC, approximately 40% are not candidates for surgery due to the presence of medical comorbid illness. Removal of an entire lobe of the lung or, in some instances, the entire lung is the recommended approach for patients with surgically resectable disease. Sublobar resections are associated with a higher incidence of local recurrence. In recent years, studies have been undertaken to define the subset of patients that could be optimally treated with sublobar resection. Advances in surgical techniques including minimally invasive surgery have led to a reduction in the morbidity and mortality associated with surgery for lung cancer.49-51

Until the earlier part of this decade, surgery alone remained the standard of care for patients with early stage NSCLC. The use of postoperative radiotherapy was noted to be detrimental to survival in a meta-analysis that analyzed studies conducted in the past 3 decades.52,53 The included time period included the era in which older radiation techniques and larger radiation ports were in common use. In the absence of prospective studies to address the role of radiation in the postoperative setting, it is not recommended for the routine care of patients who underwent a
TABLE 1. Randomized Trials of Adjuvant Chemotherapy for Early Stage NSCLC

| STUDY                                      | REGIMEN                               | MEDIAN OR PFS | MEDIAN OR 5-YEAR OS |
|--------------------------------------------|----------------------------------------|---------------|---------------------|
| Adjuvant Lung Project Italy                | Mitomycin, vindesine, and cisplatin vs observation | 36.5 mo vs 28.9 mo (HR, 0.89; 95% CI, 0.76-1.03 [P = .128]) | 55.2 mo vs 48 mo (HR, 0.96; 95% CI, 0.81-1.13 [P = .589]) |
| The Big Lung Trial (BLT)57                 | Cisplatin-based doublet vs observation | 27.0 mo vs 24.7 mo (HR, 0.97; 95% CI, 0.74-1.26 [P = .81]) | 33.9 mo vs 32.6 mo (HR, 1.02; 95% CI, 0.77-1.35 [P = .90]) |
| International Adjuvant Lung Cancer Trial (IALT)56 | Cisplatin-based doublet vs observation | 39.4% vs 34.3% (HR, 0.83; 95% CI, 0.74-0.94 [P < .003]) | 44.5% vs 40.4% (HR, 0.86; 95% CI, 0.76-0.98 [P < .03]) |
| JBR1058                                    | Cisplatin and vinorelbine vs observation | 61% vs 49% (HR, 0.60; 95% CI, 0.45-0.79 [P < .001]) | 94 mo vs 73 mo (HR, 0.69; 95% CI, 0.52-0.91 [P = .04]) |
| CALGB 963359                                | Carboplatin and paclitaxel vs observation | 89 mo vs 56 mo (HR, 0.80; 90% CI, 0.62-1.02 [P = .065]) | 95 mo vs 78 mo (HR, 0.83; 90% CI, 0.64-1.08 [P = .125]) |
| Adjuvant Navelbine International Trialist Association (ANITA) Trial60 | Cisplatin and vinorelbine vs observation | 36.3 mo vs 20.7 mo (HR, 0.76; 95% CI, 0.64-0.91 [P = .002]) | 65.7 mo vs 43.7 mo (HR, 0.80; 95% CI, 0.66-0.96 [P = .017]) |
| Japan Lung Cancer Research Group (JLCRG); adjuvant trial61 | Tegafur-uracil vs observation | 77.4% vs 73.6% (P = .25) | 88% vs 85% (HR, 0.71; 95% CI, 0.52-0.98 [P = .04]) |

NSCLC indicates non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; CALGB, Cancer and Leukemia Group B.

complete surgery. Nonetheless, subset analysis suggested a potential benefit of postoperative radiotherapy in patients with positive surgical margins and those with mediastinal lymph node-positive NSCLC52 that experience a high rate of local and systemic failure and are therefore treated with postoperative systemic therapy and radiotherapy.

For patients with early stage NSCLC who are not candidates for surgery due to medical comorbid illness, palliative external beam radiation is used for local tumor treatment and control. Recently, stereotactic body radiotherapy (SBRT) has emerged as a highly promising therapeutic option for these patients. A recent phase 2 study for medically unresectable patients demonstrated a 3-year primary tumor control rate of 97% with SBRT.54 The efficacy and safety of using SBRT for patients with tumors proximal to the central airway is currently under investigation. The promising results in patients with medically unresectable NSCLC have already led to a randomized study in Europe that compares SBRT with surgical resection in patients with early stage NSCLC. Radiofrequency ablation (RFA) is also used for the treatment of patients with early stage NSCLC who are not candidates for surgical resection. RFA is used for the treatment of smaller peripheral tumors and has been associated with high local control rates.55

Systemic Chemotherapy

Nearly two-thirds of recurrences after surgery for early stage disease occur at distant sites. Therefore, in addition to local therapy, the need for systemic therapy to eradicate micrometastasis has been recognized for a long time. Despite this, initial efforts to evaluate chemotherapy in the postoperative setting for patients with early stage NSCLC were not successful. The emergence of platinum-based chemotherapy as an effective treatment option for advanced NSCLC led to studies in patients with early stage disease. A meta-analysis reported in 1995 demonstrated a modest 14% reduction in the risk of death with the use of cisplatin-based chemotherapy, but this was not statistically significant.53 Subsequently, a number of large clinical trials with adequate power to detect modest improvements in outcome have been conducted. The International Adjuvant Lung Cancer Trial (IALT) included approximately 1800 patients with stages I, II, or III NSCLC who were randomized after surgery to a cisplatin-based, 2-drug regimen or observation (Table 1).56-61 There was an absolute improvement in the 5-year survival rate of 4% with adjuvant chemotherapy. These results were confirmed in another phase 3 study that demonstrated a 15% absolute improvement in 5-year survival with the combination of cisplatin and vinorelbine over observation in patients with stages IB and II NSCLC.58 A meta-analysis of all recent trials with adjuvant cisplatin-based chemotherapy demonstrated a 5% improvement in overall survival with adjuvant chemotherapy.62 These results have led to the use of adjuvant chemotherapy as the new standard of care for patients with early stage NSCLC.
Recently, the long-term follow-up results of the IALT and the NCI-Canada’s JBR10 study were reported. There was a higher incidence of noncancer deaths in the chemotherapy arm after 5 years of study therapy in the IALT study and the differences in overall survival and disease-free survival were no longer statistically significant. In contrast, the survival benefit with chemotherapy was maintained at 9 years of follow-up in the JBR10 study.

Although many of the adjuvant therapy studies have included patients with stages I, II, and III disease, among patients with stage I disease, the benefit from adjuvant chemotherapy has not been clearly established. In fact, the meta-analysis noted a detrimental hazard ratio for patients with stage IA disease who were treated with adjuvant chemotherapy. Among patients with stage IB disease, subset analyses of randomized studies have documented a modest benefit for patients with tumors larger than 4 cm. The role of carboplatin-based regimens is unproven as adjuvant therapy in patients with early stage NSCLC. In a phase 3 study conducted by the Cancer and Leukemia Group B (CALGB), despite an improvement in disease-free survival, there was no survival benefit reported with carboplatin and paclitaxel in patients with stage IB disease. Given the curative intent of therapy in this setting, the small advantage with cisplatin over carboplatin might be an important reason to use the former. The optimal number of cycles of adjuvant chemotherapy has not been addressed in randomized studies. Based on the present evidence, 3 to 4 cycles of cisplatin-based chemotherapy are administered in routine practice settings.

In all of the studies that evaluated postoperative chemotherapy, delivery of planned courses of chemotherapy was achieved in only 60% to 75% of the patients. This is likely related to comorbid illness and the varying recovery period after surgery for lung cancer. To improve the delivery of systemic therapy in patients with early stage NSCLC, the neoadjuvant approach has been investigated extensively. A phase 3 study conducted by the Southwest Oncology Group demonstrated an improvement in overall survival with chemotherapy followed by surgery versus surgery alone. However, these differences did not reach statistical significance because the trial was closed early. Similar trends were also noted in a European study that evaluated preoperative chemotherapy for patients with early stage NSCLC. Recently, a phase 3 study compared the administration of chemotherapy either before or after surgery with surgery alone in patients with early stage NSCLC. The delivery of chemotherapy was superior in the preoperative setting (90% vs 66%). Neoadjuvant chemotherapy was associated with a nonsignificant trend toward longer disease-free survival compared with surgery alone. This study was limited in power and included a high proportion of patients with stage I disease, a group in whom the role of chemotherapy is unproven. These studies suggest that neoadjuvant therapy is an efficacious and safe approach for patients with early stage NSCLC. The clinical circumstances under which it may be preferred over adjuvant therapy, the current standard of care, have not yet been clearly defined and it is therefore left to the judgment of the treating physician to choose the appropriate setting for systemic therapy in patients with early stage NSCLC. Presently, efforts to improve the efficacy of systemic therapy in patients with early stage NSCLC are focused on the integration of molecularly targeted agents and individualization of therapy based on biomarkers. Excision repair cross-complementing gene 1 (ERCC1) is an important mediator of DNA repair and has been noted in several studies to be a determinant of sensitivity to platinum-based therapy. In a subset analysis of the IALT, tumor specimens of patients were evaluated by immunohistochemistry for ERCC1 expression. Patients with high ERCC1 expression did not appear to derive benefit from cisplatin-based chemotherapy, although the overall survival for this group was more favorable. In the ERCC1-negative group, adjuvant chemotherapy was associated with a robust survival advantage over observation. This observation has led to prospective studies that evaluate treatment selection based on ERCC1 expression for patients with early stage NSCLC.

The EGFR inhibitors have also been investigated as adjuvant therapy for patients with early stage NSCLC. In a recent report, the use of gefitinib was associated with inferior results compared with placebo in patients with resected early stage NSCLC. Notably, there was no benefit noted with gefitinib, even in the small percentage of patients (21%) with an EGFR mutation. Pertinent limitations of this study include its early closure before full accrual and the short median duration of gefitinib therapy. Another study that evaluated erlotinib in the postoperative...
setting has completed accrual and the results are awaited. Other strategies currently under evaluation for early stage NSCLC include the combination of bevacizumab with chemotherapy and genomic approaches for risk stratification.

**Surgically Unresectable Stage III Disease**

Locally advanced disease that is not amenable to surgical resection is treated with combined modality approaches involving systemic therapy and radiotherapy. Typically, tumors that directly invade the mediastinum, major blood vessels, heart, or the vertebral body are considered surgically unresectable. In addition, patients with multistation N2 disease are also considered candidates for definitive combined modality treatment approaches.

The addition of systemic chemotherapy to radiotherapy was associated with improvement in overall survival compared with radiotherapy alone in randomized studies. The initial trials used a sequential approach involving the 2 modalities. Subsequently, a number of studies have compared the concurrent use of chemoradiotherapy with the sequential approach. Although the concurrent approach is associated with higher toxicity, there is a modest improvement in overall survival as well. Therefore, for patients with a good performance status, concurrent chemoradiotherapy has become the standard of care.

Two different chemotherapy approaches are commonly used for locally advanced NSCLC. One regimen involves the use of full doses of cisplatin and etoposide with radiotherapy. The other approach involves the use of carboplatin and paclitaxel on a weekly schedule at “radiosensitizing” doses, followed by 2 cycles of full-dose therapy. Both of these approaches have demonstrated efficacy in the concurrent chemoradiotherapy setting. The cisplatin and etoposide regimen is associated with higher toxicity, but has the potential to eradicate micrometastatic disease at an earlier time point. Conversely, the weekly regimen of carboplatin and paclitaxel has a more favorable tolerability profile and can be combined with higher doses of radiotherapy. These 2 strategies have not been directly compared in randomized clinical trials.

The optimal dose of radiotherapy for patients with locally advanced NSCLC has been the subject of many studies. The current standard of 60 to 66 grays (Gy) was established by a randomized study conducted in the 1970s. With the availability of improved radiotherapy technology, it has become possible to deliver even higher doses of radiotherapy without a substantial increase in toxicity. Several phase 2 studies have evaluated radiotherapy doses higher than 70 Gy and noted promising results. Based on this, a randomized study is currently underway to compare 74 Gy of radiotherapy with the standard 60-Gy dose for patients with locally advanced NSCLC. The use of hyperfractionated radiotherapy has also been associated with favorable results over standard once-daily fractionation in randomized studies, although this approach has been limited by the logistical challenges in delivering multiple fractions of treatment on a daily basis.

Efforts to improve the benefit of systemic therapy have focused on the integration of targeted agents and the development of newer chemotherapeutic agents. Although EGFR tyrosine kinase inhibitors can be safely administered with chemoradiotherapy, the most promising strategy involves the use of cetuximab. In a phase 3 study of patients with head and neck cancer, the addition of cetuximab to radiotherapy resulted in nearly a 2-fold improvement in the overall survival. Based on this, cetuximab is now being tested in combination with chemoradiotherapy for the treatment of patients with locally advanced NSCLC in a phase 3 study (Radiation Therapy Oncology Group [RTOG] 0617). A randomized study that evaluated gefitinib as maintenance therapy after combined modality therapy demonstrated inferior survival compared with placebo. The use of antiangiogenic agents has undergone limited evaluation for stage III disease. Two studies conducted in patients with SCLC noted the development of tracheoesophageal fistula in patients treated with bevacizumab after radiotherapy. Because of this observation and the higher risk of bleeding, the development of bevacizumab therapy in patients with locally advanced NSCLC is unlikely to be pursued further.

The use of induction or consolidation chemotherapy has not been associated with improvement in overall survival in patients with locally advanced NSCLC. Recently, pemetrexed has been combined with cisplatin or carboplatin in full systemic doses with concurrent radiotherapy. Promising results
were noted in a randomized phase 2 study by the CALGB that evaluated carboplatin and pemetrexed with concurrent radiotherapy. These favorable results have prompted an ongoing phase 3 study to compare the cisplatin and pemetrexed regimen with the cisplatin and etoposide regimen in combination with radiotherapy for patients with locally advanced NSCLC.

Multimodality approaches result in cure for approximately 20% of the patients with locally advanced NSCLC. Both improvements in systemic therapy and local therapy have contributed to the more favorable patient outcome noted in recent years. Another factor that warrants mention is the role of positron emission tomography, which has improved the accuracy of staging of lung cancer. As a result, stage migration could also have contributed to the recent improvements in outcome for patients with stage III disease.

Advanced Stage NSCLC

Approximately 50% of the patients with lung cancer have advanced stage disease at the time of diagnosis. Even patients without any cancer-related symptoms at diagnosis will manifest symptoms as their disease progresses. Therefore, the overall goals of treatment are to improve symptoms, preserve or improve quality of life, and prolong survival. The performance status of the patient remains an important determinant of overall prognosis and is a prime consideration in treatment selection. Recently, gender has also become recognized as an important prognostic factor, with females experiencing a better survival than males. In addition, the database for the new staging system demonstrated a more favorable outcome for patients without extrathoracic disease, with a median survival of 14 months compared with only 6 months in those with distant metastasis. This led to the additional subclassification of patients with metastatic disease to M1a and M1b.

Platinum-Based Chemotherapy

Systemic therapy remains the mainstay of treatment of advanced stage NSCLC. Combination chemotherapy with a platinum-based regimen has emerged as standard therapy for patients with advanced stage disease. Improvements in overall survival and quality of life have been demonstrated with platinum-based regimens over supportive care alone in randomized clinical trials. Among the platinum compounds, both cisplatin and carboplatin have been extensively studied for the treatment of NSCLC. In general, carboplatin-based regimens have a favorable tolerability profile over cisplatin-based regimens. Despite the marginally higher response rate noted with cisplatin-based regimens, considering the palliative intent of therapy, carboplatin-based regimens have found wide applicability in routine care. However, recent improvements in antiemetic therapy have rendered the use of cisplatin-based regimens more tolerable.

A number of randomized clinical trials have established the superiority of a platinum-containing, 2-drug combination over single-agent therapy. The response rate, progression-free survival, and overall survival all appear to be improved with combination regimens in patients with advanced NSCLC, although the benefits come with higher toxicity. Paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, and pemetrexed, commonly referred to as the “third-generation” cytotoxic agents, have all demonstrated efficacy when given in combination with a platinum compound in patients with advanced NSCLC. A large randomized clinical trial conducted by the Eastern Cooperative Oncology Group (ECOG) compared the efficacy of 4 commonly used combination regimens in the treatment of patients with advanced NSCLC. The combinations of cisplatin and docetaxel, cisplatin and gemcitabine, and carboplatin and paclitaxel were all associated with efficacy parameters comparable to those of the control arm of the cisplatin and paclitaxel regimen. These observations, supported by the findings of other contemporaneous clinical trials, established the notion that an “efficacy plateau” had been reached with 2-drug combinations in patients with advanced stage NSCLC. The use of 3-drug cytotoxic combinations has generally resulted in higher toxicity without clear evidence of an improvement in efficacy across clinical trials and has therefore not been pursued subsequently. With the currently available platinum-based 2-drug regimens, the median survival and one-year survival rate are 8 months to 11 months and 30% to 40%, respectively, in patients with a good performance status.

Role of Histology

Until recently, all histological subtypes of NSCLC were treated alike because a differential sensitivity
based on histology had not been appreciated in clinical trials. Recently, Scagliotti et al reported the results of a phase 3 study that compared the combination of cisplatin and pemetrexed with that of cisplatin and gemcitabine for patients with advanced stage NSCLC. With a sample size of approximately 1700 patients, this study had a predefined plan to analyze outcomes based on histology. For the overall study population, the median survival was similar at 10.3 months with both regimens. However, in patients with adenocarcinoma histology, the cisplatin and pemetrexed regimen was associated with a superior median survival (12.6 months vs 10.9 months). In addition, this regimen was also associated with a favorable tolerability profile. These results led to the approval of the cisplatin and pemetrexed regimen for patients with nonsquamous NSCLC, thus setting the precedent for histology-based treatment selection for patients with NSCLC. The biological reasons behind the higher sensitivity of adenocarcinoma to pemetrexed are not entirely clear. Some studies have linked the expression of thymidylate synthase (TS), a known target for pemetrexed, with efficacy. TS expression is lower in adenocarcinoma compared with squamous or SCLC.

The preliminary results of a phase 3 study that compared the use of carboplatin in combination with either nanoparticle albumin-bound (nab) paclitaxel or standard paclitaxel formulation as the first-line therapy for patients with advanced NSCLC also noted a differential effect by histology. Response rate, the primary endpoint of the study, was superior for the overall study population (33% vs 25%), and in patients with squamous histology, there was a greater advantage with nab paclitaxel (41% vs 24%). A biological rationale for this observation might be the expression of Secreted Protein Acidic and Rich in Cysteine (SPARC), which facilitates the accumulation of albumin in the tumor and thus increases intracellular concentrations of the cytotoxic agent. SPARC expression has been linked to a higher response rate in patients with head and neck cancers, which are predominantly of squamous histology. The nab paclitaxel regimen was also associated with a lower incidence of neuropathy. The survival data from this study will be the decisive factor in how this regimen is used in routine practice. Although these observations are interesting, it is likely that the differences in sensitivity to certain chemotherapy regimens represent an underlying biological factor rather than mere histological differences in tumors.

**Maintenance Therapy**

The optimal duration of treatment for patients with advanced NSCLC has been the subject of study ever since the role of chemotherapy was established. Randomized studies that compared the use of combination chemotherapy for a defined number of cycles versus continuation until progression or a higher number of courses failed to demonstrate an advantage for the latter approach. Therefore, the administration of 4 to 6 cycles of combination chemotherapy followed by observation became the standard of care for the first-line treatment of advanced NSCLC. With the advent of well-tolerated, novel chemotherapeutic and molecularly targeted agents, recent studies have evaluated the role of single-agent maintenance therapy after the achievement of maximal disease control with combination regimens.

This strategy is now commonly referred to as maintenance therapy or consolidation therapy. In a phase 3 study, docetaxel was given as maintenance immediately after 4 cycles of combination therapy with carboplatin and gemcitabine or after progression of disease (second-line therapy) in patients with advanced NSCLC (Table 2). Only patients with an objective response or stable disease were randomized to maintenance therapy. There was a significant improvement in progression-free survival and a trend toward a survival benefit for patients treated with maintenance therapy. Approximately 40% of the patients on the control arm did not receive the planned second-line therapy for a variety of reasons including disease progression. For patients who received the planned second-line therapy, the survival outcomes were similar to those of patients who received maintenance therapy. This observation suggests that the benefit from maintenance therapy is probably related to the increased likelihood of administration of another active chemotherapy agent immediately following the frontline therapy before disease progression.

In another phase 3 study with a different design, patients with nonprogressive disease after 4 cycles of platinum-based combination therapy were randomized to therapy with pemetrexed or placebo. For the overall patient population, the primary endpoint...
of median progression-free survival was superior with pemetrexed therapy. The overall survival was also superior with maintenance therapy. As noted in the frontline setting, the benefit from maintenance therapy was restricted to patients with nonsquamous histology. Only 67% of the patients on the control arm received second-line therapy, which could have contributed to the favorable outcome with maintenance therapy. The robust overall improvement in Median Survival by 5 months with pemetrexed in patients with nonsquamous histology led to its approval by the US Food and Drug Administration (FDA) for maintenance therapy for patients with nonsquamous NSCLC.

Improvement in overall survival has also been noted with the use of erlotinib, an EGFR inhibitor, as maintenance therapy. In a phase 3 study reported recently, patients with advanced NSCLC with disease control after 4 cycles of platinum-based therapy were randomized to receive erlotinib or placebo.121 There was a modest improvement in the median progression-free survival (12.3 weeks vs 11.1 weeks) and overall survival (12 months vs 11 months) in favor of erlotinib. The presence of activating mutations in the EGFR was highly predictive of benefit, with a hazard ratio of 0.10 with erlotinib, although this difference did not translate into a survival benefit. This is likely due to the fact that the majority of patients with an EGFR mutation on the placebo arm crossed over to receive an EGFR inhibitor after disease progression. For patients with wild-type EGFR, a modest improvement in overall survival was noted with erlotinib. Approximately 70% of patients in both arms received subsequent lines of therapy. The FDA has recently approved erlotinib for maintenance therapy for patients with advanced NSCLC based on this study. The favorable outcome with these trials was also substantiated by a meta-analysis of all studies that utilized some form of maintenance therapy. It noted a statistically significant improvement in progression-free survival and a modest improvement in overall survival with the maintenance strategy.125

Several important questions about the optimal utilization of maintenance therapy still remain and will be addressed by ongoing/planned clinical trials. One question relates to the use of an agent used in the first-line combination versus switching to an alternate agent for maintenance therapy. Until recently, all the studies that showed a strong benefit with maintenance therapy used an alternative agent. In a recent phase 3 study, after frontline therapy

### TABLE 2. Clinical Trials of Maintenance Therapy in Advanced NSCLC

| STRATEGY | REGIMEN | CONTINUATION THERAPY WITH ORIGINAL CHEMOTHERAPY AGENT | PFS | OS |
|----------|---------|-----------------------------------------------------|-----|----|
| STRATEGY | CONTINUATION THERAPY WITH ORIGINAL CHEMOTHERAPY AGENT | PFS | OS |
| TRIAL | | | | |
| Smith 2001114 | MVP × 3 cycles vs MVP × 6 cycles | 5 mo vs 5 mo | 6 mo vs 7 mo |
| Socinski 2002113 | PC × 4 cycles vs PC until progression | — | 8.5 mo vs 6.6 mo (P = .63) |
| Brodowicz 2006116 | GC vs GC followed by G | 5 mo vs 6.6 mo (P = .001) | 11 mo vs 13 mo (P = .195) |
| Park 2007117 | PC × 4 cycles vs PC × 6 cycles | 6.2 mo vs 4.3 mo (P = .001) | 15 mo vs 16 mo (P = .469) |
| Belani 2010118 | G and carboplatin followed by BSC vs G and carboplatin followed by G | 7.4 mo vs 7.7 mo (P = .575) | 8 mo vs 9.3 mo (P = .838) |
| STRATEGY | SWITCH MAINTENANCE | |
| Westeel 2005119 | MIC vs MIC followed by vinorelbine | 5 mo vs 3 mo (P = .32) | 10.4 mo vs 11 mo |
| Fidias 2007120 | G and carboplatin followed immediately by D vs G and carboplatin followed by D at progression | 5.7 mo vs 2.7 mo (P = .001) | 12.3 mo vs 9.7 mo (P = .853) |
| Cappuzzo (SATURN trial) 2010121 | Platinum doublet followed by placebo vs erlotinib | 11.1 wk vs 12.3 wk (P = .001) | 11 mo vs 12 mo (P = .0088) |
| Miller (ATLAS trial) 2009122 | Platinum doublet plus bevacizumab followed by bevacizumab vs erlotinib plus bevacizumab | 4.76 mo vs 3.75 mo (P = .0012) | Not reported |
| Perol (IFCT-GFPC 0502) 2010123 | GC followed by BSC vs G vs erlotinib | 2.9 mo vs 1.9 mo for erlotinib (P = .002) | |
| | | | 3.8 mo vs 1.9 mo for G (P = .001) |

NSCLC indicates non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; MVP, mitomycin, vinblastine, and cisplatin; PC, paclitaxel and carboplatin; GC, gemcitabine and cisplatin; BSC, best supportive care; MIC, mitomycin, ifosfamide, and cisplatin; D, docetaxel; SATURN, Sequential Tarceva in Unresectable NSCLC.
with carboplatin and gemcitabine, patients with advanced NSCLC were randomized to receive gemcitabine or supportive care alone. In this “continuation” maintenance study, there was no difference in overall survival between the 2 arms. This trial was severely limited in its utility by the high percentage of patients with an ECOG performance status of 2 (64%).

With the availability of targeted agents and chemotherapy, it is now necessary to perform direct comparisons of these agents in the maintenance setting. A phase 3 study randomized patients to maintenance therapy with erlotinib, chemotherapy (gemcitabine or vinorelbine), or observation after combination chemotherapy with cisplatin and gemcitabine. The study was not designed to compare the 2 maintenance arms directly. The median progression-free survival was superior for maintenance therapy and the survival data are awaited. Although this supports the use of either a targeted agent or chemotherapy as maintenance treatment, patient selection for *EGFR* inhibitor therapy with molecular markers has now entered mainstream practice and is likely to be used in the maintenance setting as well. Unquestionably, maintenance therapy or first-line therapy with an *EGFR* inhibitor is indicated in patients with an activating *EGFR* mutation.

Another approach that has been adopted without definite evidence involves the continuation of a targeted agent used for first-line therapy as maintenance. Bevacizumab and cetuximab, agents that inhibit the vascular endothelial growth factor (VEGF) and *EGFR* pathways, respectively, have demonstrated a survival advantage in combination with chemotherapy. Based on the design of these studies, the prolonged use of the targeted agent after maximum cycles of cytotoxic therapy has been adopted in routine practice, although their role in maintenance therapy in particular is unproven. An ongoing phase 3 study by ECOG will randomize patients treated with carboplatin, paclitaxel, and bevacizumab to either continuation of bevacizumab, a switch to pemetrexed, or the addition of pemetrexed (ECOG 5508).

From these studies, it is clear that the maintenance therapy paradigm has reached center stage for the treatment of patients with advanced NSCLC. Although it is not clear if all patients should receive maintenance therapy, those with a heavy residual disease burden and symptomatic disease may well benefit from the use of maintenance therapy. In situations in which maintenance therapy is not considered appropriate, it will be important to follow patients closely with periodic restaging studies to ensure that a subsequent line of therapy is given at the earliest evidence of disease progression.

### Molecularly Targeted Therapy

#### *EGFR* Inhibitors

Activation of the *EGFR* pathway results in the induction of proliferation, inhibition of apoptosis, increased metastatic potential, and initiation of neoangiogenesis. Expression of *EGFR* is noted in 40% to 80% of cases of NSCLC. Based on the success achieved in targeting the human epidermal growth factor receptor 2 (HER2) pathway in breast cancer, agents that inhibit the *EGFR* pathway were evaluated for the treatment of NSCLC. Initial studies with gefitinib and erlotinib in patients with refractory NSCLC demonstrated objective responses in approximately 10% to 20% of the patients. These drugs were tolerated well with skin rash and diarrhea as the most common toxicities. The utility of *EGFR* tyrosine kinase inhibitors was conclusively established in a randomized clinical trial of erlotinib versus placebo for patients with NSCLC that progressed after one or 2 prior chemotherapy regimens for advanced stage disease (National Cancer Institute of Canada [NCIC]-BR21 trial). There was a significant improvement in overall survival and progression-free survival with erlotinib. This study led to the approval of erlotinib for the treatment of patients with refractory NSCLC. A similar study conducted with gefitinib, however, revealed no difference in overall survival when compared with placebo. The latter study included patients with slightly more aggressive disease, compared with the BR21 study. Notably, a survival benefit was noted for never-smokers and patients with Asian ethnicity treated with gefitinib in a subset analysis. In all the initial studies with the *EGFR* tyrosine kinase inhibitors, women, those with an adenocarcinoma histology, never-smokers, and those of Asian ethnicity consistently demonstrated a higher response rate. This led to the search for the biological reason behind this observation. In 2004, 2 seminal studies...
reported on the identification of activating mutations in the EGFR that were correlated with objective responses with EGFR tyrosine kinase inhibitors.\textsuperscript{134,135} This finding led to prospective studies that evaluated the benefit of EGFR kinase inhibitors in patients with an EGFR mutation.\textsuperscript{136} Very high response rates of 60% to 80% were noted, thus confirming the predictive potential of EGFR mutations for gefitinib and erlotinib.\textsuperscript{137} EGFR mutations are present in approximately 10% to 15% of Caucasian patients and an even higher percentage (up to 40%) of Asian patients.\textsuperscript{135} The presence of the EGFR mutation correlates with clinical characteristics that were associated with benefit in early studies with EGFR inhibitors. Another biomarker that has been studied extensively is the EGFR gene copy number assessed by fluorescence in situ hybridization (FISH).\textsuperscript{138} Although a high EGFR gene copy number was correlated with survival after EGFR inhibitor therapy, this has not been confirmed in subsequent studies, and is therefore not useful in routine practice.

The results of a recent landmark phase 3 study conducted in Asia confirmed the role of EGFR mutation as the main predictor of outcome with EGFR tyrosine kinase inhibitors (Table 3).\textsuperscript{137,139-142} The study used a clinical enrichment strategy by including women with adenocarcinoma and a history of light cigarette use or never-smokers with advanced stage NSCLC. These previously untreated patients were randomized to therapy with either gefitinib or a standard chemotherapy regimen of carboplatin and paclitaxel. For the overall patient population, gefitinib was better tolerated and had a superior progression-free survival over chemotherapy. More importantly, in approximately 30% of the patients whose tumor tissues were analyzed for EGFR mutation, there was a significant improvement in the response rate and median progression-free survival for those with an activating mutation in exons 19 or 21. Conversely, in patients with wild-type EGFR, gefitinib was inferior to chemotherapy. A second study with a similar design was conducted in Korea and essentially duplicated these results.\textsuperscript{142} Recently, 2 randomized phase 3 studies compared gefitinib with chemotherapy in patients with a documented EGFR mutation.\textsuperscript{140,141} Both of these studies were closed early before full accrual because a highly significant efficacy advantage was noted with gefitinib. These results have now led to the paradigm of using EGFR inhibitors for first-line therapy for patients with advanced NSCLC only in the setting of a known sensitizing EGFR mutation. In these groups of patients, the response rate, median progression-free survival, and overall survival are 60% to 80%, 10 months to 12 months, and 24 months to 30 months, respectively.

Efforts to combine EGFR inhibitors with standard chemotherapy were not associated with a survival advantage over standard chemotherapy in an unselected patient population in multiple randomized studies.\textsuperscript{143,144} To test whether the combination might be beneficial in selected patients, a recent trial randomized never- or light smokers with advanced NSCLC to therapy with erlotinib alone or in combination with carboplatin and paclitaxel.\textsuperscript{145} There was no significant difference in survival outcomes between the 2 groups, even in patients with an EGFR mutation, thus excluding a role for EGFR tyrosine kinase inhibitors in combination with chemotherapy.

A completely different biological basis appears to be responsible for the anticancer effects of agents

| TRIAL                | MODE OF SELECTION | REGIMEN                         | PFS                | OS                  |
|----------------------|-------------------|---------------------------------|--------------------|---------------------|
| Mitsudomi (WJTOG 3405 Trial) 2010\textsuperscript{140} | Molecular         | Gefitinib vs cisplatin/docetaxel | 9.2 mo vs 6.3 mo (\(P < .0001\)) | Not reported        |
| Rosell 2009\textsuperscript{137} | Molecular         | Erlotinib                       | 14.0 mo (95% CI, 11.3 mo-16.7 mo) | 27.0 mo (95% CI, 22.7 mo-31.3 mo) |
| Maemondo 2010\textsuperscript{141} | Molecular         | Gefitinib vs carboplatin/paclitaxel | 10.8 mo vs 5.4 mo (\(P < .001\)) | 30.5 mo in the gefitinib group and 23.6 mo in the chemotherapy group (\(P = .31\)). |
| Mok 2009\textsuperscript{139}  | Clinical          | Gefitinib vs carboplatin/paclitaxel | 5.7 mo vs 5.8 mo (HR, 0.74; \(P < .001\)) | Not reported        |
| Lee (SIGNAL) 2009\textsuperscript{142} | Clinical          | Gefitinib vs cisplatin/gemcitabine | 6.6 mo vs 6.1 mo (\(P = .044\)) | 21.3 mo vs 23.3 mo (\(P = .420\)) |

EGFR indicates epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; 95% CI, 95% confidence interval; HR, hazard ratio.
that target the external domain of the EGFR. Cetuximab, a chimeric monoclonal antibody against the EGFR, has minimal activity when given as monotherapy for patients with advanced stage NSCLC. However, when given in combination with platinum-based chemotherapy, a modest improvement in overall survival was noted (11.3 months vs 10.1 months) over chemotherapy alone. In a second phase 3 study, there was a trend toward improvement in overall survival, but the difference did not reach prespecified statistical significance with cetuximab. Interestingly, in both of these studies, there was no improvement in progression-free survival with the addition of cetuximab to chemotherapy. Given the differential efficacy of cetuximab based on KRAS mutation status in patients with colon cancer, molecular analyses were conducted in these 2 phase 3 NSCLC studies of cetuximab. The outcomes were not different between those with and those without a KRAS mutation. In preclinical studies, the monoclonal antibodies do not appear to be effective in cell lines that bear an EGFR mutation. All of these issues point to different mechanisms being responsible for the anticancer effects of monoclonal antibodies against the EGFR and the tyrosine kinase inhibitors in NSCLC. The use of cetuximab in routine care for patients with advanced stage NSCLC remains limited in the absence of a robust predictive biomarker.

**Resistance to EGFR Inhibition**

In spite of the robust efficacy of EGFR tyrosine kinase inhibitors in appropriately selected patients, resistance to therapy ultimately develops in the vast majority of patients. In the past few years, a great deal of insight has been gained in understanding the mechanisms of resistance to EGFR inhibitors. A secondary mutation in exon 20 (T790M) of EGFR results in a structural change that alters the binding pocket for the tyrosine kinase inhibitors. These patients become insensitive to therapy with EGFR inhibitors. This mechanism accounts for secondary resistance in approximately 50% to 60% of patients with NSCLC. In addition, activation of alternate cell signaling pathways such as the c-Met pathway enables the cells to overcome the anticancer effects of EGFR inhibitors. Increasing knowledge regarding the alternate pathways and other mechanisms of resistance has already led to the evaluation of strategies to overcome or delay the onset of resistance.

A number of second-generation EGFR inhibitors that result in irreversible inhibition are at advanced stages of development. These agents have demonstrated anticaner activity in preclinical and clinical settings in tumors resistant to gefitinib and erlotinib. A phase 3 study of patients with resistance to EGFR tyrosine kinase inhibitors involving the comparison of BIBW 2992, an irreversible EGFR inhibitor, with placebo has completed accrual and the results are awaited. PF-299804, a pan-HER inhibitor, was compared with erlotinib in a randomized phase 2 study for patients with advanced NSCLC. There was a statistically significant improvement in the median progression-free survival (12 weeks vs 8 weeks) and a greater benefit in patients with wild-type KRAS (16 weeks vs 8 weeks). A confirmatory phase 3 study is being planned.

Another strategy to delay the emergence of resistance involves combination therapy with inhibitors of the c-Met and EGFR. In a randomized phase 2 study, erlotinib was given alone or in combination with ARQ-197, a small molecule c-Met inhibitor, to patients with advanced stage NSCLC. There was a significant improvement in progression-free survival and overall survival for the combination approach. These results are likely to lead to confirmatory phase 3 studies and the evaluation of other c-Met inhibitors in NSCLC.

A number of signaling molecules in the EGFR pathway are processed for activation and degradation by the heat shock protein (Hsp) family of enzymes. Because increased expression of these (Hsp) clients mediates resistance to EGFR inhibitor therapy, Hsp90 inhibitors represent a promising class of agents that have demonstrated encouraging results. Studies are currently ongoing with various Hsp90 inhibitors based on favorable early clinical leads.

**Antiangiogenic Therapy**

The growth of new blood vessels is a critical requirement for tumor progression. This complex process is mediated by a number of signals, among which VEGF has been studied the most. Strategies to inhibit VEGF, including a monoclonal antibody against the ligand or receptor and small molecule inhibitors that bind to the tyrosine kinase domain of the receptor, have been extensively undertaken.
Bevacizumab, a monoclonal antibody against VEGF, is approved by the FDA for use in combination with standard chemotherapy for patients with advanced, nonsquamous NSCLC. This was based on a phase 3 study by ECOG that randomized patients with advanced NSCLC to treatment with chemotherapy alone or in combination with bevacizumab (at a dose of 15 mg/kg).\textsuperscript{126} There was a significant improvement in overall survival (12.3 months vs 10.3 months) and progression-free survival (6.2 months vs 4.8 months) with the addition of bevacizumab. However, a second study conducted outside the United States failed to demonstrate an improvement in survival with the addition of bevacizumab to chemotherapy.\textsuperscript{157} There was a statistically significant, but clinically modest, improvement in median progression-free survival with the addition of bevacizumab. In both of these studies, a higher incidence of fever with neutropenia, hemoptysis, hypertension, and proteinuria was observed with the addition of bevacizumab to chemotherapy. In the initial studies with bevacizumab, the high incidence of hemoptysis in patients with squamous histology has rendered this agent not optimal for this subtype of NSCLC.\textsuperscript{158} Another group in which caution is indicated with bevacizumab is the elderly patient population (age \textgtr 70 years) because an unplanned subset analysis of the ECOG study noted a higher incidence of toxicity and a trend toward more treatment-related deaths in elderly patients treated with bevacizumab.\textsuperscript{159} For all of these reasons, although bevacizumab is a useful addition to the therapeutic options for NSCLC, proper patient selection is important to maximize benefit and minimize toxicity.

A recent study evaluated if the addition of erlotinib to maintenance bevacizumab would improve the overall survival of patients with advanced, nonsquamous NSCLC.\textsuperscript{122} Although an improvement in progression-free survival was observed, there was no survival advantage noted with the combination of bevacizumab and erlotinib as maintenance therapy. These results were very similar to a phase 3 study conducted for patients with advanced NSCLC that compared erlotinib as monotherapy or in combination with bevacizumab for advanced NSCLC in the second-line setting.\textsuperscript{160} There was no difference in overall survival and therefore this combination strategy is unlikely to be developed further.

Unlike bevacizumab, VEGF tyrosine kinase inhibitors have demonstrated objective response rates of approximately 10\% when given as monotherapy.\textsuperscript{161,162} However, additional toxicities such as diarrhea, mucositis, hand-foot syndrome, and fatigue are noted with many of these agents. Vandetanib, a dual inhibitor of VEGF and EGFR, was extensively evaluated in various settings for the treatment of advanced NSCLC without much success.\textsuperscript{163} Sorafenib is another VEGF tyrosine kinase inhibitor that has demonstrated single-agent activity when compared with placebo in a refractory group of patients with advanced stage NSCLC.\textsuperscript{164} However, when given in combination with platinum-based chemotherapy, no improvement in overall survival was noted in 2 large, phase 3 studies with sorafenib.\textsuperscript{165} A number of compounds that belong to this class, including sunitinib, axitinib, linifanib, and motesanib, are all in phase 2/3 studies for the treatment of patients with advanced NSCLC.

Given the unique toxicities and modest benefits associated with antiangiogenic agents in NSCLC, it is important to identify biomarkers for optimal patient selection. Baseline VEGF concentration, circulating endothelial cells, and intercellular adhesion molecule 1 (ICAM1) levels, among others, have all been studied, but no consistent predictive potential was noted.\textsuperscript{166-168} Recently, certain polymorphisms in VEGF have been noted to predict for a higher degree of benefit with bevacizumab in both patients with breast cancer and those with NSCLC.\textsuperscript{169,170} Confirmation of these interesting observations and knowledge regarding the underlying biological mechanisms will go a long way in defining the patient population that will derive robust benefits with antiangiogenic agents.

**Activation of the ALK Pathway**

A major area of excitement in NSCLC has been the recent identification of an inversion within chromosome 2 that results in a fusion gene. This includes portions of the EML4 gene and ALK in a small percentage of patients with NSCLC.\textsuperscript{39} This fusion gene results in dominant oncogenic activity and has emerged as a target for therapy. ALK translocations have been noted in never-smokers, patients with adenocarcinoma, and younger patients.\textsuperscript{41} In particular, the presence of signet cell features in the tumor tissue may serve as an enrichment criterion to screen for the ALK translocation. Patients with an ALK...
translocation appear to be less sensitive to \textit{EGFR} inhibitors and standard chemotherapy.

Crizotinib (PF-02341066 or 1066), a small molecule tyrosine kinase inhibitor, was originally under development as a c-Met targeted agent. Its ability to inhibit \textit{ALK} kinase led to its initial evaluation in a cohort of NSCLC patients with an \textit{ALK} translocation. Among the 82 patients included in a phase 1B study, a provocative response rate of 66\% was noted.\(^{171}\) Tumor shrinkage was noted in a vast majority of the patients as indicated by a disease control rate of 87\% and the median progression-free survival had not been reached at the time of the report. These highly promising results have led to a phase 3 study to compare crizotinib with standard chemotherapy in patients with \textit{ALK}-positive NSCLC. Routine screening of patients for the \textit{ALK} translocation is rapidly becoming common practice in the United States. Because the \textit{ALK} translocation appears to be mutually exclusive with \textit{EGFR} and \textit{KRAS} mutations, screening with a FISH technique in never-smokers/light smokers with wild-type \textit{EGFR} and \textit{KRAS} mutations is recommended. The discovery and subsequent targeting of \textit{ALK} translocations in NSCLC is a remarkable example of biological discoveries leading to rapid therapeutic advances and a high likelihood of success associated with targeting dominant oncogenic events in selected patient subpopulations.

Other Molecularly Targeted Agents

A number of other novel targets are currently under investigation for the treatment of NSCLC. The mammalian target of rapamycin (mTOR) axis is an important mediator of oncogenic signaling in a variety of malignancies.\(^{172,173}\) Agents that target the mTOR axis such as temsirolimus and everolimus have proven to be successful in the treatment of renal cell cancer.\(^{173,174}\) In NSCLC, everolimus has demonstrated modest single-agent activity and is now being studied in combination with chemotherapeutic agents and other cell signaling pathway inhibitors.\(^{175,176}\) Because the mTOR pathway is intimately involved in tumor metabolism, an understanding of the correlation between the effects of rapamycin and its analogues on metabolic activity in patients with lung cancer may shed further light on how best to optimally develop these compounds in the future.\(^{175,177}\) Another group of agents that have evoked a great deal of interest are the insulin-like growth factor (IGF) receptor inhibitors. Among the various monoclonal antibodies that target IGF 1 receptor (IGF-1R), figitumumab is the furthest along in clinical development. Although promising results were observed when figitumumab was given in combination with chemotherapy as first-line therapy for patients with advanced NSCLC, a subsequent phase 3 study failed to confirm the improvement in efficacy.\(^{178,179}\) A second phase 3 study that combined this agent with erlotinib was also closed early due to futility. This has cast a shadow over the agents that target IGF-1R in NSCLC. It is hoped that biomarkers that will identify susceptible patient subsets will lead to favorable results with IGF-1R inhibitors. An approach using a small molecule tyrosine kinase inhibitor to block receptor activation is also being developed.

Agents that modulate epigenetic mechanisms that influence oncogenic behavior have demonstrated promising early results. Histone deacetylase (HDAC) inhibitors have demonstrated promising results in the treatment of cutaneous T-cell lymphoma and have been investigated in solid tumors as well.\(^{180}\) A phase 2 study demonstrated promising results when vorinostat, a HDAC inhibitor, was given in combination with chemotherapy to patients with advanced NSCLC, confirming the favorable preclinical interaction between these compounds.\(^{181,182}\) However, the combination was associated with higher toxicity that necessitated further efforts to optimize the regimen to improve its safety profile. HDAC inhibitors are also being evaluated in combination with other molecularly targeted agents, and in particular with demethylating agents, based on promising preclinical observations. Table 4 provides details of approved or highly promising biologic agents in NSCLC.

Lung Cancer and Elderly Patients

The optimal management of elderly patients with lung cancer continues to evolve. It is now recognized that organ function and physical performance rather than chronologic age are the overarching factors in patients’ tolerance of anticancer therapies. Clinical investigations in the last decade have established the safety and benefit of surgical resection for early stage lung cancer in elderly patients, including those in
their eighth and ninth decades of life. Similarly, improved supportive care and novel cytotoxic and biologic agents with an improved toxicity profile have made possible the use of palliative systemic agents for advanced disease. Therapeutic benefit has now been established not just for single-agent regimens such as vinorelbine but for multiagent chemotherapy including platinum-based doublet chemotherapy regimens in elderly patients.

**Salvage Therapy for Advanced NSCLC**

The availability of tolerable and active therapeutic agents for second- or third-line treatment also contributed to the improved survival outcome noted with NSCLC in the last decade. Randomized controlled trials have established the efficacy of pemetrexed, docetaxel, and erlotinib as salvage treatment agents for patients with NSCLC who progressed after frontline therapy. In addition, gefitinib has received similar approval in Asia and Europe. Apart from the restriction of pemetrexed to patients with tumors with a nonsquamous histology, the choice between these agents in the salvage setting is driven primarily by drug toxicity profile and patient choices. It is, however, conceivable that similar to the practice standard in the frontline setting, the selection of EGFR kinase inhibitors will require the demonstrable presence of activating EGFR mutations.

**Small Cell Lung Cancer**

Despite a reduction in the percentage of patients with SCLC in recent times, it is still a considerable source of morbidity and mortality, with more than 25,000 new cases diagnosed each year in the United States. With the adoption of the new staging system, the use of the TNM staging system has been recommended over the prevailing categorization of SCLC into limited and extensive stage disease. This will allow for an improvement in the ability to establish prognosis.

Surgical resection has a very limited role in the treatment of SCLC. Patients with peripherally located tumors without evidence of mediastinal lymph node or metastatic involvement may be considered for surgical resection because high survival rates have been reported in case series studies. Since the adoption of platinum-based chemotherapy as the cornerstone of treatment of SCLC in the 1980s, very little progress has been achieved in the realm of systemic therapy. Various approaches including dose-intense chemotherapy, high-dose chemotherapy, and alternating regimens have all failed to improve survival in patients with SCLC. Therefore, the regimen of 4 cycles of combination therapy with a platinum compound and etoposide remains the current standard for both limited and extensive stage SCLC. Irinotecan, a topoisomerase inhibitor, was associated with improved survival when given in combination with cisplatin in a Japanese phase 3 study. However, 2 studies conducted in the United States found no advantage for this regimen over the combination of cisplatin and etoposide. Recently, targeted agents such as antiangiogenic agents, mTOR inhibitors, and Bcl-2 inhibitors have been studied without much success. Topotecan, a topoisomerase inhibitor, is the only proven agent in patients who developed disease recurrence after platinum-based chemotherapy, although its efficacy is restricted to patients with chemotherapy-sensitive disease. Higher response rates compared with topotecan have been noted with amrubicin, an anthracycline derivative, in phase 2 studies for refractory SCLC.

**TABLE 4. Biologic Agents and Indications in the Treatment of NSCLC**

| AGENT     | INDICATION                                                                 | PREDICTIVE MARKER                      |
|-----------|----------------------------------------------------------------------------|----------------------------------------|
| Bevacizumab | In the frontline setting in combination with platinum-based doublet     | None validated                         |
| Erlotinib | For second- or third-line management of advanced NSCLC                  | Exon 19 and 21 mutations in the EGFR gene |
| Gefitinib | Indicated in patients in the United States only in the context of a clinical study or for patients initiated on treatment prior to withdrawal of accelerated approval by the FDA and who continue to benefit; approved for treatment in Asia and in the first-line treatment setting in Europe for EGFR mutant tumors | Exon 19 and 21 mutations in the EGFR gene |
| Cetuximab | No FDA indication but overall survival advantage in combination with platinum-based doublet chemotherapy in a phase 3 trial | No validated marker                    |
| Crizotinib | Promising early phase trial; confirmatory phase 3 trial still ongoing    | EML4-ALK translocation by FISH          |

NSCLC indicates non-small cell lung cancer; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; EML4-ALK, echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization.
This is now being evaluated in a phase 3 study for second-line therapy.\textsuperscript{195}

The use of thoracic radiotherapy and prophylactic cranial irradiation (PCI) is associated with modest improvements in survival for patients with limited stage disease. Recently, a randomized study in patients with extensive stage SCLC demonstrated an improvement in overall survival with PCI.\textsuperscript{196} Although this study was limited in not staging the brain before the initiation of PCI, the robust survival results have led to the consideration of PCI in patients who have a good response to combination chemotherapy. Ongoing studies are evaluating newer classes of molecularly targeted agents such as the Hedgehog inhibitors and the IGF-1R pathway inhibitors. A greater understanding of mediators of resistance and sensitivity to platinum is also necessary to improve the efficacy of combination chemotherapy for SCLC.

**Future Perspectives**

The treatment options for patients with lung cancer have improved considerably in recent years. Improvements in survival have been noted for patients with every stage of the disease with the integration of new systemic therapy options, improvements to local therapy, and supportive care measures. A number of molecularly targeted agents that modulate a wide array of cell signaling pathways are currently under development. The remarkable success achieved with the use of \textit{EGFR} tyrosine kinase inhibitors and the \textit{ALK} inhibitors are the initial steps toward an era of individualized treatment options for patients with NSCLC. Several groups are now involved in screening tumor specimens for dominant oncogenic drivers in individual patients to guide treatment selection. Notable among these efforts is a recent initiative funded by the NCI that has led to a Lung Cancer Mutation Consortium (Principal Investigator: Paul Bunn, MD, University of Colorado). This group includes a number of academic institutions across the United States with the goal of conducting in-depth molecular analysis of tumor specimens from patients with adenocarcinoma of the lung. A total of 13 known molecular abnormalities including 8 mutations are evaluated in the tumor specimens. By developing novel clinical trials that are opened across the institutions to target each of these molecular events, the group is evaluating a variety of individualized treatment approaches for patients with NSCLC. Because these molecular changes are noted in much smaller subsets of patients, such clinical trials are unlikely to complete accrual within a single institution in a reasonable time and therefore require such collaborative efforts to accelerate discovery. In addition, the mechanism also allows for technology and databases to be shared across institutions, thus providing access for patients to new technology without having to travel great distances.

As biomarker evaluation becomes an integral part of clinical trials, the need to obtain sufficient diagnostic tissue specimens, preferably core needle biopsies, and standardized processing cannot be overemphasized. This requires a shift from the current practice of obtaining fine-needle biopsies for the original diagnostic purpose. It will also be necessary to obtain additional research biopsies as was done in a recent study that assigned treatment to patients based on baseline biomarker status (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination [BATTLE] trial).\textsuperscript{197} In this effort, nearly 300 patients with advanced stage NSCLC underwent a research biopsy for treatment selection. In addition to patient acceptance, such studies also require additional resources that will have to be funded by existing and new mechanisms. Development of new drugs will continue to be an important area of focus. The 3 most common molecular abnormalities in NSCLC, namely mutations in \textit{p53}, \textit{KRAS}, and \textit{LKB1}, are all targets for therapy and require novel agent/combination approaches.

The tremendous increase in the knowledge of lung cancer biology notwithstanding, a number of important questions remain unanswered. With lung cancer in never-smokers having been recognized as a unique entity, insights into the underlying mechanism and etiological factors will help in the development of novel therapies for this group of patients. The differences in lung cancer biology based on gender are another important area of research that will hopefully lead to the development of gender-driven therapeutic approaches. As newer therapeutic options are developed, participation of patients on clinical trials must be encouraged and supported by health care delivery systems. Currently, fewer than 5% of the patients diagnosed with cancer participate in therapeutic clinical trials.\textsuperscript{198} Finally, efforts to
reduce the burden of cigarette smoking in the general population have to be pursued with greater vigor. The first steps in the new era of lung cancer therapy have been taken, and the outlook for patients with lung cancer appears brighter by the day.

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