Hypothesis/Commentary

Advances in the Diagnosis and Treatment of Non–Small Cell Lung Cancer

Rathi N. Pillai and Suresh S. Ramalingam

Abstract

The diagnostic and therapeutic landscape of non–small cell lung cancer (NSCLC) has changed dramatically in the past 50 years since the Surgeon General’s report on smoking and lung cancer. Early detection is now a reality for lung cancer. The use of low-dose computed tomography scans for early detection decreases mortality and is beginning to be used in routine clinical practice. Technological advances such as positron emission tomography and endobronchial ultrasound have improved the accuracy of NSCLC staging. The cure rate for early-stage NSCLC has improved as a result of multimodality treatment approaches. The role of systemic therapy has also expanded to earlier stages of the disease. In recent years, the initial steps toward personalized medicine by utilization of targeted treatments based on tumor genotype have been undertaken. Emerging technological advances and greater insights into tumor biology are poised to greatly reduce the burden of lung cancer in the years to come. Mol Cancer Ther; 13(3); 557–64. ©2014 AACR.

Introduction

Tobacco use is a leading cause of preventable deaths and is the primary risk factor for lung cancer development (1). The current prevalence of cigarette smoking in the United States is 19% of the adult population, or 43.8 million adults: 21.6% of men and 16.5% of women in the United States are smokers (2). Despite reductions in the incidence of smoking in both sexes, lung cancer mortality among women smokers has been increasing over the past 50 years and is finally approaching the mortality rates seen in male smokers (3). Non–small cell lung cancer (NSCLC) remains the most lethal cancer, with more than 150,000 deaths estimated in 2013 (4). Changes in the manufacturing of cigarettes and smoking behaviors have also altered the epidemiology of NSCLC, with a shift toward higher incidence of adenocarcinoma and decline in squamous cell carcinoma (5). Besides public health initiatives to reduce tobacco use, several advances in diagnostic techniques and therapeutics have impacted outcomes in NSCLC. The development of improved imaging and diagnostic techniques can detect NSCLC earlier and improve outcomes. Chemotherapy also increases survival in the early-stage disease. Improved understanding of the biology of NSCLC has also led to exciting new therapies for metastatic disease. We describe the notable changes in lung cancer that occurred in recent years in this article.

Early Detection

Because most lung cancers remain clinically silent until they metastasize to other sites, the majority of patients present with advanced stages of disease, where curative therapy is no longer an option. Early studies utilizing chest X-ray (CXR) and sputum cytology for early detection of lung cancer failed to show any mortality benefit (6, 7). More recently, the National Lung Cancer Screening Trial (NLST) demonstrated a reduction in mortality with CT screening (8). This trial randomized 53,454 participants between the ages of 55 to 74 years with at least a 30 pack-year history of smoking or had quit within the previous 15 years to screening with annual CXR or low-dose helical computerized tomography (LDCT) of the chest, annually for 3 years. With a median duration of follow-up of 6.5 years, there was a high rate of adherence with 95% participants in the LDCT group and 93% in the CXR group completing all 3 screenings. The incidence of lung cancer in the LDCT group was 645 cases per 100,000 person years compared with 572 cases per 100,000 person years in the CXR group. The increased sensitivity of LDCT comes at the cost of a higher number of false positive tests: although 24.2% of participants in the LDCT had a positive screen, 96.4% of these were false-positive compared with only 6.9% positive screen screens in the CXR group, with a 94.5% false-positive rate. The mortality from lung cancer decreased from 309 deaths per 100,000 person years in the CXR group to 247 deaths per 100,000 person years in the LDCT group, which is a relative reduction in lung cancer mortality of 20% (95% CI, 6.8–26.7; P = 0.004). More
importantly, a 2-fold increase in the number of stage IA cancers was observed in the LDCT group (46% vs. 25%). LDCT can detect more lung cancers at earlier stages compared with CXR, which results in a significant reduction in mortality. The number of subjects needed to screen to prevent one lung cancer death is 320 (9).

The results of NLST have already led to the adoption of screening recommendations by a number of professional organizations related to health maintenance. Notable among them was the decision by the U.S. Preventive Services Task Force to recommend screening for adults of ages 55 to 79 that have a 30-pack-year history of smoking or have quit in the past 15 years. There are still open questions about the implementation of lung cancer screening in defining the optimal population to screen, the initiation of screening, and the duration of screening. Application of a prediction model for lung cancer death incorporating factors such as age, sex, race, family history, pack years of smoking, years since smoking cessation, family history of lung cancer, and personal history of emphysema could increase the yield of LDCT screening. If only the 60% of individuals at highest risk were screened, LDCT screening captured 88% of preventable lung cancer deaths and reduced the number needed to screen to 161 (10). Early detection of lung cancer heralds a new era in lung cancer research and will hopefully shift the disease from diagnosis at an advanced stage to early-stage disease that is amenable to curative therapies.

Staging
Defining the extent of disease in patients with NSCLC is integral to determining optimal treatment approaches. The tumor-node-metastasis (TNM) classification system for staging was recently updated after the analysis of an international database composed of more than 100,000 patients (11). Important changes in the 7th edition include the reclassification of additional tumor nodules in the same lobe as the primary tumor as T3 instead of T4, additional tumor nodules in an ipsilateral lobe as T4 rather than M1, and the reclassification of malignant effusions from stage IIIB to stage IV. In addition, because patients with extrathoracic metastases have worse outcomes than patients with metastatic disease limited to the chest, these patients are now separated into MIb and MIA categories.

Recent advances in imaging with positron emission tomography (PET) scan and noninvasive mediastinal staging with endobronchial ultrasound (EBUS) have improved patient selection for surgery. In a meta-analysis of 39 studies comparing mediastinal staging with computed tomography (CT) versus PET scans, PET scans were more accurate than CT scans (12). The median sensitivity of CT was 61% with median specificity of 79% compared with 85% and 90%, respectively, with PET. The addition of PET to conventional staging improved the selection of patients for surgical resection in a randomized trial of 188 patients in the Netherlands (13). The primary endpoint was the number of futile thoracotomies, defined as procedures performed for benign disease, exploration only, pathologic stage IIIA with N2 involvement or stage IIIB, or postoperative death or relapse within 12 months of randomization. The addition of PET upstaged 27% compared with only 12% in the conventional staging group. There were 39 (41%) futile thoracotomies in the conventional staging group compared with only 19 (21%) in the PET group; the relative risk reduction was 51% (95% CI, 32–80; \( P = 0.003 \)) and absolute reduction was 20%. Using PET as part of staging prevents unnecessary surgery in 1 of every 5 patients.

PET and CT have been compared with the updated technology of integrated PET–CT for accuracy of tumor staging, using pathologic assessment of tumor stage as reference standard in a small prospective study of patients with NSCLC (14). Integrated PET–CT proved more accurate in tumor staging than CT (\( P = 0.001 \)), PET (\( P < 0.001 \)), or visually correlated PET and CT (\( P = 0.013 \)) and in nodal staging compared with PET alone (\( P = 0.013 \)). Integrated PET–CT also decreased futile thoracotomies similar to PET alone: 52% in the conventional staging group to 35% in the group with PET–CT (\( P = 0.05 \); ref. 15). For every 5 PET–CTs performed, 1 futile thoracotomy is avoided; however, this does not result in survival difference. In a direct comparison of mediastinal staging with PET–CT compared with invasive staging with pathologic confirmation of suspicious lymph nodes in 52 patients, the sensitivity of PET–CT was 84% with a specificity of 85% (16). Although PET and PET–CT have improved the accuracy of staging, these technologies do not replace the need for tissue sampling of mediastinal lymph nodes in certain patients.

Accurate mediastinal staging is imperative to determine whether a patient is a candidate for surgical resection. Mediastinoscopy has been the accepted standard for mediastinal staging and can access the left and right paratracheal lymph node stations 2 and 4 and the subcarinal lymph nodes at station 7 (17). EBUS has increased the diagnostic yield of transbronchial needle biopsies through bronchoscopy, a less invasive procedure that accesses the same lymph node stations plus the peribronchial lymph nodes at stations 10 and 11. One of the early studies utilizing EBUS achieved a sensitivity of 94% and specificity of 100% when compared with operative findings (18). In a prospective comparison of CT, PET, and EBUS in 102 Japanese patients, EBUS had a much higher sensitivity and specificity of 92.3% and 100%, respectively, compared with PET, which was 80% sensitive and 70.1% specific (19). A meta-analysis of 11 studies with 1,299 patients who underwent EBUS found a pooled sensitivity and specificity of EBUS of 93% and 100%, respectively (20). The sensitivity of EBUS increased to 94% in a subgroup of patients selected with imaging compared with only 76% in patients who had no PET or CT selection. The ASTER [Assessment of Surgical sTaging versus EBUS and endoscopic ultrasound (EUS) in lung cancer: a Randomized controlled trial] study randomized 241 patients with resectable lung cancer with enlarged or FDG-avid hilar or mediastinal lymph nodes or a central lung lesion to...
immediate surgical staging or minimally invasive staging with EBUS and EUS followed by surgical staging if no mediastinal nodal metastases were found (21). The combination strategy resulted in sensitivity of 94% (95% CI, 85%–98%) compared with only 79% (95% CI, 66%–88%) with surgical staging alone ($P = 0.02$). The use of EBUS and EUS alone resulted in similar sensitivity to surgical staging at 85% (95% CI, 74%–92%). The combination strategy also reduced the number of futile thoracotomies by more than half (18% in mediastinoscopy group versus 7% in combination group, $P = 0.02$). The use of PET and EBUS has revolutionized the management of early-stage lung cancer and improved surgical outcomes by optimizing patient selection.

**Molecular Classification**

The application of genomics to NSCLC has revealed a diverse spectrum of unique driver mutations in patients with adenocarcinoma and squamous cell carcinomas (Table 1). The first systemic analysis of the mutational landscape in NSCLC was the Lung Cancer Mutation Consortium (LCMC), a collaborative effort between 14 institutions to characterize the presence of 10 driver mutations in tumor samples from patients with advanced adenocarcinoma of the lung (22). The driver mutations evaluated were KRAS, epidermal growth factor receptor (EGFR), BRAF, HER2, PIK3CA, AKT1, NRAS, MEK1, EML4-ALK, and MET. The initial findings were reported at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2011. Of the 516 patients analyzed, 54% had a mutation identified, and 97% of these mutations were mutually exclusive. The most common mutations are: KRAS 22%, EGFR 17%, EML4-ALK 7%, and BRAF 2%. In updated data from ASCO 2013 with 1,007 patients tested, 62% had at least one driver mutation (23). Based on these findings, 28% of the patients were directed to a targeted therapy for their mutation. The median survival for patients with a driver mutation who received targeted therapy was 3.5 years compared with 2.4 years in those who did not receive a targeted therapy, which was comparable to the survival of patients without a driver mutation at 2.1 years ($P < 0.0001$). The French National Cancer Institute has a similar program called Biomarkers France, which plans to assess 10,000 patients with NSCLC for EGFR, EML4-ALK, KRAS, HER2, BRAF, and PIK3 alterations (24). Data from the first 2,500 patients reported that 46.2% patients had a mutation, and 56.9% of patients had first line therapy guided by these results. The median survival for the overall patient population was 11.4 months. Cooperative efforts to genetically characterize lung adenocarcinoma have led to discovery of new driver mutations, which have the potential to revolutionize the treatment of NSCLC.

The Cancer Genome Atlas (TCGA) has undertaken a massive sequencing effort in squamous cell lung cancers (25). This ambitious characterization of early-stage squamous cell carcinoma of the lung utilized multiple platforms, including whole genome sequencing, exome sequencing, and transcriptome sequencing. Compared with other tumors assessed by TCGA, squamous cell lung cancers have a very high rate of somatic mutations, with a mean of 165 somatic rearrangements per tumor and 360 mutations per tumor with 228 nonsilent mutations. Pathways involved in squamous differentiation, such as SOX2/TP63, NOTCH1 and 2, ASC4, and FOXP1 were altered in 44% of tumors, whereas 34% had mutations in oxidative stress pathways (KEAP1, CUL3, NFE2L2). Interestingly, 70% tumors had alterations in PI3K, KRAS, or another receptor tyrosine kinase pathway, which could be potentially druggable. These data can help direct the development of targeted therapies for patients with squamous cell carcinoma, which has lagged behind lung adenocarcinoma.

## Systemic Chemotherapy in Curative Settings

The study of adjuvant chemotherapy began in the 1980s and a large meta-analysis provided early evidence of the survival benefit of the addition of chemotherapy in the treatment of patients with early-stage NSCLC (26). In 1,394 patients with early-stage NSCLC treated with cisplatin-based regimens compared with surgery alone, there was a trend toward improved survival (HR = 0.87), resulting in...
Table 2. Adjuvant chemotherapy trials in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Stages included</th>
<th>Chemotherapy</th>
<th>HR death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IALT</td>
<td>1,867</td>
<td>I–III</td>
<td>- Cisplatin/etoposide</td>
<td>0.86 (0.76–0.98) P &lt; 0.03</td>
</tr>
<tr>
<td>ALPI</td>
<td>1,209</td>
<td>I–IIIA</td>
<td>- Mitomycin C/vindesine/cisplatin</td>
<td>0.96 (0.81–1.13) P = 0.589</td>
</tr>
<tr>
<td>Big Lung Trial</td>
<td>381</td>
<td>I–III</td>
<td>- Cisplatin/vindesine</td>
<td>1.02 (0.77–1.35) P = 0.90</td>
</tr>
<tr>
<td>JBR-10</td>
<td>482</td>
<td>IB–II</td>
<td>- Cisplatin/vinorelbine</td>
<td>0.78 (0.61–0.99) P = 0.04</td>
</tr>
<tr>
<td>ANITA</td>
<td>840</td>
<td>IB–IIIA</td>
<td>- Cisplatin/vinorelbine</td>
<td>0.80 (0.66–0.96) P = 0.017</td>
</tr>
<tr>
<td>CALGB 9633</td>
<td>344</td>
<td>IB</td>
<td>- Carboplatin/paclitaxel</td>
<td>0.83 (0.64–1.08) P = 0.12</td>
</tr>
</tbody>
</table>

an absolute survival benefit of 5% at 5 years (P = 0.08). Based on these findings, several large randomized adjuvant chemotherapy trials were attempted with mixed results (Table 2).

The Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis combined data from the recent adjuvant studies (JBR-10, ALPI, ANITA, IALT, and BLT) with 4,584 patients and a median follow-up of 5.2 years (27). Chemotherapy improved survival with HR = 0.89 (95% CI, 0.92–0.96; P = 0.005), with an absolute survival benefit of 5.4% at 5 years. In a subgroup analysis of patients by stage, there was an improvement in overall survival (OS) for patients with stage II and stage III disease, with HR = 0.83 (95% CI, 0.73–0.95) and HR = 0.83 (95% CI, 0.72–0.94), respectively. The survival was not improved for stage IB disease (HR = 0.93; 95% CI, 0.78–1.10). However, in a subgroup analysis of the JBR-10 trial, patients with tumor size of >4 cm had a trend toward benefit from chemotherapy (HR = 0.66; 95% CI, 0.38–1.14; P = 0.13). This was also seen in the CALGB 9633 (HR = 0.69; 95% CI, 0.48–0.99; P = 0.043). Thus overall, the use of adjuvant chemotherapy in patients with resected NSCLC improves survival, with a definite benefit in patients with stage II and III disease.

Patients with stage III disease with bulky mediastinal lymph node involvement or T4 tumors are generally considered to have surgically unresectable disease. Combined modality approaches with concurrent chemoradiation have become the standard of care for patients with unresectable stage III NSCLC. The addition of chemotherapy concurrently increases efficacy of radiation for local control and has the added benefit of targeting micrometastatic disease. The use of concurrent radiotherapy with chemotherapy has improved response rates and survival over sequential chemoradiotherapy. There is a potential for cure even without surgery, with 5-year survival rates of approximately 15% to 20% (28–30). In otherwise healthy patients treated with induction chemoradiation, surgical resection may be beneficial if the primary tumor can be removed with a lobectomy. There was a high postoperative mortality seen in patients who underwent pneumonectomy following induction chemoradiation (31).

Systemic Chemotherapy in Metastatic Disease

Similar to the use of chemotherapy in the adjuvant setting, chemotherapy in patients with metastatic disease results in prolonged survival and improved quality of life. In an updated meta-analysis of 2,714 patients with advanced NSCLC in 16 randomized controlled trials, the use of chemotherapy increased 1-year survival rate by 9% (32). The standard of care for patients with a good performance status is platinum-based doublet therapy (Table 3; ref. 33). In patients who achieve disease stabilization or objective response, the use of maintenance therapy, which is continued administration of a single drug until disease progression has also resulted in improved survival (34). Bevacizumab, erlotinib, and pemetrexed have been used in this setting (35–37). The development of salvage therapies such as docetaxel, erlotinib, and pemetrexed have allowed for treatment options in the second- and third-line settings, thereby prolonging survival of patients with improved symptom control and quality of life with metastatic NSCLC (38–41).

Individualized Therapy

Perhaps the most exciting development in lung cancer has been the personalization of therapy in advanced stages of disease. This was first realized with the discovery of the importance of histology in determining therapy in NSCLC. Bevacizumab, a monoclonal antibody targeting VEGF, is approved with chemotherapy only for patients with nonsquamous histology, because of the increased risk of hemoptysis in patients with squamous cell carcinoma (35, 42). In the ECOG 4599 study, the addition of bevacizumab to carboplatin and paclitaxel resulted in

![Table 2](table2.png)
improved OS (12.3 months versus 10.3 months with placebo, HR = 0.79; \( P = 0.003 \); ref. 35). In another phase III study of bevacizumab combined with cisplatin and gemcitabine, there was no survival benefit, although there was a statistically significant and clinically modest improvement in progression-free survival (PFS; ref. 42). On the basis of these two studies, bevacizumab has been approved with platinum doublet therapy in patients with nonsquamous histology. Pemetrexed is also limited to patients with nonsquamous histology. In a subgroup analysis of a phase III randomized trial, cisplatin/pemetrexed regimen was superior to cisplatin/gemcitabine in patients with nonsquamous histology (median survival 11.8 months vs. 10.8 months; HR = 1.23; 95% CI, 1.00–1.23; \( P = 0.05 \)). This has been hypothesized to be because of the higher levels of thymidylate synthase in squamous cell carcinoma, which is associated with resistance to pemetrexed.

The development of EGFR tyrosine kinase inhibitors (TKI) has shown the fulfilled promise of a successful biomarker to select therapy. The Iressa Pan-Asia Study (IPASS) demonstrated a significant improvement in PFS with gefitinib compared with carboplatin/paclitaxel in a clinically selected population (44). Based on improved response rates seen in women, never smokers, and Asian patients in phase II studies, IPASS limited enrollment of Asian patients with adenocarcinoma and former light or never smokers. While this study was enrolling, somatic \( EGFR \) mutations were characterized in patients who responded to gefitinib, including exon 19 deletions and the L858R mutation in exon 21 (45). Patients in the IPASS study with \( EGFR \) mutations had a significantly prolonged PFS when treated with gefitinib (HR = 0.48; 95% CI, 0.36–0.64, \( P < 0.001 \)), whereas wild-type \( EGFR \) patients had inferior PFS with gefitinib (HR = 2.85; 95% CI, 2.05–3.98, \( P < 0.001 \)). Multiple studies have now compared EGFR TKIs to chemotherapy in the frontline therapy of patients with advanced or recurrent NSCLC with sensitizing \( EGFR \) mutations (46–49). All of these studies showed a significant improvement in the primary endpoint of PFS with targeted therapy of \( EGFR \) mutation compared with systemic chemotherapy, with response rates with TKI ranging from 61% to 83% (Table 4). EGFR TKIs are generally well tolerated with rash and diarrhea as the most frequent toxicities in contrast to chemotherapy; patients also report improved quality of life on TKIs compared with chemotherapy (44, 48). It is interesting that none of these studies have shown a survival benefit, although this can be explained by high crossover rate in patients who received chemotherapy. However, these data provide compelling evidence for

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>Regimen</th>
<th>Patients</th>
<th>ORR (%)</th>
<th>Median OS (months)</th>
<th>( P ) value (for OS comparison)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scagliotti (2002)</td>
<td>Cisplatin/gemcitabine</td>
<td>205</td>
<td>30</td>
<td>9.8</td>
<td>NS</td>
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<tr>
<td></td>
<td>Cisplatin/paclitaxel</td>
<td>204</td>
<td>32</td>
<td>9.9</td>
<td></td>
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<tr>
<td></td>
<td>Cisplatin/vinorelbine</td>
<td>203</td>
<td>30</td>
<td>9.5</td>
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<tr>
<td>Schiller (2002) ECOG 1594</td>
<td>Cisplatin/paclitaxel</td>
<td>303</td>
<td>21</td>
<td>7.8</td>
<td>NS</td>
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<tr>
<td></td>
<td>Cisplatin/gemcitabine</td>
<td>301</td>
<td>22</td>
<td>8.1</td>
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<td></td>
<td>Cisplatin/docetaxel</td>
<td>304</td>
<td>17</td>
<td>7.4</td>
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<tr>
<td></td>
<td>Carboplatin/paclitaxel</td>
<td>299</td>
<td>17</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>Fossella (2003) TAX 326</td>
<td>Cisplatin/docetaxel</td>
<td>408</td>
<td>32</td>
<td>11.3</td>
<td>0.044</td>
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<td></td>
<td>Carboplatin/docetaxel</td>
<td>406</td>
<td>24</td>
<td>9.4</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Carboplatin/vinorelbine</td>
<td>404</td>
<td>25</td>
<td>10.1</td>
<td></td>
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<td>Sandler (2006) ECOG 4599</td>
<td>Carboplatin/paclitaxel/bevacizumab</td>
<td>434</td>
<td>35</td>
<td>12.3</td>
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<td></td>
<td>Carboplatin/paclitaxel</td>
<td>444</td>
<td>15</td>
<td>10.3</td>
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<tr>
<td>Reck (2009, 2010) AVAiL</td>
<td>Cisplatin/gemcitabine/bevacizumab Low-dose bevacizumab: 7.5 mg/kg</td>
<td>345</td>
<td>34</td>
<td>13.6</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>High-dose bevacizumab: 15 mg/kg</td>
<td>351</td>
<td>30</td>
<td>13.4</td>
<td>0.76</td>
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<tr>
<td></td>
<td>Cisplatin/gemcitabine/placebo</td>
<td>347</td>
<td>20</td>
<td>13.1</td>
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<tr>
<td>Scagliotti (2008)</td>
<td>Cisplatin/pemetrexed</td>
<td>862</td>
<td>31</td>
<td>10.3</td>
<td>NS</td>
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<tr>
<td></td>
<td>Cisplatin/gemcitabine</td>
<td>863</td>
<td>28</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>Socinski (2012)</td>
<td>Carboplatin/nab-paclitaxel</td>
<td>521</td>
<td>33</td>
<td>12.1</td>
<td>0.271</td>
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<tr>
<td></td>
<td>Carboplatin/paclitaxel</td>
<td>531</td>
<td>25</td>
<td>11.2</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.

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**Table 3.** Platinum doublet chemotherapy trials in metastatic NSCLC

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the use of EGFR TKI in the first-line therapy of patients with sensitizing EGFR mutations. In the United States, erlotinib was the first EGFR inhibitor to be approved for the treatment of patients with EGFR mutation. Afatinib, an irreversible inhibitor of EGFR, HER2, and ErbB4 receptors, for EGFR mutated adenocarcinomas has also received U.S. Food and Drug Administration (FDA) approval recently on the basis of results from the LUX-Lung 3 study (50). When compared with cisplatin/pemetrexed, patients with EGFR mutations had a significant increase in PFS when treated with afatinib (Table 4). EGFR mutations predict better response and PFS with EGFR targeted therapy in patients with advanced NSCLC. The next generation of EGFR inhibitors is already under development for patients who acquire resistance to therapy with erlotinib or gefitinib.

The EML4-ALK translocation results in constitutive activation of the anaplastic lymphoma kinase (ALK), thereby driving lung tumorigenesis. EML4-ALK occurs in 3% to 5% NSCLC and tends to occur more frequently in never smokers, with a median age at diagnosis of 52 years and has a male predominance (51). Crizotinib is a dual inhibitor of ALK and MET that has been FDA approved for the treatment of NSCLC with the EML4-ALK translocation. The approval was based on an expansion cohort of a phase I study of crizotinib that demonstrated an overall response rate (ORR) of 60.8% and median PFS of 9.7 months (52). Crizotinib improves outcomes in patients in the second-line setting compared with pemetrexed or docetaxel (53). The primary endpoint of PFS increased from 3 to 7.7 months with crizotinib (HR = 0.49; 95% CI, 0.37–0.64; \( P < 0.001 \)) and ORR was 65%. The most frequent adverse events were visual effects, gastrointestinal toxicity, and peripheral edema. Again, targeted therapy with crizotinib was associated with a significantly improved quality of life compared with chemotherapy (\( P < 0.001 \)).

In the past year, two new gene rearrangements have been described in lung adenocarcinomas. The KIF5B-RET fusion has been described in 1% to 2% of lung adenocarcinomas and occurs independent of other alterations such as EGFR and KRAS (54–56). Patients with KIF5B-RET fusions tend to be younger nonsmokers (57). Patients have been treated with TKIs inhibiting RET, such as sunitinib, sorafenib, and vandetanib, with anecdotal reports of objective responses. ROS1, a member of the insulin receptor, can also be rearranged in NSCLC. It has been described in 1% to 2% adenocarcinomas (58). Crizotinib has promising activity in targeting ROS1 with an ORR of 56% and 6-month PFS of 71% (59).

BRAF is a serine threonine kinase that is mutated in 2% of lung adenocarcinomas, occurring more frequently in smokers unlike many other genetic alterations (23, 60). At least half of BRAF mutations are the V600E, which is an activating mutation. Dabrafenib, a V600E inhibitor used in melanoma, is being tested in a phase 2 study of patients with V600E BRAF mutated NSCLC. Dabrafenib has promising activity, with a reported ORR of 54% in 17 patients treated to date (61). Dabrafenib was well tolerated with the most frequent toxicities being decreased appetite, fatigue, asthenia, dyspnea, and nausea.

**Conclusions**

Advances in screening, staging, multimodality, and systemic therapy have led to improved survival in patients with NSCLC. We are beginning to realize the potential of genomics in the treatment of NSCLC. Future studies will determine the utility of targeted therapy in early-stage NSCLC. Continued success will depend on collaborative research to genetically characterize NSCLC in individual patients and develop successful drugs even for rare subtypes of NSCLC.

**Disclosure of Potential Conflicts of Interest**

Suresh S. Ramalingam is a consultant/advisory board member for Astra Zeneca, Genentech, Lilly, Novartis, and Amgen. No potential conflicts of interest were disclosed by the other authors.


